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Original Research Article

A study of the prevalence of gonadal dysfunction and its association with increasing disease severity in patients diagnosed with chronic kidney disease at a tertiary care center in Kolkata, West Bengal

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ABSTRACT

Background: Hypergonadotropic hypogonadism is a well described hormonal derangement associated with chronic kidney disease, also known as uremic hypogonadism. The objective of this study was to assess the prevalence of gonadal dysfunction associated with chronic kidney disease and to study the co-relation of gonadal dysfunction with disease severity.
Methods: In this cross-sectional observational study, 50 patients with diagnosed chronic kidney disease were included during the one-year period from May 2015 to April 2016. The clinical and biochemical parameters related to gonadal dysfunction were evaluated in these cases.
Results: Out of the 28 male CKD patients, 19 (68%) patients had Serum Testosterone values less than 90 ng/dl, 18 (64%) patients had a serum leutinizing hormone (LH) level greater than 9 mIU/ml and 19 (68%) patients had a serum follicle stimulating hormone (FSH) level greater than 13 mIU/ml. Out of 22 female CKD patients, 14 (64%) patients had serum estradiol value less than 50 pg/ml, 12 (54%) patients had Serum LH level greater than 80 mIU/ml and 20 (91%) patients had a S. FSH level greater than 26 mIU/ml. Out of a total of 50 patients in this study, 34 patients showed evidence of gonadal dysfunction, the majority of them belonging to stage 5 CKD.
Conclusions: Out of the 34 patients showing gonadal dysfunction, 5 (15%) patients were in stage 3 CKD, 11 (32%) patient were in stage 4 CKD and 18 (53%) were in stage 5 CKD. It may be proposed that gonadal dysfunction is very common in CKD patients and the frequency of sexual dysfunction increases as the renal function deteriorates.

Keywords: Chronic kidney disease, Gonadal dysfunction, Renal function, Uremic hypogonadism

INTRODUCTION

Chronic kidney disease (CKD) or End stage renal disease (ESRD) commonly affects the endocrine system, encompassing a wide variety of syndromes and clinical disorders. The kidney is a potent endocrine organ, a key modulator of endocrine function and an important target for hormonal action. As a direct consequence, the uremic state is associated with abnormalities in the synthesis or action of many hormones, including the hypothalamic-pituitary-gonadal (HPG) axis; hypergonadotropic hypogonadism being a well described hormonal derangement associated with CKD, which has also been termed as uremic hypogonadism.[1-4]

Diagnosis of hypogonadism is usually based on at least two consecutive serum testosterone assessments with confirmation of clinical symptoms.[5] To avoid circadian variation, guidelines advocate taking the blood samples in fasting conditions, usually early in the morning from 7.00

to 9.00 am.[6] The occurrence of testosterone deficiency is estimated to vary from 6% to 9.5% in males of ages between 40 to 75 years, rising to a 15% to 30% prevalence in diabetic or obese men.[7,8] In CKD patients, this prevalence is much higher, with rates of testosterone deficiency and insufficiency found to be approximately 66% and 24% respectively.[9] Endogenous testosterone concentrations may also vary according to the modality of renal replacement therapy as HPG axis dysfunction rarely improves with the initiation of hemodialysis (HD) or peritoneal dialysis (PD), but rather worsens.[3,10-12] Successful kidney transplantation is the most effective therapy for restoring normal sexual function, especially in younger patients.[13,14] Although testosterone levels usually improve within 6-12 months after kidney transplantation, approximately 25% of male renal transplant recipients have sustained hypogonadism 1-2 years after transplantation.[10,11,14,15] This gonadal dysfunction plays an important role in the development of sexual dysfunction, ultimately leading to infertility.

Sexual dysfunction begins much before reaching Stage 5 CKD, and usually does not reverse fully with renal replacement therapy.[16,17] Although there is limited literature on sexual problems (other than fertility related) in CKD patients, it is known that male sexual dysfunction in CKD includes decreased libido, erectile dysfunction, premature or delayed ejaculation, and difficulty in achieving orgasm; while female CKD patients have decreased libido, difficulty in achieving orgasm, lack of vaginal lubrication, pain during intercourse, and infertility. The gonadal dysfunction worsens with progression of CKD as up to 40% of male patients and 55% of female patients on hemodialysis have difficulty in achieving orgasm.[16] 33% patients report no sexual activity and 44% report only up to one sexual activity per week. Menstrual irregularities in CKD patients include amenorrhea (most common), premature menopause, oligomenorrhea, polymenorrhea and menorrhagia. Pregnancy is extremely uncommon as one progresses from CKD Stage 3 to 5.[18] Frequency of conception among females of childbearing age undergoing renal replacement therapy ranges from 0.3 to 1.5% per year.

