Australian Journal of Basic and Applied Sciences, 2(3): 481-487, 2008
ISSN 1991-8178

Gonadal Dysfunction in Chronic Renal Failure

[1]Nihal M. El-Assaly, [1]Naema I. El-Ashry, [2]Emam Waked and [3]Mervat El-Damarawy

[1]Departments of Clinical Chemistry, Theodor Bilharz Research Institute., Gizza, Egypt.
[2]Nephrology, Theodor Bilharz Research Institute., Gizza, Egypt.
[3]Intensive care, Theodor Bilharz Research Institute., Gizza, Egypt.

Abstract: To find early and safe parameters for detecting the pituitary-gonadal axis disturbances in chronic kidney disease (CKD) men, possible tools for their correction, restoring the gonadal function in those patients before irreversible pathology, prevention of their progression and protecting those patients as much as we can from psychological and physical stresses which are commonly present in CKD. Material and methods: The study was conducted on 60 male subjects classified into two groups: group A 40 uremic patient and group B 20 normal controls. The 40 uremic patients were on maintenance hemodialysis were included in our study. The patients had their hemodialysis sessions thrice weekly, 4 hours each, using calcium dialysate Blood samples were collected predialysis, liver enzymes, serum total alkaline phosphatase, serum creatinine and blood urea, serum calcium ,phosphorus, serum intact parathormone (iPTH) by ELISA, serum Prolactin (PRL), serum Folicular stimulating hormone (FSH), serum Lutenising hormone (LH), serum testosterone, serum progesterone and serum Estradiol (E2) all sex hormones were done by Electrochemiluminescence immunoassay "ECLIA. Results: our results showed elevation of serum iPTH, PRL, LH, PRO and E2 and lower serum levels of testosterone. With a positive correlation between both iPTH and PRL, iPTH and LH, negative correlation between testosterone levels and PRL and LH. Serum FSH levels were elevated but of no significance denoting a reversible affection of seminiferous tubules. Conclusion: treatment strategies include optimizing dose of dialysis, correction of hyperparathyroidism, reduction in plasma prolactin levels, correction of anaemia, trial psychotherapy is warranted, antidepressant, may be helpful to those patients as long as their plasma FSH levels are within normal or slightly high than normal as this indicate a still functioning seminiferous tubules and reversible condition. Finally successful kidney transplantation may restore normal sexual function, especially in younger patients.

Key words: Chronic renal failure, sex hormones, hypothalamic- gonadal axis hormones, and sexual dysfunction in uremic men.

INTRODUCTION

Disturbances in sexual function are a common feature of chronic renal failure. Approximately 50% of uremic men complain of erectile dysfunction while an even greater percentage of both men and women complain of decreased libido and a marked decline in the frequency of intercourse Procci WR *et al* (1981). The genesis of sexual dysfunction is multifactorial and is primarily organic in origin. In addition to the uremic milieu, peripheral neuropathy, autonomic insufficiency, peripheral vascular disease, and pharmacologic therapy all play an important role in the genesis of this problem. In addition, psychological and physical stresses are also commonly present in those patients Toorians AW *et al* (1997).

In men with chronic renal failure, disturbances in the pituitary-gonadal axis can be detected with only moderate reductions in the glomerularfiltration rate (GFR) and progressively worsen as the renal failure progresses. Chronic renal failure is associated with impaired spermatogenesis and testicular damage, often leading to infertility. These disorders rarely normalize with initiation of hemodialysis or peritoneal dialysis and, in fact, often progress. By comparison, a well-functioning renal transplant is much more likely to restore normal sexual activity, although some features of reproductive function may remain impaired Holdsworth SR *et al,* (1978).

