Original Article

SEX HORMONES AND ERECTILE DYSFUNCTION IN HEMODIALYSIS PATIENTS

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ABSTRACT

Objective: To determine the prevalence of Erectile Dysfunction (ED) in hemodialysis patients (HD) and to study the associated changes in sex hormones in these patients.

Methodology: This is a hospital based cross sectional study conducted at hemodialysis units of Shalamar and Mayo Hospitals, Lahore from January to March 2008. All male patients with ESRD on maintenance (HD), whose spouses were alive and able to perform intercourse, were included in the study. Patients with cognitive and communication deficits were excluded from study. International index of erectile function-5(IIEF-5), adopted in Urdu was used for determination of prevalence of ED. Demographic data was collected and sex hormones {total testosterone, Dihydroepiandrosteronediones (DHEA), Follicle Stimulating Hormone (FSH), Leutinizing Hormone (LH) and serum Prolactin} were measured.

Results: A total number of fifty patients were included in the study. The major cause of ESRD was diabetes mellitus 28 (56%). The prevalence of ED was 86% with a mean IIEF-5 score 10.36 + 7.13. The majority of patients, 33 (66%), were suffering from a severe degree of ED. The total testosterone level was low in 30 (60%) patients and DHEA were low normal in most of patients, 46 (92%). Compared to patients with non-ED, those with ED had a significantly lower DHEA (1.93 ± 0.73 vs 0.81 ± 0.11, p value = 0.007). Total testosterone and DHEA had a negative correlation with age and diabetes mellitus. FSH showed a variable response in these patients, it was low (< 1.55 mIU/ml) in three, normal (1.55 + 9.74 mIU/ml) in 39 and high (> 9.74 mIU/ml) in eight patients. LH was low (< 1.2 mIU/ml) in two, normal (1.2 + 7.8 mIU/ml) in thirty three and high (> 7.8 mIU/ml) in fifteen patients. FSH and LH showed a positive correlation with duration of dialysis. Prolactin level was low in 21(42%) patients. Total testosterone, FSH, LH and Prolactin had no association with ED.

Conclusion: The majority of the patients suffering from ESRD, on maintenance HD had ED. DHEA was significantly lower in patients with ED, compared to those with no-ED. Total testosterone and DHEA had an inverse relationship with diabetes and age of the patients. Total testosterone, FSH, LH and prolactin did not affect erectile function.

KEY WORDS: Haemodialysis, erectile dysfunction, DHEA.FSH, LH, Prolactin, IIEF-5.

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INTRODUCTION

Disturbed sexual function is reported to be present in about 50-80% patients with End Stage Renal Disease (ESRD).[1,2] Amongst all sexual dysfunctions, ED is the most common in male dialysis patients. ED is defined as the inability

to attain and maintain an erection sufficient for satisfactory sexual performance and is associated with changes in quality of life.[3] ED is known as an important risk factor for cardiovascular disease.[4] Nitric Oxide (NO) plays a key role in penile erection by initiating smooth muscle relaxation after sexual stimulation. ED is caused by neurological, vascular, endocrinological, psychological abnormalities, aging and certain medications. Disturbances in hypothalamic pituitary gonadal axis of men with renal disease has been seen with only moderate reduction in glomerular filtration rate (GFR) and this progressively worsens as the renal failure progresses.[5]

Common hormonal changes in sexual dysfunction in chronic kidney disease (CKD) are low serum concentration of total and free testosterone, hyperprolactenemia, hyperoestrogenemia and elevated serum LH level. Patients on HD show further deterioration in level of plasma testosterone. Hyperparathyroidism play an important role in the genesis of hypotestosteronemia. In Pakistan, due to paucity of indigenous data, the frequency of ED in dialysis patients is not known. This cross-sectional study was conducted to determine the prevalence of ED and to study the associated changes in sex hormones in our patients on HD.