With increasing life expectancy and prevalence of life style diseases, the US has seen a 30% increase in the prevalence of chronic kidney disease (CKD) in the last decade.[19] Unfortunately, from India there are no longitudinal studies and limited data exists on the prevalence of CKD. In western countries, diabetes and hypertension account for over 2/3rd of the cases of CKD whereas in India, diabetes and hypertension today account for 40–60% cases.[20,21] With the rising prevalence of these diseases in India, prevalence of CKD is only expected to rise, and this obviously becomes the key target population to address for the future.

About 10% of the population worldwide is presently affected by CKD, and millions die each year due to lack of accessibility of affordable treatment. Over 2 million people worldwide currently receive treatment with dialysis or kidney transplants to stay alive, yet this number may only represent 10% of people who actually need treatment for survival.[22] In the year 2005, there were approximately 58 million deaths worldwide, with 35 million attributed to chronic disease, according to the World Health Organization (WHO).[23]

In India, the age-adjusted incidence rate of ESRD recently in India has been estimated to be about 229 per million population, and more than 100,000 new patients enter renal replacement programs annually.[18] On the other hand, because of scarce resources and the lack of community based screening programs, only 10% of the Indian ESRD patients receive any renal replacement therapy at all.[24,25] It is possible that early detection of kidney disease through screening programs might have an impact on this problem through earlier intervention. The Screening and Early Evaluation of kidney disease project (SEEK) was designed and performed to generate data to determine the prevalence and risk factors for CKD in India, and according to its results the prevalence of CKD was observed to be 17.2% with over 6% patients having CKD stage 3 or worse with risk factors similar to those reported in earlier studies.[26] Early diagnosis and treatment is necessary in cases of CKD, as it can slow down and even halt the progression of disease. Thus with the background of these facts and figures, the objective of this cross sectional study was to evaluate gonadal dysfunction in patients of CKD, as well as to ascertain its relationship with the severity and progression of the disease.

METHODS

This was a cross-sectional observational study and patients were selected from the Ward and outpatient department of General medicine as well as the Endocrinology clinic at Calcutta National Medical College and Hospital, according to inclusion and exclusion criteria after obtaining proper consent. Both male and female patients already diagnosed with CKD during the period from May 2015 to April 2016 were included via simple random sampling, and those excluded were psychiatric patients as well as patients unwilling to participate in the study. Detailed history with relevant points was taken from patients or their relatives, and a thorough clinical examination including general survey and systemic examination was done. The necessary ethical clearance was taken from the Institutional ethics committee, Calcutta National Medical College and Hospital.

Biochemical and hormonal investigations included hemoglobin levels, leucocyte count, differential count, platelet count and peripheral smear examination, along with markers such as total bilirubin, serum transaminases, alkaline phosphate, albumin, globulin, serum sodium, potassium, calcium and phosphate, blood urea and serum creatinine. The immunological profile comprised of Follicle stimulating hormone (FSH) and Luteinizing hormone (LH) levels, along with serum levels of

testosterone, estrogen and prolactin. Ultrasonography of the whole abdomen (USG W/A) with Kidney ureter and bladder ultrasonography (USG KUB) was done for detecting gonadal and renal abnormalities.

Statistical analysis

The recorded data was analyzed by Statistical package for social sciences (SPSS) version 16.0 IBM and a Chi-square Test was applied for Non–parametric data comparison. A p value less than or equal to 0.05 was considered as statically significant.

The distribution of serum testosterone and serum estradiol, serum LH, serum FSH and serum prolactin levels among patients with CKD have been summarized below in Tables 1-4 respectively. The distribution of CKD patients who were on hemodialysis at the time of this study has been given in Table 5.

RESULTS

Table 1 shows that out of 28 male CKD patients, 19 (68%) patients had a serum testosterone value less than 90 ng/dl, 5 (18%) patients had a value between 90-300 ng/dl and 4 (14%) patients had a value greater than 300 ng/dl. Out of 22 female CKD patients, 14 (68%) patient had a serum estradiol value less than 50 pg/ml and 8 (32%) patients had a value between than 50-350 pg/ml.

Table 1: Distribution of serum testosterone and serum estradiol levels in CKD patients.