Corresponding Author: Dr. Nihal M. El Assaly, Clinical Chemistry Department, Theodor Bilharz Research Institute, El Warak, Embaba, Gizza, Egypt.
Email: nihal_assaly@yahoo.com. Tel. +20235401019

A number of observations suggest that gonadal failure is an important consequence of chronic renal failure. The finding that LH levels are typically increased is consistent with the presence of testicular damage. However, the lack of Leydig cell hypertrophy and normal estradiol levels also raise the possibility of functional hypogonadism. The finding that LH levels are only modestly increased in chronic renal failure suggests a diminished response of the hypothalamic-pituitary axis to lowered testosterone levels and impaired regulation of gonadotropin secretion. One explanation for the blunted rise in LH in response to low levels of testosterone is that the hypothalamic-pituitary axis in chronic renal failure is reset in such a way that it is more sensitive to the negative feedback inhibition of testosterone. In this manner, the axis begins to assume a similar characteristic as seen in the pre-pubertal state where there is extreme sensitivity to the inhibitory effect of gonadal steroids Handelsman DJ (1985).

Compared with testosterone, the total plasma estrogen concentration is often elevated in advanced renal failure. However, the physiologically important estradiol levels are typically in the normal range. As with the lack of hypertrophy and hyperplasia of leydig cells, normal levels of estradiol suggest a functional gonadotropin deficiency or resistance in uremia because increased LH levels should enhance the testicular secretion of estradiol Karagiannis A, (2005).

Furthermore, decreased urinary LH excretion in uraemia causes elevated LH blood levels and LH subtypes. Less acidic and bioactive LH forms might thus contribute to the decrease in testosterone production Prem AR (1996). Follicle-stimulating hormone (FSH) secretion is also increased in men with chronic renal failure, although to a more variable degree such that the LH/FSH ratio is typically increased. FSH release by the pituitary normally responds to feedback inhibition by a peptide product of the Sertoli cells called inhibin. The plasma FSH concentration tends to be highest in those uremic patients with the most severe damage to seminiferous tubules and presumably the lowest levels of inhibin. It has been suggested that increased FSH levels may portend a poor prognosis for recovery of spermatogenic function after renal transplantation (Phocas I. 1995. and Palmer B.F. 1999).

Hyperprolactinaemia in renal insufficiency is partially induced by a decreased metabolic clearance but also by autonomic overproduction. At least primary hyperprolactinaemia leads to (secondary) hypogonadism. Co-morbidity, especially critical illness, might further contribute to disturbances of sexual hormone synthesis (Palmer BF 1999) Palmer BF. Increased prolactin secretion in chronic renal failure may be related in part to the development of secondary hyperparathyroidism. An infusion of parathyroid hormone (PTH) in healthy men enhances prolactin release, a response that can be suppressed by the administration of L-dopa Isaac R *et al* (1978) Furthermore, partial inhibition of PTH release by the administration of calcitriol led in one study to an elevation in plasma testosterone levels, a reduction in plasma gonadotropin concentrations, and improved sexual function Massry SG (1977). However, this benefit could not be confirmed in a controlled trial of calcitriol therapy Blumberg A (1980). Depletion of total body zinc stores may also play an etiologic role in uremic hyperprolactinemia Caticha O, *et al* (1996).

Secondary hyperparathyroidism is frequently encountered in patients with chronic renal failure due to several factors including phosphate retension, hypocalcemia and defective vitamin D metabolism. Brown EM (1991). In 2003 Chou et al had found that sexual function of male patients with symptomatic hyperparathyroidism can possibly be improved by parathyroidectomy and auto- transplantation. Decreases in the levels of prolactin, calcium, phosphorus, and iPTH are also noticed after parathyroidectomy. They also, did found that after parathyroidectomy, the sperm motility index and percentage of active motility can be improved. So they speculate that increases in fertilization and paternity in uremic male patients can be expected after surgery Chou FE (2003).

In 2007 Anantharaman *et al* stated that endocrine abnormalities are common in patients with chronic kidney disease (CKD) and lead to sexual dysfunction, hyperparathyroidism; alterations in the hypothalamic-pituitary axis are seen early in CKD and tend to worsen after patients start dialysis. Hypogonadism plays a dominant role in male sexual function. In patients on dialysis, treatment strategies include optimizing dose of dialysis, correction of hyperparathyroidism. Successful kidney transplantation may restore normal sexual function, especially in younger patients Anantharaman P *et al* (2007).

