







# Endocrine contribution to the sexual dysfunction in patients with advanced chronic kidney disease and the role of hyperprolactinemia

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## Abstract

In this study, we investigated the prevalence of sexual dysfunction among males with advanced chronic kidney disease and the effect of treating hyperprolactinemia among these patients. In this prospective study, patients were assessed with history, physical examination, hormonal assessment, and two questionnaires, IIEF and AIPE. Patients with hyperprolactinemia received treatment with cabergoline 0.5 mg once per week for 6 months and were re-evaluated. A total of 102 patients were included in this study, 75 (73.53%) were on hemodialysis, 13 (12.75%) on peritoneal dialysis and 14 (13.73%) on medical treatment alone. Ninety (88.24%) patients had premature ejaculation, 85 (83.33%) had anything from mild-to-moderate-to-severe erectile dysfunction. The incidence of hypogonadism and hyperprolactinemia was 34.4%. Patients treated with cabergoline ( $n = 26$ ) showed a significant increase in LH levels ( $p = .003$ ) and a significant decrease in prolactin levels ( $p = .003$ ). Testosterone levels and the incidence of erectile dysfunction or premature ejaculation did not improve significantly. There is a high incidence of sexual dysfunction among patients. Treatment of hyperprolactinemia is effective in correcting prolactin levels, but does not improve erectile dysfunction or premature ejaculation. Therefore, treating hyperprolactinemia is not an overall effective treatment for erectile dysfunction in these patients.

## KEYWORDS

end-stage renal disease, erectile dysfunction, hyperprolactinemia, hypogonadism, premature ejaculation

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## 1 | INTRODUCTION

Advanced chronic kidney disease (ACKD) is found in two million people worldwide (USRDS Annual Data Report, 2018). A common problem with ACKD patients is sexual dysfunction with approximately 70% of men with ACKD report erectile dysfunction (ED) which is significantly higher than the prevalence of ED in the general population (31%) (Laumann et al., 1999; Navaneethan et al., 2010). Men with ACKD can present with erectile, ejaculatory, orgasmic dysfunctions and combination of more than one sexual symptom (Finkelstein & Finkelstein, 2002).

Erectile dysfunction in males with ACKD is multifactorial, including endocrinological, vascular and psychological (Bortolotti et al., 1998). ACKD with decrease in GFR causes many hormonal imbalances due to changes in the hypothalamus-pituitary-gonadal (HPG) axis, an interruption of feedback loops, and decreased metabolism of hormones. The decreased metabolism and interruption of feedback loops result in decreased GnRH, elevated LH, variably high FSH levels and lower testosterone levels which eventually leads to hypogonadism (Holley, 2004; Snyder & Shoskes, 2016). Abnormally high serum prolactin level is seen in up to 50% in patient's on hemodialysis due to increased prolactin secretions and a reduced metabolic clearance rate. This can be explained by development of secondary hyperparathyroidism, depletion of zinc or medications. Hyperprolactinemia contributes to the continual low testosterone levels and erectile dysfunction through inhibition on the HPG axis as well as direct inhibition of testosterone at the testicular level (Cowden et al., 1978; Gómez et al., 1980; Handelsman, 1985; McKenna & Woolf, 1985; Sievertsen et al., 1980). Among the other factors that can lead to ED, patients with ACKD may also have increased vascular calcification and atherosclerosis (Goodman et al., 2000). Many ACKD patients also have underlying conditions such as diabetes mellitus (DM), hypertension and cardiovascular disease that are considered the primary causation of ACKD in approximately 40%–50% of patients. These are common comorbidities and risk factors for ED (Mesquita et al., 2012; Rosas et al., 2001).

Premature ejaculation (PME) is one of the most common male sexual dysfunctions affecting around 30% of population (Carson & Gunn, 2006). Aslan et al. (2003) reported a similar prevalence of PME (31.6%) in ACKD patients. Controversy still exists regarding the correlation of testosterone level and premature ejaculation (PME). Where some studies reported higher testosterone level in PME patients (Mohseni et al., 2014), few studies stated lower testosterone level in these patients especially in secondary PME (Aslan et al., 2003; Tahtali, 2020).