	Serum testosterone (300-1200 ng/dl)			Serum estradiol (50-350 pg/ml)	
Range	**<90**	**90-300**	**>300**	**<50**	**50-350**
Number of patients	19	5	4	14	8
Percentage (%)	68	18	14	64	36

Table 2: Distribution of serum LH levels in CKD patients.

	Serum LH in males (1-9 mIU/ml)		Serum LH in females (20-80 mIU/ml)	
Range	**1-9**	**>9**	**20-80**	**>80**
Number of Patients	10	18	10	12
Percentage (%)	36	64	46	54

As depicted above in Table 2 and Table 3, out of 28 male CKD patients, 18 (64%) patients had a serum LH level greater than 9 mIU/ml while 10 (36%) patients had a value between 1-9 mIU/ml. Out of 22 female CKD patients, 12(54%) patients had serum LH level greater than 80 mIU/ml and 10 (46%) patients had a value between 20-80 mIU/ml. High levels of serum LH were seen in 18 out of 28 Male CKD patients and in 12 out of a total of 22 Female CKD patients.

Table 3: Distribution of serum FSH levels in CKD patients.

	Serum FSH in males (1-13 mIU/ml)		Serum FSH in females (3-26 mIU/ml)	
Range	**1-13**	**>13**	**3-26**	**>26**
Number of Patients	9	19	2	20
Percentage (%)	32	68	9	91

Table 4: Distribution of serum prolactin levels in CKD patients.

	Serum prolactin in males (4-23 mIU/ml)		Serum prolactin in females (4-30 mIU/ml)	
Range	**4-23**	**>23**	**4-30**	**>30**
Number of Patients	3	25	3	19
Percentage (%)	11	89	14	86

Table 5: Distribution of patients on hemodialysis in relation to sex.

Sex	Number of patients undergoing hemodialysis	
	Yes	**No**
Male (n=28)	16 (57%)	12 (43%)
Female (n=22)	18 (82%)	4 (18%)

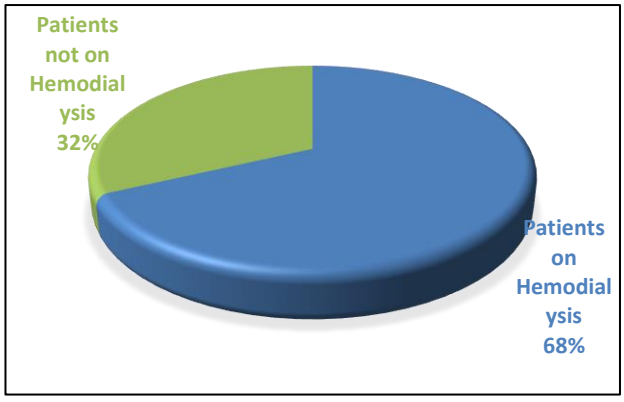

Figure 1: Distribution of patients on hemodialysis.

Out of 28 male CKD patients, 19 (68%) patients had a serum FSH level greater than 13 mIU/ml and 9 (32%) patients had serum FSH level between 1-13 mIU/ml.

Table 6: Comparison of age and levels of gonadal hormones during stage 3/stage 4 with stage 5 CKD.

Criteria	Stage 3 and 4 CKD	Stage 5 CKD /ESRD	P value
Age, mean ± SD (years)	40.37±9.46	63.34±12.67	0.02
Serum Testosterone (ng/dl) (Males)	94.45±44.23	72.86±13.90	<0.001
Serum Estradiol (pg/ml) (Females)	75.77±43.28	34.57±5.58	0.04
Serum LH (mIU/ml) (Males)	7.56±1.42	17.16±3.57	0.01
Serum LH (mIU/ml) (Females)	56.33±15.55	116.78±5.32	0.002
Serum FSH (mIU/ml) (Males)	15.87±6.65	26.45±8.62	0.04
Serum FSH (mIU/ml) (Females)	28.86±7.72	38.80±8.86	0.013
Serum Prolactin (ng/ml) (Males)	25.15±10.22	25.65±12.33	0.08222
Serum Prolactin (ng/ml) (Females)	34.16±11.56	34.31±13.50	0.28

Out of 22 female CKD patients, 20 (91%) patients had a serum FSH level greater than 26 mIU/ml and 2 (9%) patients had a serum FSH level between 3-26 mIU/ml. The high levels of serum FSH were found to be in 19 (68%) male CKD patients, and in 20 (91%) female CKD patients.

Table 7: Distribution of CKD patients having gonadal dysfunction according to stages of CKD.