In 2002 Marja-Terttu *et al* concluded that renal transplantation corrects the hyperprolactinemia induced by uremia and is followed by rapid onset of restoration of the hypothalamic-pituitary-gonadal axis Marja-terttu Saha *et al* (2005).

Aim of the Work: To find early and safe parameters for detecting the pituitary-gonadal axis disturbances in CKD men, possible tools for their correction, restoring the gonadal function in those patients before irreversible pathology, prevention of their progression and protecting those patients as much as we can from psychological and physical stresses which are commonly present in CKD.

Statistical Analysis: Results were expressed as means ± standard deviation of the means (SD) or number (%). Differences between group A and group B was performed using unpaired student t test. Correlation between parameters was performed using Spearman's rank correlation coefficient. SPSS computer program (version 13 windows) was used for data analysis. P value less than 0.05 was considered significant; less than 0.01 was considered highly significant and less than 0.001 was considered very highly significant.

Subjects and Methods: The study was conducted on 60 male subjects classified into two groups: group A 40 uremic patient and group B 20 normal controls. The 40 uremic patients were (age range 24-60 years, mean 48.8 $\pm$ 9.4 years) on maintenance hemodialysis (duration on dialysis, range 36-72 months, mean 50 $\pm$ 2.2 months) were included in our study. The patients had their hemodialysis sessions thrice weekly, 4 hours each, using acetate dialysate (3.5 mmol/l) and 1.3 m^2 hollow fiber cuprophan membranes. One microgram of active vitamin D was given to every patient after each session. The underlying renal diseases were hypertensive nephrosclerosis (8 patients), diabetic nephropathy (12 patients), obstructive uropathy (6 patients), chronic glomerulonephritis (8 patients), drug nephropathy (3 patients) and unknown etiology (3 patients). Exclusion criteria were cancer, HIV and hepatitis infection.

All the patients were subjected to full clinical assessment, laboratory investigations: blood urea, serum creatinine, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum calcium, serum inorganic phosphorus, serum total alkaline phosphatase (AP), serum intact parathyroid hormone (iPTH), serum prolactin (PRL), serum folicular stimulating hormone (FSH), serum lutenising hormone (LH), serum estradiol (E2) , serum progesterone (Pro) and serum testosterone (T).

Sample Collection and Laboratory Techniques: Blood samples were collected predialysis, the time of collection was the early morning. Serum was separated and stored at-70 C^o and the following investigations and techniques were performed:

- Liver enzymes (serum ALT and AST) and serum total alkaline phosphatase by auto-analyser dimension.
- Kidney functions (Serum creatinine and blood urea), serum calcium and phosphorus by auto-analyser dimension.
- Serum intact parathormone (iPTH) by ELISA method for quantitative measurement of human intact parathyroid hormone (Biosource – Europe S.A) Hackens WHL (1986).
- Serum Prolactin (PRL)
- Serum Folicular stimulating hormone (FSH)
- Serum Lutenising hormone (LH)
- Serum Estradiol (E2)
- Serum Testosterone (T)
- Serum Progesterone (Pro)

All sex hormones had been done by Electro-chemiluminescence immunoassay "ECLIA" is intended for use on the Roche elecyses 2010 and Modular analytics E170, immunoassay analysers.

RESULTS AND DISCUSSION

Results: Clinical data in (table1). Standard laboratory data are summarized in (table 2). Studied parameters in normal and CKD patients in table 3. Fig 1 showing the relation between the mean value of the studied parameters in the CKD patients. Table 4 that showed the correlation between intact Parathormone (iPTH) and LH*, PRL, PRO, FSH, T and E2* where r were significantly positive with LH,PRL, PRO and E2; r= 0.180, 0.8288, 0.4030, and 0.1715 respictevely; and a negative correlation between (iPTH) and FSH and T were r = 0.5629 and 0.1351. Fig 2: showing the correlation of the studied parameters levels and the iPTH value. Also in all our patients results LH/FSH ratio were high.

Discussion: Chronic kidney disease and chronic renal failure causes major effects on the male reproductive system, notably impairment of spermatogenesis, steroidogenesis , hypogonadism and sexual function, as well as psychological disturbances through effects at all levels of the hypothalamic–pituitary–testicular axis. Disturbances of the axis can be detected with only moderate reductions in the glomerular filtration rate (GFR) and progressively worsen as the renal failure progresses Procci WR (1981).