Lo et al. (2017) investigated the prevalence of hyperprolactinemia in patients with ACKD and found elevated serum prolactin levels in most of the patient cohort. Another study conducted by Bolat et al. reported the hormone levels of males with ACKD and the efficacy of Tadalafil. It found that 26 out of the 30 patients tested had testosterone levels that were below normal limits. It also found the mean serum prolactin level to be higher than the normal limit (Bolat et al., 2017). Some studies suggested the effectiveness of

cabergoline in treating erectile dysfunction in patients with or without hyperprolactinemia (De Rosa et al., 2004; Nickel et al., 2007). However, no studies discussed this effect in patients with ACKD.

Most of the studies conducted on sexual function in ACKD are either outdated or focused only on the underlying causes. Also, very few articles address how to manage ED in ACKD patients. Therefore, more research is necessary to look into the effect of correcting abnormal endocrinopathies caused by ACKD in order to provide more research data to facilitate the clinical treatment of this problem. The study aimed to investigate (a) the prevalence of sexual dysfunction in ACKD patients, (b) the effect of ACKD on the HPG axis and (c) the effect of correcting hyperprolactinemia on sexual function in patients with ACKD.

## 2 | MATERIALS AND METHODS

This prospective cross-sectional study was conducted at Hamad Medical Corporation, Doha, Qatar. The study was conducted from 1 January 2017 to 31 December 2018. All patients approached to be included in the study were married males with ACKD on hemodialysis, peritoneal dialysis or they had chronic kidney disease and were on regular follow-up in the outpatient for over one year at the institute. Patients already receiving treatment for erectile dysfunction and patients receiving medications that may affect sexual functions (e.g. cytotoxic drugs, androgens, oestrogens, thiazides, alpha blockers) were excluded from this study. A proper sample size could not be calculated as this was the first study looking into the effect of correcting hyperprolactinemia on sexual function in patients with ACKD. This pilot study would help to plan future studies.

Patients accepted to join the study, signed an informed consent after obtaining approval by the institute's Local Ethics Committee (IRB approval 17079).

All recruited patients were subjected to full history taking including age, comorbidity, medications and marital status. All patients were also subjected to a physical examination including a general examination and a local genital examination of the penis, scrotum and prostate. All patients were provided two questionnaires at the beginning of the study, the International Index of Erectile Function (IIEF) and the Arab Index of Premature Ejaculation (AIPE) (Arafa & Shamloul, 2007; Rosen et al., 1999). A hormonal assessment was also done at the beginning of the study. Patients with hyperprolactinemia were counselled to receive treatment with Cabergoline 0.5 mg once per week. Another hormonal assessment was done after 6 months in addition to filling out the two questionnaires again. This process is outlined in Figure 1.

### 2.1 | Hormonal assessment

Blood samples for the hormonal assay were collected from each patient between 7 and 9 a.m. The hormonal analysis was conducted at the institute's endocrine laboratory using the immunoassay