Number of patients with CKD according to Stage of Disease	Number of patients having gonadal dysfunction		P value
	Yes	**No**	
Stage 3 (n=13)	5	8	
Stage 4 (n=17)	11	6	
Stage 5/ ESRD (n=20)	18	2	0.02

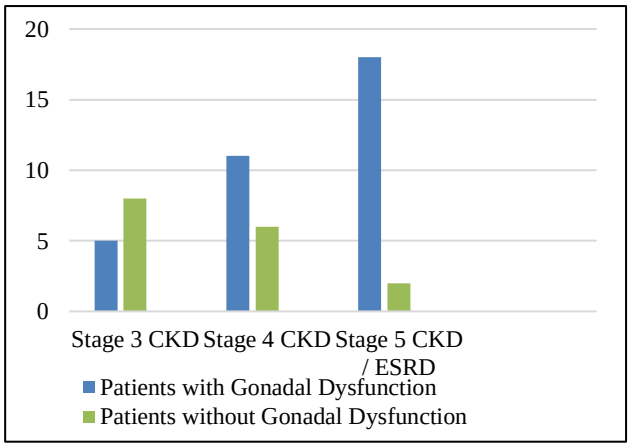

Figure 2: Distribution of CKD patients having gonadal dysfunction according to stages of CKD.

As shown in Table 4, 25 (89%) out of 28 male CKD patients had a serum prolactin level greater than 23 ng/ml, while 3 (11%) patients had serum prolactin levels between 4-23 ng/ml. Out of 22 female CKD patients, 19 (86%) patients had serum prolactin levels greater than 30 ng/ml, while 3 (14%) patients had serum prolactin levels between 4-30 ng/ml. The high levels of serum prolactin among CKD patients were found to be in 25 (89%) males and 19 (86%) females. As depicted in Table 5, 16 (57%) among 28 male CKD patients and 18 (82%) among 22 female CKD patients were on treatment by hemodialysis.

Table 6 summarizes the comparison of patient parameters such as age and levels of gonadal hormones between patients of stage 3/4 and stage 5 CKD, and Table 7 depicts the association of gonadal dysfunction with increasing disease severity in patients with CKD.

DISCUSSION

The present study was carried out in 50 cases of CKD to observe the prevalence of gonadal dysfunction in CKD as well as to study the association of gonadal dysfunction with increasing disease severity. All the cases fulfilled the inclusion and exclusion criteria of the study as per the methodology.

The mean age of patients in the study was 52.27±14.56 years. Of a total of 50 patients, 12 (24%) belonged to 51-60 age group, 10 (20%) belonged to 41-50 age group, 9 (18%) in the 71-80 age group, 8 (16%) in the 61-70 age group and the rest 11 (22%) patients in the 21-40 years age group. 28 patients (56%) were male and 22 patients (44%) were female.

Out of 28 male CKD patients, 19 (68%) patients had a serum testosterone value less than 90 ng/dl, 5 (18%) patients had a value between 90-300 ng/dl and 4 (14%) patients had a value greater than 300 ng/dl. This signified that 24 out of a total of 28 male CKD patients had a lower Serum Testosterone level than normal, showing a statistically significant association with a p<0.001. These findings were in accordance with a study done in 2008 by Carreo et al in 11,607 patients of age group 40-79 years, which showed that 50- 70% of CKD patients with ESRD had severe gonadal dysfunction with low testosterone levels.27

Out of 22 female CKD patients, 14 (68%) patient had a serum estradiol value less than 50 pg/ml and 8 (32%) patients had a value between than 50-350 pg/ml. In our study, levels of serum estradiol were lower in stage 5 CKD

patients as compared to those in Stages 3 and 4. The distribution was seen to be significant with a p value of 0.04. In 1982, Zingraff et al performed a similar study with 28 female CKD patients, in which 6 patients had regular cycles, 6 had irregular cycles, 7 had amenorrhea and 9 patients were in the post-menopausal group. All 22 patients had low serum estradiol levels.[28] Another study done by Eckersten et al in 144 patients belonging to the age group 19-44 years, showed low levels of serum estradiol in patients with ESRD.[29]

Out of 28 male CKD patients, 18 (64%) patients had a serum LH level greater than 9 mIU/ml while 10 (36%) patients had a value between 1-9 mIU/ml. Out of 22 female CKD patients, 12(54%) patients had serum LH level greater than 80 mIU/ml and 10 (46%) patients had a value between 20-80 mIU/ml. High levels of serum LH were seen in 18 out of 28 male CKD patients and in 12 out of a total of 22 female CKD patients. The distribution was found to be significant with a p value of 0.01 (males) and 0.002 (females).