The disorders of the pituitary–gonadal axis rarely normalize with initiation of hemodialysis or peritoneal dialysis and, in fact, often progress. Transplantation leading to restoration of normal renal function can reverse most of the hormonal changes of chronic renal failure, although some changes resulting from prolonged dialysis may be irreversible Hackens WHL (1986). That is why our aim is to restore the gonadal function in CRF patients before irreversible pathology.

In this study, a significant increase in serum iPTH level $P< 0.05$ compared to the reference group. Other authors, who found a significant inverse correlation between PTH and glomerular filteration rate (Brown EM 1991), reported similar results. Our results also show a high serum prolactin level were $P<0.005$ compared to the reference group with a highly positive correlation between iPTH level and PRL level, This results comes into agreement with many authors who concluded that elevated iPTH which occur in uremic patients could be the main cause of increased production of PRL, since the kidney plays little, if any, role in the catabolism of this hormone (Isaac R, *et al* 1978).

Table 1: Clinical data in of the study patients.

Variables	Patients results ---------- Mean + SD	P
Age (years)	47.86 ± 10.56	0.462
Duration on dialysis (months)	56.03 ± 44.44	0.702
Depression	15 (37.5%)	
Decreased libido	28 (70%)	
Reduced frequency of intercourse	32 (80%)	
Partial or total impotence	8 (20%)	
Reduced nocturnal penile tumescence	7 (17.5%)	
Decreased volume of ejaculate	40 (100%)	
Atrophic testes	0 (0%)	
Gynecomastia	6 (15%)	

Table 2: Results of the laboratory data of the study patients.

Variables	Control results ---------- Mean + SD	Patients results ---------- Mean + SD	P
Age (years)	32.7 ± 9.5	47.86 ± 10.56	0.462
Duration on dialysis (months)		56.03 ± 44.44	0.702
Serum calcium (mg%)	9.0 ± 0.65	5.851 ± 1.623	0.499
Serum phosphorus (mg%)	4.2 ± 0.6	3.883 ± 1.741	0.421
Blood urea (mg%)	42.3 ± 5.75	110.73 ± 47.0	0.158
Serum creatinine (mg%)	0.85 ±0.65	11.0919 ±3.132	0.024 *
Serum total alkaline phosphatase (U/l)	95.6± 21.34	230.65 ± 174.39	0.001 *
Serum ALT (U/ml)	19.5 ± 12.5.	25.38 ± 13.12	0.082
Serum AST (U/ml)	33.7 ± 18.5	43.58 ± 19.86	0.097
Serum PTH (pg/ml)	34.95±17.4	121.375±21.0	0.005*

*P $\leq$ 0.05 = Significant compared to the reference group

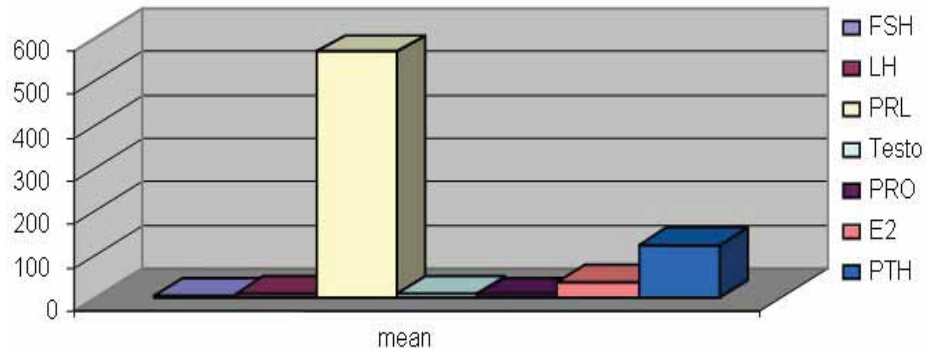

Fig. 1: Showing the relation between the mean values of the studied parameters of the CKD patients.