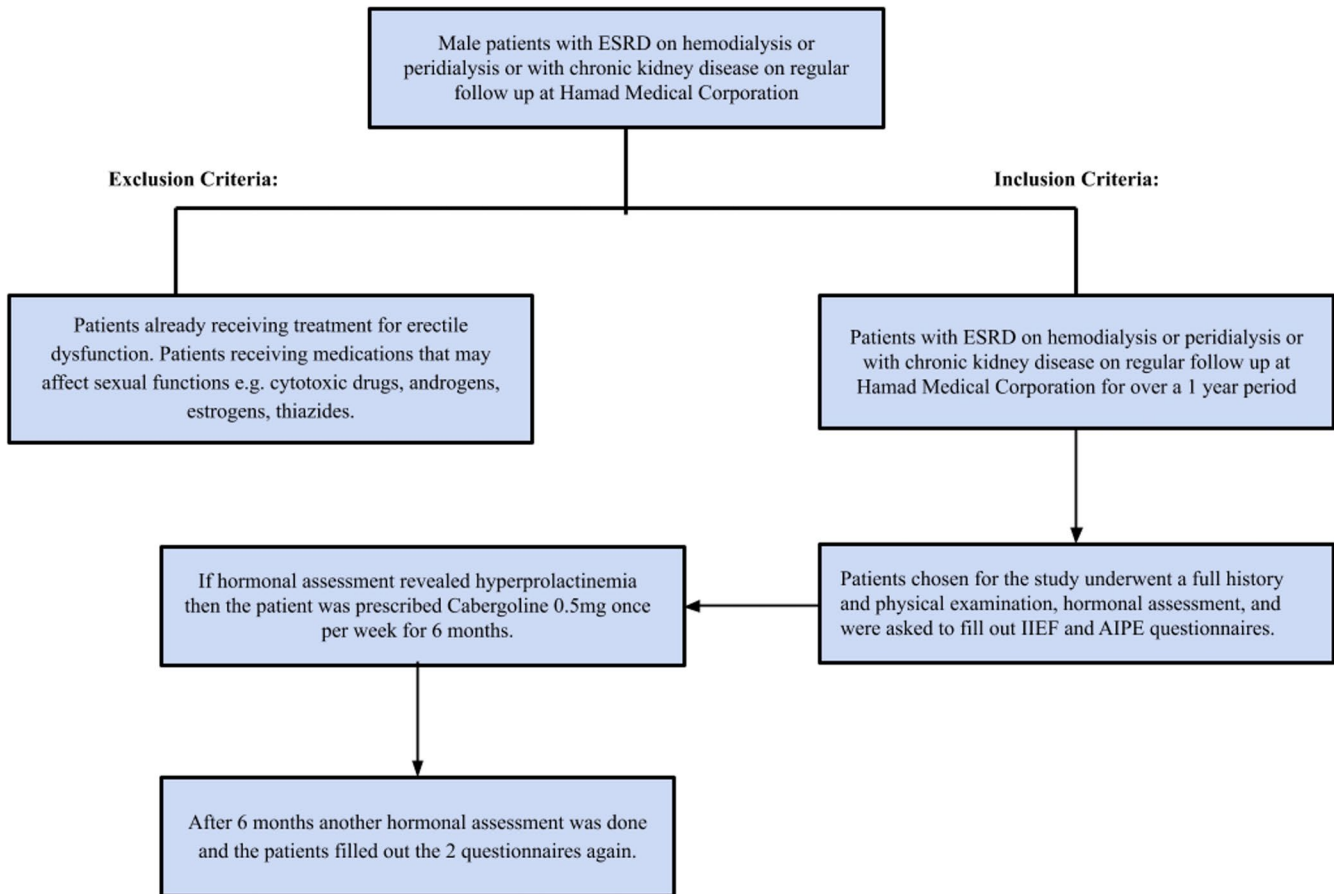


FIGURE 1 Methodology diagram

chemiluminescence method, Architect i1000SR@ (Abbott systems). The hormonal profile included the following: oestradiol (normal range 73–275 pmol/L), follicle-stimulating hormone (normal range 1–19 IU/L), luteinising hormone (normal range 1–9 IU/L), prolactin (normal range 73–407 mIU/L) and total testosterone (normal range 10.4–35 nmol/L).

## 2.2 | Questionnaires

The two validated questionnaires used to assess the patients' sexual function were the IIEF and the AIPE. The scoring criteria for the IIEF is as follows: severe erectile dysfunction [1–10], moderate dysfunction [11–16], mild-to-moderate dysfunction [17–21], mild dysfunction [22–25] and no dysfunction [26–30]. The scoring criteria for AIPE are as follows: severe [7–13], moderate [14–19], mild-moderate [20–25], mild [26–30] and no PE [31–35].

## 2.3 | Statistical analysis

The statistical analysis included the Shapiro–Wilk test for normality to identify the distribution of the study variables. Frequencies (%) were used to report categorical data, while the mean  $\pm$  SD (SE) was used to present continuous values. Spearman's correlations

were performed to assess the relationship between various study variables. Wilcoxon signed rank test was used to compare changes in hormone, IIEF-5 and AIPE results before and after treatment with cabergoline. A *p*-value below .05 was considered statistically significant. Statistical analysis of collected data was performed using SPSS version 20 (IBM).

## 3 | RESULTS

A total of 500 patients were screened for inclusion in the study. Only 102 met the inclusion and exclusion criteria. Of these 102 patients, 75 (73.53%) were on hemodialysis, 13 (12.75%) were on peritoneal dialysis, and 14 (13.73%) had chronic kidney disease (CKD). The comorbidities of the patient cohort include 53 patients (51.96%) with diabetes mellitus type I, 49 patients (48.04%) with diabetes mellitus type II, 35 patients (34.31%) with coronary heart disease, 99 patients (97.06%) with hypertension and 26 patients (25.49%) with dyslipidemia.

Table 1 shows the clinical characteristics of the patients. The incidence of PME was 88.24% (90 patients) while incidence of ED was 83.33% (85 patients) with ED ranging from mild to severe. The incidence of hyperprolactinemia was like that of hypogonadism and was 34.4% (35 patients) among the patient cohort.

