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Effect of Renal Transplantation on Gonadal Hormones in Male Patients with End Stage Renal Disease

Mohamed Elsayed Elsafty [1,*] MSc., Fawzy Hamed Hasan [2,] MD, Alsayed Mohamed Rashed [2] MD

** Corresponding Author:*
Mohamed Elsayed Elsafty
medoelsafty13@gmail.com

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[1]*Department of Internal Medicine, Maadi Medical Military Complex, Egypt.*

[2]*Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Egypt*

ABSTRACT

Background: Testosterone deficiency is common in chronic kidney disease patients, clinical studies reported in the literature demonstrate that about 50–70% of men on dialysis are affected by hypogonadism.
Aim of the work: Changes in sex hormones (free testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin) in male patients with chronic kidney disease (CKD), end-stage renal disease (ESRD) on regular hemodialysis, and post-renal transplantation patients were investigated.
Patients and Methods: This was a prospective comparative study conducted on 90 patients (30 male CKD patients stage 4, 30 male ESRD patients on regular hemodialysis and 30 male patients with post renal transplantation), at Maadi Military Medical Complex during the period from January 2020 to July 2021.
Result: In post-renal transplantation group-3, there was a highly significant rise in baseline free and total Testosterone, LH, and FSH when compared to the other groups (p 0.01 correspondingly). In post-renal transplantation group-3, there was a significant drop in baseline Estradiol and Prolactin associated to the other groups (p 0.01 correspondingly). In post-renal transplantation group-3, there was a highly significant rise in follow-up (12-month) free and total Testosterone, LH, and FSH when compared to the other groups (p 0.01 correspondingly). In the post-renal transplantation group-3, there was a highly significant drop in Estradiol and Prolactin at the 12-month follow-up linked to the other groups (p 0.01 correspondingly).
Conclusion: Kidney transplantation has been connected to improve erectile function in ESRD patients. This is directed by a rise in serum testosterone and a decrease in luteinizing hormone and prolactin levels.

Keywords: *Renal Transplantation; Gonadal Hormones; End Stage Renal Disease; chronic kidney disease.*

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INTRODUCTION

Hypogonadism, or testosterone (T) levels below assay reference ranges, is widespread in people with end-stage renal disease (ESRD), with prevalence rates ranging from 50 to 70% in different studies. Low testosterone has been associated to an increased risk of morbidity and mortality in males with ESRD[1]. Primary gonadal failure, hypothalamic–pituitary–gonadal axis dysfunction, and maybe a change in oestrogen homeostasis [2]can all contribute to hypogonadism in ESRD.

Many men with renal failure experience pituitary and gonadal changes, which disrupt the hypothalamic-pituitary-gonadal axis and contribute to hypogonadism. Renal failure is linked to a decrease in luteinizing hormone (LH) synthesis in the gonadal axis, which can lead to hypogonadism. Renal failure is linked to a reduction in luteinizing hormone (LH) synthesis as well as a reduction in prolactin clearance. Hyperprolactinemia is caused by a reduction in prolactin clearance, which can limit LH production and, as a result, testosterone production [3].

Renal transplantation significantly improved the eugonadal phenotype in at least some patients, with plasma testosterone levels tripling. A closer look found an increase in testosterone, as well as decreases in LH, FSH, and prolactin[4].

PATIENTS AND METHODS

This was a prospective comparative study directed on 90 patients (30 male chronic kidney disease patients (CKD) stage 4, 30 male ESRD patients on regular hemodialysis and 30 male patients with post renal transplantation), at Maadi Military Medical Complex during the period from January 2020 to July 2021.

Inclusion criterion: Male < fifty years.

Exclusion criteria: Age more than fifty years or less than 18 years, patients with primary hypogonadism, hemochromatosis, patients on cancer treatment (chemotherapy and radiotherapy), pituitary tumors, hypopituitarism of any etiology, and inflammatory diseases such as tuberculosis and sarcoidosis.

All participants were informed about the study's purpose and laboratory or radiological procedures. All participants signed a consent form. All patients were informed of the results of the examinations performed at the conclusion of the study and received appropriate advice and therapy. This research was carried out in conformity with the World Medical Association's Code of Ethics (Declaration of Helsinki) for human studies.

Patient's randomization:Group 1: 30 male chronic kidney disease patients (CKD) stage 4**,Group 2:** 30 male ESRD patients on regular hemodialysis three sessions per week and four hours per session for at least 6 months**,Group 3:** 30 male patients with post renal transplantation and gonadal hormones was investigated at 1, 3, 6 and 12 months after renal transplantation.