In a similar study done by Zingraff et al in 1982, 28 female CKD patients were evaluated for gonadal dysfunction. 5 patients among the 19 premenopausal females and all 9 post-menopausal women were found to have increased serum LH levels.[28] Another study done by Veldhuis et al in 1993 showed that 50% among a total of 24 CKD patients had raised serum LH levels.[30] Similar findings were found by Swamy et al who found that 6 premenopausal and 7 postmenopausal patients among 13 women had increased serum LH levels.[31] In 1988, Rudolf et al showed increased serum LH levels in their study among 11 CKD patients.[32]

Out of 28 male CKD patients, 19 (68%) patients had a serum FSH level greater than 13 mIU/ml and 9(32%) patients had serum FSH level between 1-13 mIU/ml. Out of 22 female CKD patients, 20 (91%) patients had a serum FSH level greater than 26 mIU/ml and 2 (9%) patients had a serum FSH level between 3-26 mIU/ml. The high levels of serum FSH were found to be in 19(68%) male CKD patients, and in 20 (91%) female CKD patients. The distribution was found to be significant with a p value of 0.04 (males) and 0.013 (females).

In this study, levels of serum FSH and Serum LH progressively increase with the progression of CKD, which shows a significant association between the two. This was in accordance with a study done by Eckersten et al showing an increase in FSH and LH levels in Stage 5 CKD patients.[30] Similar findings were observed by Zingraff et al, Swamy et al and Rudolf et al.[28-31]

Out of 28 male CKD patients, 25 (89%) patients had a serum prolactin level greater than 23 ng/ml, while 3 (11%) patients had serum prolactin levels between 4-23 ng/ml. Out of 22 female CKD patients, 19 (86%) patients had serum prolactin levels greater than 30 ng/ml, while 3 (14%) patients had serum prolactin levels between 4-30 ng/ml. The high levels of serum prolactin among CKD patients were found to be in 25 (89%) males and 19 (86%) females, which suggests that the distribution was not significant with a p value of 0.0822 (males) and 0.28 (females).

These results were found to be similar to those observed by Peces et al in 1979 in which 12 CKD patients had increased serum prolactin levels above their base line33 as well as in a study done by Eckersten et al who showed a higher mean value of prolactin in stage 5 CKD patients.[29]

16 (57%) among 28 male CKD patients and 18(82%) among 22 female CKD patients were on treatment by hemodialysis. According to a similar study conducted in 1975 by Abram et al in 32 male CKD patients aged between 21- 60 years, 45% had reduced gonadal function before starting treatment with dialysis, 30% had reduced gonadal function after dialysis, and the rest 25% had normal gonadal function. Those patients having reduced gonadal function had serum LH and FSH levels greater than normal, along with decreased libido.[26]

In this study, out of a total of 50 CKD patients, 34 patients showed evidence of gonadal dysfunction. The number of patients having gonadal dysfunction increased with the progressing stages of CKD i.e. 5 patients in stage 3 CKD, 11 in stage 4 CKD and 18 in stage 5 CKD/ESRD, which shows a statistically significant association with a p value of 0.02. Similar studies were done by Peces et al in 1979 involving 12 CKD patients, and by Holly et al in 1997 in 76 female CKD patients showing majority of CKD stage 5 patients with menstrual irregularities due to hypogonadism.[33,34]

CKD patients have significant changes in normal gonadal function. In view of this present study among 50 subjects, we found decreased levels of parameters such as serum testosterone and serum estradiol along with increased levels of serum LH, Serum FSH and serum prolactin in CKD patients, which suggests that these abnormal hormonal levels might be substantially influenced by the progression of CKD.

There were some limitations in this study, such as the lack of a proper sexual history given by patients and a small sample size. Since this was a cross sectional hospital based study, further studies are still needed to study gonadal dysfunction in these patients.

CONCLUSION

Out of the 34 patients showing gonadal dysfunction, 5 (15%) patients were in stage 3 CKD, 11 (32%) patient were in stage 4 CKD and 18 (53%) were in stage 5 CKD. Thus it may be proposed that gonadal dysfunction is very common in CKD patients and the frequency of sexual dysfunction increases as the renal function deteriorates. Patients with CKD should have routine screening of hematological, biochemical and hormonal profile assays, and simultaneously early and adequate management of this

metabolic disease should be provided based on proper guidelines. As gonadal dysfunction is common in both male and female CKD patients and the frequency of sexual dysfunction increases as the renal function deteriorates, it also becomes essential to provide necessary psychological support and counseling in addition to primary disease management for these cases.

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