

## Level of Reproductive Hormones in Men and Women after Successful Kidney Transplantation

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### Abstract

This study was designed to shed a light on the reproductive function in men and women after successful kidney transplantation (KT). Forty five adult patients (25 men and 20 women) were included; these patients met the inclusion criteria (serum creatinine  $\leq$  1.4 mg/dl; glomerular filtration rate (GFR)  $\geq$  60 ml/min at least 3 months after KT). Twenty two healthy individuals (12 men and 10 women) were included as control group. Assessment of the renal function tests [blood urea, serum creatinine, and GFR] and determination of the level of the reproductive hormones [luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin (PRL) in men and women; and testosterone and 17- $\beta$ -estradiol ( $E_2$ ) in the men and the women, respectively] had been carried out. The correlation between level of these hormones and the renal function tests was also studied in the patients. The results of the renal function tests showed that patients had higher blood urea and serum creatinine than the controls, while GFR was lower in the patients as compared to controls. Regarding to the reproductive hormones, it was found there were no significant differences in levels of LH, FSH and testosterone between men patients and men controls, while PRL was significantly ( $P < 0.05$ ) higher in the male patients as compared to the male controls. The results revealed that no significant differences in levels of LH, FSH and  $E_2$  between women patients and women controls, while PRL was significantly ( $P < 0.01$ ) higher in the female patients than the female control. When the correlation between the level of the reproductive hormones and the renal function tests was studied in men and women kidney transplanted patients, the findings showed that a significant negative correlation ( $r = -0.48$ ,  $P < 0.05$ ) and a highly significant negative correlation ( $r = -0.74$ ,  $p < 0.01$ ) were found between levels of FSH and serum creatinine in men and women patients, respectively. While a significant positive correlation was found between levels of PRL and blood urea in each of men ( $r = 0.48$ ,  $P < 0.05$ ) and women ( $r = 0.49$ ,  $P < 0.05$ ) patients.

Keywords: kidney transplantation, reproductive hormones, renal function tests, end-stage renal disease.

### Introduction

Among the treatments available for end-stage renal disease (ESRD), hemodialysis, peritoneal dialysis, and kidney transplantation (KT); the latter is a successful treatment modality for ESRD and the preferred mode of renal replacement therapy. Male and female patients with ESRD commonly experience sexual dysfunction and infertility as a result of endocrine aberrations, vasomotor dysfunction, prescribed medications, and psychological factors<sup>(1;2)</sup>. Alterations on sex steroid production and metabolism are already seen when moderate reductions in the glomerular filtration rate (GFR) arise<sup>(3)</sup>.

It has been reported that the period of ESRD preceding KT is associated with disorders in hypothalamic-pituitary-

gonadal (HPG) function in both genders. In male patients, there is high prolactin (PRL) level (hyperprolactinaemia)<sup>(4)</sup>, abnormal gonadotropin-releasing hormone (GnRH) pulsatility<sup>(1)</sup>, high luteinizing hormone (LH) and follicle-stimulating hormone (FSH) values, low testosterone levels and reduced spermatogenesis<sup>(5)</sup>. In female patients, amenorrhea or oligomenorrhea associated with anovulation and decreased 17- $\beta$ -estradiol ( $E_2$ ) secretion were reported frequently<sup>(6)</sup>.

Although abnormalities in the HPG axis are well recognized in both genders during ESRD<sup>(3;1)</sup>, conflicting data are available after KT. Several studies have shown that male and female HPG dysfunction was found to be either reversed<sup>(7)</sup>, differently improved<sup>(8)</sup> or altered after successful KT<sup>(9)</sup>. Holdsworth

*et al.* stated that after KT, although some features of reproductive function may remain impaired; endocrine function generally improves after recovery of renal function<sup>(10)</sup>. In 2003, Akbari *et al.* reported that a well-functioning renal transplant is more likely to restore normal sexual activity<sup>(8)</sup>.

In this study, we estimate the level of reproductive hormones in the sera of men and women after successful KT. Also, the correlation between level of these hormones and renal function tests was investigated.