All patients were subjected to: Full medical history**,**Through medical examination includes (Body mass index and waist circumference, measurement of blood pressure),Laboratory investigation:Complete blood count,Renal functions tests (blood urea and serum creatinine),Liver function test (Aspartate Aminotransferase, Alanine Aminotransferase),Serum calcium, phosphorus and parathyroid hormone (PTH),C- reactive protein (CRP), ESR, Serum albumin, Total protein and ferritin,Free testosterone, LH, FSH, prolactin, Free T4 and TSH by LIAISON.

Statistical Methodology:

MedCalc version 18.11.3 was used for data entry, processing, and statistical analysis (MedCalc, Ostend, Belgium). We employed Kruskal-Wallis, Friedman's, factorial ANOVA, Spearman's correlation, and ROC Curve analysis to determine significance. Data were supplied, and appropriate analysis was performed for each variable based on the kind of data (parametric and non-parametric). For parametric numerical data, mean, standard deviation (SD), and range are used, while for non-parametric numerical data, median and inter-quartile range (IQR) are used. Non-numerical data frequency and proportion Significant was defined as a P value of less than 0.05.

RESULTS

Variable	Group-1 (30)	Group-2 (30)	Group-3 (30)	Kruskal-Wallis test
	Median (IQR)	Median (IQR)	Median (IQR)	P value
Hb (g/dL)	9.8 (9.4 – 10.5)	9.5 (9 – 10.5)	10.6 (10.2 – 11.2)	< 0.0001**
PLT (10^3/µL)	231 (188 – 254)	231 (188 – 254)	252 (229 – 296)	= 0.014*
TLC (10^3/µL)	5.7 (4.6 – 6.5)	5.7 (4.6 – 6.5)	5.7 (4.7 – 6.8)	= 0.6874
ALT (U/L)	37.5 (28 – 43)	35.5 (24 – 44)	29 (27 – 38)	= 0.1224
AST (U/L)	44.5 (32 – 52)	40.5 (27 – 53)	32.5 (29 – 42)	= 0.0786
Urea (mg/dL)	99 (85 – 121)	167 (136 – 205)	28.5 (22 – 37)	< 0.0001**
Creat. (mg/dL)	5.8 (5.3 – 6.5)	10.4 (9.1 – 11.2)	0.9 (0.7 – 1.1)	< 0.0001**
Ca (mg/dL)	8.8 (8.5 – 9.3)	8.6 (8.2 – 9.2)	9.9 (9.7 – 10.3)	< 0.0001**
Po4 (mEq/L)	4.5 (3.9 – 5.1)	4.9 (4.2 – 5.3)	3.1 (2.6 – 3.9)	< 0.0001**
PTH (ng/dL)	205.5 (168 – 266)	339 (294 – 488)	42.5 (33 – 50)	< 0.0001**
T. proteins (mg/dL)	7.05 (6.1 – 7.9)	7.5 (6.8 – 8.1)	7 (6.4 – 7.9)	= 0.2331
Alb. (g/dL)	4.2 (3.8 – 4.7)	3.9 (3.7 – 4.1)	4.4 (4.1 – 5.1)	< 0.0001**
ESR (mm/h)	8 (6 – 10)	6 (3 – 10)	7.5 (6 – 9)	= 0.2991
CRP (mg/dL)	6.5 (4 – 10)	5 (4 – 8)	6.5 (4 – 9)	= 0.3468
Ferritin (mg/dL)	180 (155 – 197)	163 (139 – 188)	275 (213 – 300)	< 0.0001**
F. T4 (ng/dL)	0.8 (0.79 – 1.1)	0.95 (0.89 – 1.12)	0.89 (0.78 – 1.14)	= 0.0895
TSH (mIU/L)	2 (1.2 – 2.9)	2.4 (1.6 – 3.3)	2.25 (1.4 – 3.1)	= 0.3495

Table 1: Comparison between the 3 groups as regards baseline laboratory data using Kruskal-Wallis test.

Comparative study between the 3 groups revealed; highly significant increase in baseline hemoglobin, platelets, Ca, albumin, ferritin, in post-renal transplantation group-3; compared to other groups ($p < 0.01$ respectively). Comparative study between the 3 groups revealed; highly significant decrease in baseline urea, creatinine, Po4, PTH, in post-renal transplantation group-3; compared to other groups ($p < 0.01$ respectively). Comparative study between the 3 groups revealed non-significant difference as regards baseline TLC, ALT, AST, T. proteins, ESR, CRP, free T4 and TSH ($p > 0.05$) (Table 1).