METHODOLOGY

This study was conducted at the haemodialysis units of Shalimar Hospital and Mayo Hospital, Lahore. All male ESRD patients on regular HD from Jan 2008 to April 2008, who had alive spouses and able to perform intercourse were included in the study. Patients with acute renal failure and with cognitive/communication deficits were excluded. All patients were informed and consent about the study was taken. Each subject completed a self-administered five-items validated questionnaire,[6] the IIEF-5, adapted in Urdu,[7] which is an abridged version of the 15-items International Index of Erectile Function,[8] which is commonly known as the Sexual Health Inventory for Men (SHIM).

The five items included in the abbreviated IIEF-5 address the National Institutes of Health's definition of ED, discriminate well between men with and without ED, and reflect the severity of ED. On the basis of IIEF-5, categorization of ED was done into mild (IIEF-5; 16-21), moderate (IIEF-5; 11-15) and severe (IIEF5;<11). Demographic data was collected on a performa and blood samples of these patients were drawn to measure endocrine parameters {total testosterone, Dihydroepiandrosteronediones (DHEA), Follicle Stimulating Hormone (FSH), Leutinizing Hormone (LH) and serum Prolactin}.

Statistical Analysis: Descriptive analysis was performed, categorical variables were presented as percentage(%), and continuous variables as mean + SE. The values of sex hormones were compared between patients with-ED and with-no ED, Students's T-test was used to compare the difference in means of the continuous variables. Pearson correlation coefficient were determined to study the association between covariates. A p-value of < 0.05 was considered as statistically significant. Multivariate analaysis was done using Logistic Regression to assess the significant hormones which affect ED in HD patients.

RESULTS

The total numbers of the patients in the study were 50. The mean duration on dialysis was 16+ 14.49 months. The main causes of ESRD were diabetes mellitus 28 (56%) and hypertension 14 (28%) Table-I. The prevalence of ED was 86%, mean IIEF-5 score was 10.36 ± 7.13. Most of the patients, 33 (66%) were in severe category of ED, while 10 patients (19.6%) were in mild to moderate degree of ED while 14% had normal ED. Total testosterone, DHEA, FSH, LH & Prolectin levels were 238 + 19.63 ng/ml, 0.971 + 1.04 µg/ml, 8.1 + 1.61 mIU/ml, 8.9 + 1.78 mIU/ml, 968.9 + 1554 mIU/ml respectively. The total testosterone was low (< 260 ng/ml) in majority 30 (60%) of the patients. DHEA was low normal in most 46 (92%) of the patients. Compared to patients with NON-ED, those with ED had a significantly lower DHEA (p value=0.007) in univariate analysis.

Table-I: Etiology of end stage renal disease

1.	Diabetes Mellitus	56%
2.	Hypertension	24%
3.	Nephrolithiasis	8%
4.	Ch GN	8%
5.	ADPKD	4%

In Logistic Regression Model, DHEA is a significant predictor (p=0.008) of ED and HD patients as shown in Table-II. Age and diabetes mellitus had an inverse correlation with serum total testosterone and DHEA. FSH showed a variable response in these patients, it was normal (1.55- 9.74mIU/ml) in 39, low (< 1.55) in three, and high (> 9.74) in eight patients. LH also showed a variable response, it was normal (1.2-7.8 mIU/ml) in thirty three, low (< 1.2 mIU/ml) in two, and high (> 7.8mIU/ml) in fifteen patients. FSH and LH had a negative association with duration of dialysis. Prolactin was low and normal (< 380mIU/L) in most 29 (58%) of the patients and rest of the patients 21(42%) were having high level (> 380mIU/ml). Among patients with high prolactin levels, 93% had ED. Table-III shows comparison of sex hormone levels among patients with and without ED.