## Materials and Methods

### Subjects

The subjects comprised 45 adult patients (25 men and 20 women  $\geq$  18 yr of age) following successful KT. These patients met the inclusion criteria (serum creatinine  $\leq$  1.4 mg/dl; GFR  $\geq$  60 ml/min at least 3

months after KT). Twelve men and ten healthy women age - and body mass index (BMI) - matched with the patients selected to participate in this study as controls.

The following data were assessed in each patient: age, sex, weight, height, previous dialysis duration (months), time since transplantation (months), and details of immunosuppressive therapy. The body mass index (BMI) was calculated as weight (kg) divided by the square of height (m<sup>2</sup>). The clinical data of the patients and controls are shown in Table (1). All patients were on maintenance, combined immunosuppressive therapy, stable for at least 3 months, and receiving cyclosporine A and prednisone, while azathioprine was used in 16 patients and 20 patients were on mycophenolate mofetil.

**Table (1)**  
*The clinical data of the 45 patients and 22 controls in the study.*

<i>Variable</i>	<i>Patients</i>	<i>Controls</i>
Male/ Female	25/20	12/10
Age (years)	34 $\pm$ 9	32 $\pm$ 8
BMI (kg/m <sup>2</sup> )	26.6 $\pm$ 3.9	25.2 $\pm$ 2.6
Previous dialysis duration (months)	7 $\pm$ 5	–
Time since transplant (months)	25 $\pm$ 21	–

*Data are mean  $\pm$  SD*

*BMI = body mass index*

### Sample collection

Blood samples (5 ml) were withdrawn from all subjects by veinpuncture for measurement of renal function tests and reproductive hormones. Blood samples were left at room temperature for about half an hour then the sera were separated by centrifugation for 15 minutes at 3000 rpm and stored at -20°C until analysis.

### Renal function tests

Renal function measured by the following tests:

Blood urea:- Blood urea was determined by colorimetric method<sup>(11)</sup>. Biolabo kit was used in this colorimetric method.

Serum creatinine:- Serum creatinine was estimated according to Jaffe reaction<sup>(12)</sup>.

Human kit was used in this colorimetric method.

Glomerular filtration rate:- GFR was calculated according to the Cockcroft-Gault equation<sup>(13)</sup>.

### Endocrine evaluation

Circulating LH, FSH, and PRL were measured in the serum of all subjects. Serum concentrations of testosterone in men and E<sub>2</sub> in women were measured. All women with regular menstrual cycle were evaluated in the early follicular phase (days 3-6). All measurements were performed by commercially available kits from the Beckman coulter company, France; LH, FSH, and PRL using immunoradiometric assay; testosterone and E<sub>2</sub> using a radioimmunoassay.

### Statistical Analysis

Statistical analysis was done using Statistical Package for Social Science (SPSS), version 12, computer software. Data are expressed as mean  $\pm$  SD. Student's t-test was used to compare the group of patients and controls. Linear correlation coefficients and their significance were determined to assess the dependence between endocrine features and renal function tests. The level of significance was determined at  $P < 0.05$ <sup>(14)</sup>.

### Results

#### Renal Function Tests

The results of renal function tests (Table (2)) revealed that patients had significantly ( $P < 0.05$ ) higher blood urea and serum creatinine than the control groups, while GFR was significantly ( $P < 0.01$ ) lower in the patients as compared to control groups.

**Table (2)**  
*Renal function tests in patients and control groups.*

Renal function tests	Patients	Controls	P value
Blood urea (mg/dl)	35 $\pm$ 7	30 $\pm$ 5	$P < 0.05$
Serum creatinine (mg/dl)	1.2 $\pm$ 0.2	0.9 $\pm$ 0.2	$P < 0.05$
Glomerular filtration rate (ml/min)	87 $\pm$ 22	102 $\pm$ 19	$P < 0.01$

Data are mean  $\pm$  SD

#### The Reproductive Hormones in Men after Kidney Transplantation

Level of the reproductive hormones in male patients and controls are shown in Table (3). There were no significant

differences in levels of LH, FSH and testosterone between patients and controls, while PRL was significantly ( $P < 0.05$ ) higher in the patients than in control group.