**TABLE 1** Characteristics of the study population

Variable	Data
Number of years on dialysis (mean $\pm$ SD)	4.72 $\pm$ 4.83
AIPE results (Frequency (%))	
No PE	3 (2.94)
Probable PE	9 (8.82)
PE	90 (88.24)
IIEF-5 results (Frequency (%))	
Severe ED	24 (23.53)
Moderate-severe ED	30 (29.41)
Mild-to-moderate ED	31 (30.39)
Mild ED	15 (14.71)
No ED	2 (1.96)
Clinical data	
BMI (mean $\pm$ SD)	29.95 $\pm$ 9.35
E2 (Pmol/L) (median (IQR))	126.5 (89.25–161)
LH (IU/L) (median (IQR))	7 (5–10)
FSH (IU/L) (median (IQR))	4 (3–6)
PRL (mIU/L) (median (IQR))	338 (246.75– 524.25)
Testo (nmol/L) (median (IQR))	12.7 (9–16)
Hyperprolactinemia (Frequency (%))	35 (34.4%)
Hypogonadism (Frequency (%))	35 (34.4%)

Abbreviations: BMI, body mass index; PE, premature ejaculation; ED, erectile dysfunction; E2, oestradiol; LH, luteinising hormone; FSH, follicle-stimulating hormone; PRL, serum prolactin level; Testo, total testosterone level; IQR, inter-quartile range.

**TABLE 2** Correlations between continuous variables

	total_IIEF5	PE_total	PRL (mIU/L)	Testo (nmol/L)
BMI	0.025	0.043	0.027	-0.107
Age	-0.310**	0.280**	-0.173	-0.031
total_IIEF5	1	-0.339**	0.033	0.080
PE_total	-0.339**	1	-0.161	-0.020
E2 (Pmol/L)	-0.268**	0.073	-0.098	0.226*
LH (IU/L)	-0.042	-0.176	0.011	0.179
FSH (IU/L)	-0.118	-0.120	0.118	-0.039
PRL (mIU/L)	0.033	-0.161	1	-0.239*
Testo (nmol/L)	0.080	-0.020	-0.239*	1

Note: Spearman Correlation; \*\* highly significant <0.001; \* significant <0.05.

Abbreviations: BMI, body mass index; PE, premature ejaculation; E2, oestradiol; LH, luteinising hormone; FSH, follicle-stimulating hormone; PRL, serum prolactin level; Testo, total testosterone level.

An increase in age was found to be significantly correlated with an increase in ED and PME. ED assessed by IIEF was found to be

significantly correlated with PME assessed by AIPE. Also, prolactin was found to be significantly correlated with hypogonadism. All other correlations were insignificant (Table 2).

Of the 35 patients diagnosed with hyperprolactinemia, 26 accepted treatment with Cabergoline. 22 patients were on hemodialysis and four patients on peritoneal dialysis. The changes in hormone levels and questionnaire results after treatment with Cabergoline are shown in Table 3. There was a significant increase in LH levels and a significant decrease in prolactin levels ( $p = .003$  for both). However, there was no statistically significant improvement in the testosterone levels ( $p = .906$ ). The results of the questionnaires showed no improvement in the incidence of erectile dysfunction or PME ( $p = .279$  and  $p = .224$ ) respectively.

## 4 | DISCUSSION

In males with ACKD, the incidence of erectile dysfunction and hyperprolactinemia is much higher than that in otherwise healthy males (Chen et al., 2001; Juergense et al., 2001; Türk et al., 2001). Our study found a high incidence of erectile dysfunction, ejaculatory dysfunction, hypogonadism and hyperprolactinemia in patients with ACKD. Cabergoline was found to be effective in treating hyperprolactinemia by correcting the prolactin levels but did not significantly improve erectile dysfunction.

Our study found that the decrease in prolactin levels following treatment reduced the inhibition on the HPG enabling LH to begin to be produced in proper quantities to stimulate the production of testosterone (Ayub & Fletcher, 2000), and however, the testosterone levels did not increase as expected. This can be due to the other associated factors known to cause low testosterone in our patient cohort such as advanced age, the uremic effect on Leydig cell as well as associated comorbidities especially DM that can lead to low testosterone (Bao & Johansen, 2015; Palmer & Clegg, 2017).