Table 3: Studied parameters in normal and CKD patients

	FSH (mIU/ml)	LH (mIU/ml)	PRL (mIU/ml)	Testoerone (ng/ml)	PRO (ng/ml)	E2-(pg/ml)	PTH (pg/ml)
Normal group	7.8±3.1	5.07±2.1	2.84±120	21.9±5.1	2.5±1.27	26.12±9.6	34.9±17.4
CKD group	6.42±4.92	9.24±5.16	568.8±326.7	11.36±5.82	8.37±3.67	36.33±8.32	121.375±21.0
P	0.184	0.005**	0.005**	0.005**	0.33	0.005**	0.005**

P** $\leq$ 0.005 = Significant LH/FSH ratio: 1.75±0.89

Table 4: Correlation between Studied parameters in CKD patients

Variables	PTH	FSH	LH MU	PRL MU	Testo NMO	Pro NMO	E2 PMO
PTH r		0.5213	0.1800	0.829	-0.13515	-0.0403	0.1715
P		0.01	0.18	0.001	-	-	-
FSH r	0.5213		0.2336	-0.1444	0.2827	-0.2827	0.1163
P	0.01		0.1	-	0.1	0.1	-
LH MU r	0.1800	0.2336		0.1734	-0.1237	-0.05034	0.2125
P		0.1		-	-	-	0.1
PRL MU r	0.829	-0.1444	0.1734		0.2159	0.1409	-0.1774
P		>0.1	-		-	-	-
TestoNMO r	-0.13515	0.2827	-0.1237	0.2159	-	-0.0316	-0.2147
P	>0.1	0.05	-	0.1	-	-	0.1
Pro NMO r	0.0403	-0.2827	-0.05034	0.1409	-0.0316	-0.0316	-0.1747
P	>0.1	0.05	-	-	-	-	-
E2 r	0.1715	0.1163	0.2125	-0.1774	-0.2147	-0.1747	0.4836
P	>0.1	-	-	-	0.1	-	0.01

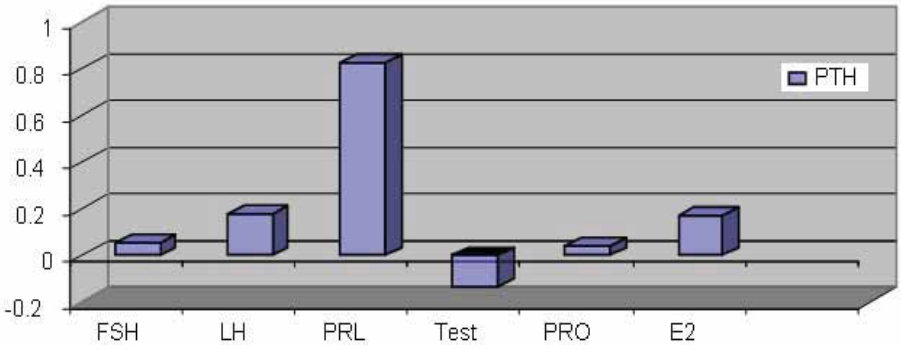

Fig. 2: Showing the correlation of the studied groups in relation to iPTH level.

Hyperprolactinemia is frequent in uremic patients, due to a functional disturbance in hypothalamic regulation of pituitary prolactin secretion, which appears to be autonomous and resistant to stimulatory or suppressive manoeuvres (Gomez F 1980). Control of secondary hyperparathyroidism with 1, 25(OH) 2 vitamin D may be of benefit in lowering prolactin levels and improving sexual function in some patients. Furthermore, partial inhibition of PTH release by the administration of calcitriol led in one study to an elevation in plasma testosterone levels, a reduction in plasma gonadotropin concentrations, and improved sexual function (Massry SG, 1977). These observations led to the evaluation of therapy with bromocryptine, which reduces prolactin secretion. Although it can lower prolactin levels to near normal in men with advanced renal disease, there has been an inconsistent effect on sexual potency and libido (Gomez F 1980).