Variable	Group-1 (30)	Group-2 (30)	Group-3 (30)	Kruskal-Wallis test
	Median (IQR)	Median (IQR)	Median (IQR)	P value
F. Testosterone (ng/dL)	4.18 (3.9 – 4.23)	2.95 (2.45 – 3.38)	15.8 (15.2 – 16.5)	< 0.0001**
T. Testosterone (ng/dL)	0.9 (0.84 – 1.2)	0.7 (0.63 – 0.9)	9.9 (9.5 – 10.2)	< 0.0001**
Estr-adiol (pg/ml)	39.5 (34 – 44)	58 (47 – 71)	11.6 (10.8 – 12.6)	< 0.0001**
LH (IU/L)	2.89 (2.6 – 3.1)	1.87 (1.7 – 2.2)	6.1 (5.77 – 6.25)	< 0.0001**
FSH (IU/L)	2 (1.42 – 2.44)	1.55 (0.97 – 1.25)	4.8 (4.7 – 5.1)	< 0.0001**
Prolactin (ng/dL)	18.4 (17.8 – 18.8)	19.8 (19.4 – 20.7)	5.5 (4.7 – 6.9)	< 0.0001**

Table 2: Comparison between the 3 groups as regards baseline gonadal hormone profile using Kruskal-Wallis test.
In a comparison of the three groups, post-renal transplantation group-3 showed a highly significant rise in baseline free and total Testosterone, LH, and FSH when compared to the other groups (p 0.01 correspondingly). In a comparative analysis of the three groups, it was discovered that post-renal transplantation group-3 had a highly significant decrease in baseline Estradiol and Prolactin when compared to the other groups (p 0.01 correspondingly) (Table 2).

Variables	Repeated 3 measures ANOVA (3-F: between the 3 groups)	
	F ratio	P value
F. Testosterone (ng/dL)	5764.12	<0.001**
T. Testosterone (ng/dL)	5481.89	<0.001**
Estradiol (pg/ml)	131.03	<0.001**
LH (IU/L)	1589.65	<0.001**
FSH (IU/L)	1285.05	<0.001**
Prolactin (ng/dL)	2153.80	<0.001**

ANOVA: analysis of variance, 3-F: 3-factor study. #logarithmic transformation was done to non-parametric data.

Table 3: Comparison between the 3 groups of patients as regards serial laboratory measurements using repeated measures ANOVA test (2-Factor study).
During the serial baseline and follow-up assessments, there was an increase in free Testosterone in post-renal transplantation group-3 compared to the other groups (p 0.01). During the serial baseline and follow-up assessments, there was an increase in total Testosterone in post-renal transplantation group-3 compared to the other groups (p 0.01). During the serial baseline and follow-up assessments, there was a decrease in Estradiol in post-renal transplantation group-3 compared to the other groups (p 0.01). During the serial baseline and follow-up assessments, there was an increase in LH in post-renal transplantation group-3 compared to the other groups (p 0.01). During the serial baseline and follow-up assessments, there was an increase in FSH in post-renal transplantation group-3 compared to the other groups (p 0.01). During serial baseline and follow-up measurements, there was a decrease in prolactin in post-renal transplantation group-3 when compared to the other groups (p 0.01). (Table 3).

Associated Factor		12-months T. testosterone level	
		Rho	P
Clinical	**Age** (years)	-0.360	=0.0005**
	BMI	0.0782	=0.4636
	WC (cm)	0.0341	=0.7497
Laboratory	**Hb** (g/dL)	0.407	=0.0001**
	PLT (10^3/µL)	0.291	=0.0054**
	TLC (10^3/µL)	0.108	=0.3114
	ALT (U/L)	-0.00696	=0.9481
	AST (U/L)	-0.0787	=0.4609
	Urea (mg/dL)	-0.649	<0.0001**
	Creat. (mg/dL)	-0.648	<0.0001**
	Ca (mg/dL)	0.653	<0.0001**
	Po4 (mEq/L)	-0.629	<0.0001**
	PTH (ng/dL)	-0.663	<0.0001**
	T. proteins (mg/dL)	-0.0836	=0.4332
	Alb. (g/dL)	0.316	=0.0024**
	ESR (mm/h)	0.0872	=0.4137
	CRP (mg/dL)	0.0656	=0.5391
	Ferritin (mg/dL)	0.387	=0.0002**
	F. T4 (ng/dL)	0.0400	=0.7082
	TSH (mIU/L)	0.108	=0.3112

rho: Spearman's rho (correlation coefficient).

Table 4: Spearman's correlation analysis for baseline Factors associated with 12-months T. testosterone level.

Spearman's correlation analysis shows that; baseline hemoglobin, platelets, Ca, albumin and ferritin, had a highly significant positive correlation with 12-months T. testosterone level ($p < 0.01$ respectively). Spearman's correlation analysis shows that; age, baseline urea, creatinine, Po4 and PTH, had a highly significant negative correlation with 12-months T. testosterone level ($p < 0.01$ respectively) (Table 4).

Variable	AUC	SE	Best Cut off point (Criterion)	Sensitivity (%)	Specificity (%)	P value
Renal transplantation	1.000	0	>0.95	100	100	<0.0001**

ROC (Receiver operating characteristic), AUC= Area under curve, SE= Standard Error.