DISCUSSION

Erectile dysfunction, decreased libido, low frequency of intercourse, oligo- and azoospermia and gynaecomastia are common problems among male uremic patients. Endocrine abnormalities are common feature of Chronic Kidney Disease (CKD) and are not reversed by dialysis. Patients with ESRD suffer from a wide variety of hormonal abnormalities which may contribute to sexual dysfunction and infertility. Over 50 percent of uremic men complain of sexual dysfunction.[9,10] In this study there was a very high prevalence (84.3%) of ED in HD patients. A similar high prevalence of ED has been reported from Iran (87.5%),[11] Turkey (82.9%)[12], Egypt (82.5%)[13] and Brazil (86.4%).[14] In this study diabetes mellitus was a major (28.56%) cause of ESRD and was directly related with ED. In our study diabetic patients had low serum total testosterone. A similar finding were observed by another study.[15] According to Rhoden et al, diabetic male patients have low levels of testosterone than general population, and uncontrolled diabetes is associated with impaired reproductive capacity.[16]

Testosterone is a steroid hormone, directly involved in erectile physiology, increases libido, male fertility and growth of spermatogenic tissue in testies. In this study, it was low in majority 30 (60%) of the patients which leads to decreased interest in sexual drive. The total testosterone was not significantly different in patients with ED compared to those with Non-ED in our study (p value=0.169). This result of our study does not compare with another study by Kapoor et al.[17] The reason for this difference could be due to the fact that we measured total teststerone level in our study rather than free testosterone which is more specific. In our study 93% of the patients with low testosterone had impaired erectile function and testerone level had an inverse relationship with age (p value=0.043). As age advances total testosterone level decreases which affects the erectile function. As majority of dialysis patients in our

Table-II: Logistic regression model N=50

Sr#.	*Hormone*	*ß*	*S.E*	*Significance*	*Exp (ß)*
1.	Total Testosterone	0.003	0.003	0.421	1.003
2.	DHEA	0.861	0.397	0.030*	2.365
3.	FSH	0.03	0.059	0.596	1.031
4.	LH	0.032	0.052	0.533	1.033
5.	Prolactine	0.000	0.001	0.536	1.000
6.	Constant	- 4.075	1.326	0.002	0.017

* Statistically significant value

Table-III: Comparison of sex hormones among ESRD patients with and without ED

Hormone	*No ED*	*ED*	*P-Value*
Total Teststerone(ng/ml)	305.71 ± 59.82	227± 20.47	0.16
DHEA(mg/ml)	1.93 ± 0.73	0.813 ± 0.115	0.007*
FSH(mIU/ml)	13.35 ± 9.38	7.24±	0.19
LH(mIU/ml)	15.25 ± 9.71	7.91 ± 1.39	0.15
Prolactin(mIU/ml)	822.50 ± 424.03	992.84 ± 247.53	0.79

* Statistically significant value

study were diabetic this could have been the reason for the low level of testosterone in these patients. A similar observation was reported by Dhindas et al.[18] According to them diabetic men have lower level of testosterone than non diabetic men.

In this study total testosterone had an inverse correlation with serum urea level (p value = 0.04). This result supports the fact that uremic milieu affects the endocrine function of the body. Low testosterone level can be explained by a local toxic effect of uremia on the testis. This raised urea level may be due to inadequate dialysis or increased protein intake. In a third world country like Pakistan, per capita income is less than 500 US Dollar/month. The cost of dialysis ranges from 350 to 400 US Dollar/ month, so they can not afford thrice weekly dialysis (twelve hours per week) and their urea level are raised which affects the hypothalamic-pituitary gonadal axis and decreases testosterone. Furthermore, low testosterone levels are unable to induce hypothalamic pituitary stimulation for the production of gonadotrophin which further aggravates the situation. Along with this, Leydig-Cell resistance seems to be responsible for the moderately decreased production of testosterone. Testicular damage in CKD leads to impaired spermatogenesis. The factors responsible for testicular damage in uremia are not well understood. It is possible that plasticizer in dialysis tubing, such as phthalate, may play a role in propagating the abnormalities once patients begin maintenance dialysis. Increased frequency of low testosterone level is observed by other studies.[19] According to this study 24% patients were having low testosterone.