In this study plasma LH levels were significantly elevated compared to the reference group P< 0.005, with a moderate positive correlation with iPTH level. LH level was increased due to diminished response of the hypothalamic-pituitary axis to lowered testosterone levels, and that the hypothalamic-pituitary axis in chronic renal failure is reset in such a way that it is more sensitive to the negative feedback inhibition of testosterone, impaired regulation of gonadotropin secretion (Handelsman DJ: 1985). The significant reduction (70%) in renal filtration and whole body clearance rate of LH and also could be due to a factor in uremic serum capable of blocking the LH receptor (Dunkel L ,1997).

In our study plasma FSH and PRO levels are slightly elevated with no significance compared to the reference group, with a reduced circulating serum testosterone. Many other authors who proved that mean progesterone and follicle - stimulating hormone levels in patients were not significantly different from those of control subjects (Joven J., 1985) also approved this result. Also we revealed an elevation of LH/FSH ratio (1.75±0.89) although FSH levels were normal in most of the patients (De Celis R etal 1985). The slightly high levels of FSH in some patients and others show a completely normal level could be good sign as the FSH

level correlate with the most severe damage to seminiferous tubules. It has been suggested that increased FSH levels may portend a poor prognosis for recovery of spermatogenic function after medical treatment or even transplantation (Phocas I 1995 and Palmer BF, 1999).

Our study also revealed a low plasma Testosterone level were P< 0.005 compared to the reference group with a significant negative correlation with plasma iPTH LH and PRL levels. This result was also approved by many other authors as testosterone which is normally reduced in CKD patients due to primarily organic origin also the rise of LH in response to low levels of testosterone is that the hypothalamic- pituitary axis in chronic renal failure is reset in such a way that it is more sensitive to the negative feedback inhibition of testosterone (Procci WR 1981., Handelsman DJ 1985 and Daniell HW 2006).

Also our study revealed increase E2 levels were P<0.005 and with a positive correlation with LH and PRL and a negative correlation with testosterone level. This also, was approved by others who proved that the total plasma estrogen concentration is often elevated in advanced renal failure, although a normal levels of estradiol suggest a functional gonadotropin deficiency

or resistance in uremia because increased LH levels should enhance the testicular secretion of estradiol (Karagiannis A 2005 and. Alice Schmidt 2006).

Conclusion: Plasma FSH levels are a very important tool before treatment strategies in CRF patients as well as iPTH and prolactin. Treatment strategies include optimizing dose of dialysis, correction of hyperparathyroidism, reduction in plasma prolactin levels, correction of anaemia, trial psychotherapy is warranted, antidepressant, may be helpful to those patients as long as their plasma FSH levels are within normal or slightly high than normal as this indicate a still functioning seminiferous tubules and reversible condition. Finally successful kidney transplantation may restore normal sexual function, especially in younger patients.

REFERENCES

Alice Schmidt, Anton Luger and Walter H. Hörl, 2006. Sexual hormone abnormalities in male patients with renal failure, [1]Division of Nephrology and Dialysis and[2] Division of Endocrinology, Department of Internal Medicine III, University of Vienna, Vienna, Austria.

Anantharaman, P and RJ Schmidt, 2007. Sexual function in chronic kidney disease. Adv Chronic Kidney Dis: 14(2): 119-25.

Blumberg, A., A. Wildbolz, C. Descoeudres, U. Hennes, M.A. Dambacher, J.A. Fischer and P. Weidmann, 1980. Influence of 1,25 dihydroxycholecalciferol on sexual dysfunction and related endocrine parameters in patients on maintenance hemodialysis. Clin Nephrol, 13: 208-214.

Brown, E.M., 1991. Extracellular Ca sensing regulation of parathyroid cell function and role of and other ions as extracellular first messenger. Physiol Rev, 71: 371-411.

Caticha, O., D.Y.J. Norato, M.A. Tambascia, A. Santana, A. Stephanou and N.J. Sarlis, 1996. Total body zinc depletion and its relationship to the development of hyperprolactinemia in chronic renal insufficiency. J Endocrinol Invest, 19: 441-448.

Chou, F.E., C.H. Lee, C.T. Lee, F.J. Huang and K.L. Hsu, 2003. Spermatogenesis after parathyroidectomy in patients with symptomatic secondary hyperparathyroidism. J AM Coll Surg 196(6): 854-8.