Table 5: Roc-curve of renal transplantation to predict 12-months T. testosterone level increase.

By using ROC-curve analysis, renal transplantation predicted 12-months T. testosterone level increase, with perfect (100%) accuracy, sensitivity= 100% and specificity= 100% ($p < 0.001$) (Table 5).

DISCUSSION

This was a prospective comparative study directed on 90 male patients; to changes in sex hormones (free testosterone, L-H, F-SH and pro-lactin) in male patients with chronic kidney disease (CKD), ESRD on consistent hemodialysis and post renal transplantation patients.

In the current study, the post-renal transplantation group-3 showed a highly significant decrease in baseline urea, creatinine, Po4, and PTH when compared to the other groups (p 0.01 correspondingly**.(**

According to Reinhardt et al. [4]**,**kidney purpose improved rapidly in all cases resulting RTx (median eGRF: 10.4 ml/min pre-RTx; median eGFR: 50.6 ml/min post-RTx).

In terms of baseline gonadal hormones, this study found that post-renal transplantation group-3 had a highly significant rise in free and total Testosterone, LH, and FSH, associated to the other groups (p 0.01 correspondingly).

Kidney transplantation in men with CKD is related with overall development in sex hormone profiles, according to a study by Dumanski and Ahmed [6].

In a study of 30 persons with ESRD on HD who were followed through kidney transplantation, normalisation of LH and PRL levels, as well as a rise in testosterone levels, were noted**.**Despite the fact that kidney transplant recipients had lower testosterone levels than healthy controls, testosterone and LH levels in 24 males were examined after kidney donation. Our findings contradicted those of Sikora-Grabka et al. [5], who found that serum concentrations of both LH and FSH fell significantly during the observation period. This explains why the FSH/LH ratio did not alter much during the research period.

As regards estradiol and prolactin in our study, showed highly significant decrease in baseline In post-renal transplantation group-3, estradiol and prolactin levels were significantly higher than in the other groups (p 0.01 for both). Sikora-Grabka et al. [5], Kang et al. [7], and Perri et al. [8] all agreed on this**.**

According to Sikora-Grabka et al. [5], the serum concentration of PRL was lower at the end of the study than at the start, but the difference did not achieve statistical significance when multiple comparisons were corrected**.**

Changes in testosterone (T) levels were reported in three studies, while prolactin (PRL), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels were reported in two studies. according to Kang et al. [7]. (L-H). The kidney transplantation group had lower PRL levels (SMD 1.46, 95 percent C-I: 2.22 to 0.69) and LH levels (SMD 0.97, 95 percent C-I: 1.39 to 0.55).In our study further analyzed and compared all 90 (paired) patients according to the serial (gonadal hormone measurements) (baseline and follow up); with entering a grouping factor (Group-1, 2 or 3)**.** Also, we found marked increase in free Testosterone in post-renal transplantation group-3; compared to other groups; during the serial baseline and follow up measurements ($p < 0.01$). Which came in agreement with Kang et al. [7] reported that, In the renal transplantation group, serum testosterone levels are up, but serum PRL and LH levels were lower. There was no discernible difference in serum FSH levels between the two groups.

During the serial baseline and follow-up assessments, we discovered a significant rise in total Testosterone in post-renal transplantation group-3 (p 0.01), compared to the other groups. According to Rahman et al.[9], four papers were assessed for variations in testosterone production before and after transplantation using a meta-analysis. A substantial difference in serum testosterone levels existed before and after transplantation, according to the meta-analysis**.**

During the serial baseline and follow-up measurements, we discovered a significant drop in Estradiol in post-renal transplantation group-3 when compared to other groups. E2 concentrations transiently fell following RTx, with a considerable decline from pre-RTx to 1 month after RTx and a subsequent increase from 1 month to 3 months after RTx, eventually returning to pre-RTx levels after 6 months, according to Reinhardt et al. [4]. As a result, the E2/T ratio declined dramatically from pre-RTx to one and three months after RTx, and thereafter remained stable**.**

During the serial baseline and follow-up assessments, we discovered a significant drop in Prolactin in post-renal transplantation group-3 (p 0.01), compared to the other groups. Prolactin serum concentrations fell immediately after RTx and were constant until the end of follow-up, according to Reinhardt et al. [4]. Only one patient had increased PRL levels 12 months after RTx, despite the fact that 29% of patients were hyperprolactinemic before to treatment.

CONCLUSION

In cases with end-phase renal illness, kidney transplantation may improve erectile function. This could be due to the alteration of endo-crine hormone abnormalities in kidney transplant recipients, as seen by increased serum testosterone and decreased LH and PRL levels.

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