DHEA is a natural steroid hormone precursor (prohormone) produced from cholesterol by the adrenal glands, the gonads and adipose tissue. In males DHEA has strong association with ED and inversely related with mortality. DHEA levels normally peak in a man's late 20s and early 30s, declining to nearly one third their youthful levels as men ages. In this study, patients with normal erectile function have DHEA of 1.93 ± 0.73 ug/ml as compared to level of 0.813 ± 0.115 ug/ml in patients with ED, which was statistically significant (p vale = 0.007). Among patients with low DHEA, 89% had ED. In this study, age and diabetes mellitus had a negative association with DHEA. As the age advances patients had a lower level of DHEA. A similar observation was made by Saima et al.[20] Reiter et al[21], did a double blind, randomized and placebo controlled study to see the effect of DHEA replacement on ED patients. He studied a group of forty male with ED aged 41-69 years over a 24-week period. The researchers found a statistically significant increase in all domains of IIEF-5 score in the DHEA group compared to control group, including improved erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction.

FSH is a hormone synthesized and secreted by gonadotropes in the anterior pituitary gland controlled by the pulses of Gonadotropin Releasing Hormone (GnRH). In this study, FSH was not significantly different between patients with ED and with NON-ED (p value=0.427), but it had a strong association with duration of dialysis (0.002). In this study, FSH showed variable response in dialysis patients and the mean level was 8.1+ 1.61ng/dl. It was low in 3 (6%),

normal in 39 (78%) and high in 8 (16%). A similar result was observed by MM Schleicher et al.[22]

LH is a hormone produced by anterior pituitary gland. It stimulates Leydig cells production of testosterone, an androgen that exerts both endocrine activity and intratesticular activity such as spermatogenensis. In this study, LH hormone was normal in most 33 (66%) of the patients and there was no significant difference between patients with-ED and with Non-ED (p value= 0.58). Even this normal LH level did not contribute to the elevation of testosterone. The lack of a more robust response of LH to low levels of circulating testosterone suggests a derangement in the central regulation of gonadotropin release. Infusion of GnRH increases LH levels to the same degree as in healthy subjects; however, the peak value and return to baseline may be delayed.[23] In this study, fifteen patients (30%) showed increased level of LH. Recent studies have shown evidence of a factor in the serum of renal failure patients capable of blocking LH receptors, thus providing an explanation for the sluggish response of Leydig cell to infusion of HCG.[24]

Prolactin is peptide hormone primarily associated with lactation. Elevated prolactin level is usually found in dialysis patients.[25] In this study although high prolactin level dose not have an association with ED but it was raised in 21(42%) patients. Among patients with high prolactin levels, 86% patients had ED. Its secretion in CKD patients is autonomous and resistant to stimulatory and suppressive maneuvers. Along with increased production decreased metabolic clearance plays an important role in hyperprolactenemia. Secondary hyperparathyroidism may lead to increased secretion of prolactin and hypotestosteronemia which causes (secondary) hypogonadism.[26] Giorgina B. Piccoli et al reported a case of prolactinoma in dialysis patients. In this patient prolactin level was very high (76.1ug/l, 129 ng/ml). This patient was treated with cabergoline and sexual potency was restored. Normalization of hormonal patterns followed within 2 months. Deficiency of total body zinc plays an etiologic role in uremic hyperprolactenemia.[27]

Limitations of the study: This study has certain limitations: We have not studied serum parathyroid hormone in our patients but there is a need to establish the role of this hormone in sexual behaviour of ESRD patients. Secondly, we did not separately measure the level of depression which is directly related with ED. Thirdly, we have not measured lipid profile (fasting) in these patients which is an important risk factor for ED because it was difficult for the dialysis patients to keep fasting for 12 hours. Finally, we did not use any test which could measure and highlight the direct effect of nitric oxide on ED.

We conclude that majority of the patients suffering from ESRD, on maintenance HD had ED. DHEA was significantly lower in patients with ED, compared to those with Non-ED. Total testosterone and DHEA had an inverse relationship with diabetes and age of the patients. Total testosterone, FSH, LH and Prolactin did not affect erectile function.

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