A study done by Albajj et al. (2006) looked into the prevalence of hypogonadism in male patients with ACKD and reported that 26.3% of its patient cohort to have significantly low testosterone levels. This is comparable to our finding of 34.4% incidence of hypogonadism within our patient cohort.

A study by Snyder and Shoskes looked at hypogonadism and testosterone replacement therapy for patients with end-stage renal disease. This study also found the incidence of sexual dysfunction among this patient population to be >80% (Snyder & Shoskes, 2016). Our study also found the incidence of sexual dysfunction to be >80% with 88.24% having PME and 83.33% having ED ranging from mild-to-severe dysfunction. A study by Cowden et al. looked into hyperprolactinemia in patients with renal disease. The study found the incidence of hyperprolactinemia among its patient cohort to be 32%, which is very similar to our study's findings (Cowden et al., 1978).

A study by Weizman et al. investigated the incidence of erectile dysfunction and the effect of correcting hyperprolactinemia in patients with ACKD in 1983 and included 59 patients. The study concluded that hyperprolactinemia and other hormonal imbalances are

**TABLE 3** Changes in hormones, IIEF-5 and AIPE results after treatment with cabergoline ( $n = 26$ ) (median (IQR))

	Pre-treatment	Post-treatment	p-value
E2 (Pmol/L)	142 (90–163.5)	138.5 (103–187.5)	.509
LH (IU/L)	5 (3–8)	8 (6–16.5)	.003
FSH (IU/L)	6 (5–11)	5 (3.75–8)	.073
PRL (mIU/L)	567 (427–1030)	298.5 (108.75–542.25)	.003
Testo (nmol/L)	10.54 (5.5–17.5)	12.5 (7.75–15.5)	.906
total_IIEF5	11 (7.5–15)	14 (7–16)	.279
PE_total	15 (10.75–17)	15 (11.5–20)	.224

Note: Wilcoxon signed ranks test.

Abbreviations: E2, oestradiol; LH, luteinising hormone; FSH, follicle-stimulating hormone; PRL, serum prolactin level; Testo, total testosterone level; IQR, inter-quartile range.

due to decreased metabolism and interruption of the hypothalamus-pituitary axis. It also concluded that erectile dysfunction in patients with ACKD is multifactorial and must be treated as such. However, Weizman et al. found bromocriptine to be an effective treatment for correcting prolactin levels and improving sexual dysfunction. This treatment was only given to five participants, which is not a large enough number to conclude that bromocriptine is an effective treatment for hyperprolactinemia and sexual dysfunction. The study also used a self-report four-point rating scale to assess improvement in sexual dysfunction before and after treatment which is outdated and not reliable. Therefore, it is unclear if there was a real improvement in sexual function following correction of hyperprolactinemia (Weizman et al., 1983).

The prevalence of PME in the present study was 88.2% using AIPE. Aslan et al. was the only study who previously reported the prevalence of PME in ACKD patients with a prevalence of 31.6%. This discrepancy in prevalence may be attributed to difference in inclusion criteria and tools of assessment. They studied patients with no complaint of ED and having regular sexual intercourse. Diagnosis of PE was not done using any validated questionnaire, but instead they depended on the definition of PE of having uncontrolled ejaculation  $\leq 2$  min after the vaginal penetration in  $>50\%$  of sexual encounters (Aslan et al., 2003).

The main limitation within our study was the small sample size. There are no recent studies done on the treatment of hyperprolactinemia, and therefore, there was no other study to calculate a proper sample size against. Another limitation was absence of a control group.

## 5 | CONCLUSION

Male patients with ACKD show higher incidences of sexual dysfunctions and abnormal endocrinopathies such as ED, PME, hypogonadism and hyperprolactinemia. Treatment of hyperprolactinemia was effective in correcting prolactin levels, but an improvement in ED was not found. Therefore, patients with ACKD who have erectile dysfunction should be treated from many different aspects, this includes the following: correction of hormone levels and treatment of underlying

conditions such as diabetes mellitus and atherosclerosis should all be addressed in their management. To further look into clear treatment, a larger, multi-centre research study should be conducted.

## AUTHORS' CONTRIBUTIONS

Hazem Miqdad, data collection. Rania Ibrahim, dialysis co-ordinator helped in distributing the questionnaires. Heba Ateya, dialysis co-ordinator helped in distributing the questionnaires. Farid Keyvanifard, andrologist helped in semen analysis. Mohamed Abohalawa, andrologist helped in semen analysis.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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