Daniell, H.W., 2006. Erythropoietin resistance during androgen deficiency. Archives of Internal Medicine, September 25,166(17): 1923-1923.

De Celis R and N Pendron-Nuevo, 1999. Male fertility of kidney transplant patients with one or ten years of evolution using a conventional immunosuppressive regimen.Archives of Andrology, 42: 9-20.

Dunkel, L., Raivio T., Laine J. and C. Holmberg, 1997. Circulating luteinizing hormone receptor inhibitor(s) in boys with chronic renal failure: Kidney International, 51: 777-784.

Gomez, F., R de la Cueva, J.P. Wauters and T Lemarchand-Beraud, 1980. Endocrine abnormalities in patients undergoing long-term hemodialysis: The role of prolactin. Am J Med 68: 522-530.

Hackens, W.H.L. and C.J.M. Lips, 1986. Clinical implication of estimation of intact PTH versus total immunoreactive PTH in normal subjects and hyperparathyroid patients. J Clin Endocrinol Metab, 63: 44-7.

Handelsman, D.J., 1985. Hypothalamic-pituitary gonadal dysfunction in renal failure, dialysis and renal transplantation. Endocrinol Rev, 6: 151-182.

Holdsworth, S.R., de Kretser D.M. and Atkins R.C., 1978. A comparison of hemodialysis and transplantation in reversing the uremic disturbance of male reproductive function. Clin Nephrol, 10: 146-150.

Isaac, R, RE Merceron, G Caillens, J.P Raymond and R Ardaillou, 1978. Effect of parathyroid hormone on plasma prolactin in man. J Clin Endocrinol Metab, 47: 18-23.

Joven, J., C. Villabona, J. Rubiés-Prat, E. Espinel and R. Galard, 1985. Hormonal profile and serum zinc levels in uraemic men with gonadal dysfunction undergoing haemodialysis. Clin Chim Acta., 148(3): 239-45.

Karagiannis, A. and F. Harsoulis, 2005. Gonadal dysfunction in systemic diseases , European journal of endocrinology, 152: 501-513.

Lim, V.S. and VS. Fang, 1976. Restoration of plasma testosterone levels inuremic men with clomiphene citrate. Journal of Clinical Endocrinology and Metabolism 43: 1370-1377.

Marja-terttu Saha, H.T. Heikki, Saha, Leo K Niskanen, Kaija T Samela and Amos I Pasternack, 2002. Time course of serum prolactin and sex hormones following successful renal transplantation., Nephron, 92: 735-737.

Massry, S.G., D.A. Goldstein, W.R. Procci and O.A. Kletzky, 1977. Impotence in patients with uremia: A possible role for parathyroid hormone. Nephron, 19: 305-310.

Palmer, B.F., 1999. Sexual dysfunction in uremia: JASN, 10: 1381-1388.

Phocas, I., A. Sarandakou, D. Rizos and A. Kapetanaki, 1995. Serum α-immunoreactive inhibitin in males with renal failure, under haemodialysis and after successful renal transplantation. Andrologia, 27: 253-258.

Prem, A.R., S.V. Punekar, M. Kalpana, A.R. Kelkar and V.N. Acharya, 1996. Male reproductive function in uraemia: Efficacy of haemodialysis and renal transplantation. Br J Urol, 78: 635-638.

Procci, W.R., Goldstein D.A., Adelstein J. and Massry S.G., 1981. Sexual dysfunction in the male patient with uremia: A reappraisal. Kidney Int 19: 317-323.

Reckelhoff, J.F., Yanes L.L., Iliescu R., Fortepiani L.A. and JzGranger J.P., 2005. Testosterone supplementation in aging men and women: possible impact on cardiovascular-renal disease
Am J Physiol Renal Physiol, November 1,289(5): F941-F948.

Toorians, A.W., E. Janssen, E. Laan, L.J.G. Gooren, E.J. Giltay, P.L. Oe, A.J.M. Donker and W. Everaerd, 1997. Chronic renal failure and sexual functioning :Clinical status versus objectively assessed sexual response. Nephol. Dial Transplant, 12: 2654-2663.