**Table (3)**  
*Level of the reproductive hormones in male patients and male controls.*

The reproductive hormones	Male patients	Male controls	P value
Luteinizing hormone (mIU/ml)	7.5 $\pm$ 3.4	6.2 $\pm$ 1.6	NS
Follicle-stimulating hormone (mIU/ml)	8.2 $\pm$ 2.1	5.6 $\pm$ 1.4	NS
Prolactin (ng/ml)	8.6 $\pm$ 3.7	5.3 $\pm$ 1.1	$P < 0.05$
Testosterone (ng/ml)	5.3 $\pm$ 2.0	6.8 $\pm$ 1.4	NS

Data are mean  $\pm$  SD

#### The Reproductive Hormones in Women after Kidney Transplantation

Menstrual history of 20 women studied in this research indicated that before KT 8 women had menstrual disturbances; 4 of them suffered from oligomenorrhea, while 4 of them suffered from amenorrhea. After KT recovery of menses occurred in 3 women after 3 months, while in other 5 women occurred after 4 months.

Results of the reproductive hormones in female patients and controls are shown in Table (4). The results revealed that no significant differences in levels of LH, FSH and  $E_2$  between the patients and controls, while a significant ( $P < 0.01$ ) increased levels of PRL was observed in the patients in comparison to the controls.

**Table (4)**  
*Level of the reproductive hormones in female patients and female controls.*

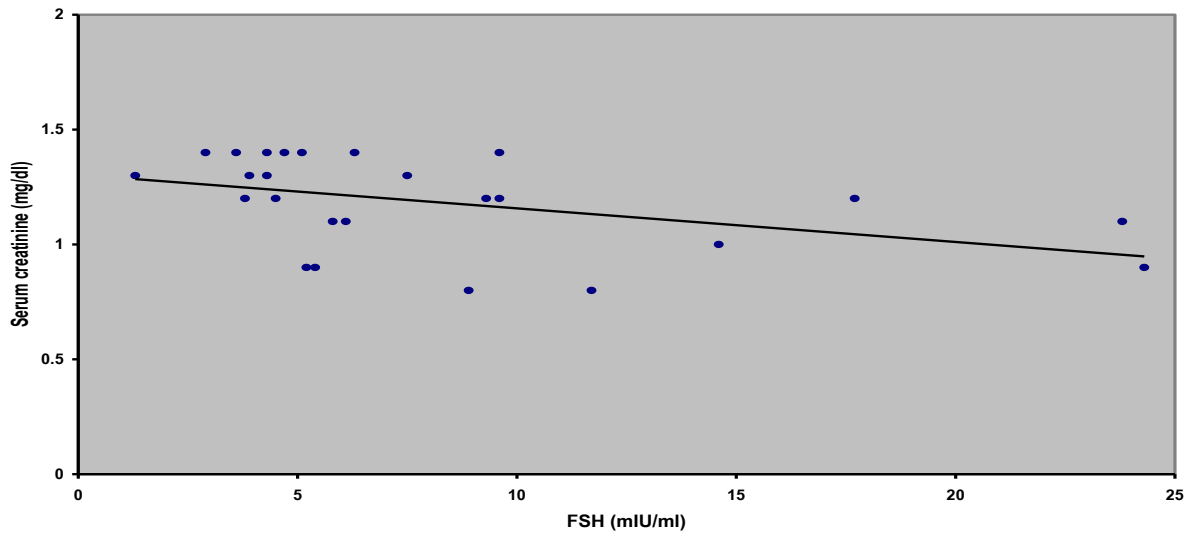
The reproductive hormones	Female patients	Female controls	P value
Luteinizing hormone (mIU/ml)	6.5 $\pm$ 1.5	4.3 $\pm$ 1.2	NS
Follicle-stimulating hormone (mIU/ml)	6.2 $\pm$ 3.4	5.1 $\pm$ 1.9	NS
Prolactin (ng/ml)	12.4 $\pm$ 4.6	7.0 $\pm$ 1.1	$P < 0.01$
Estradiol (pg/ml)	200 $\pm$ 98	136 $\pm$ 56	NS

Data are mean  $\pm$  SD

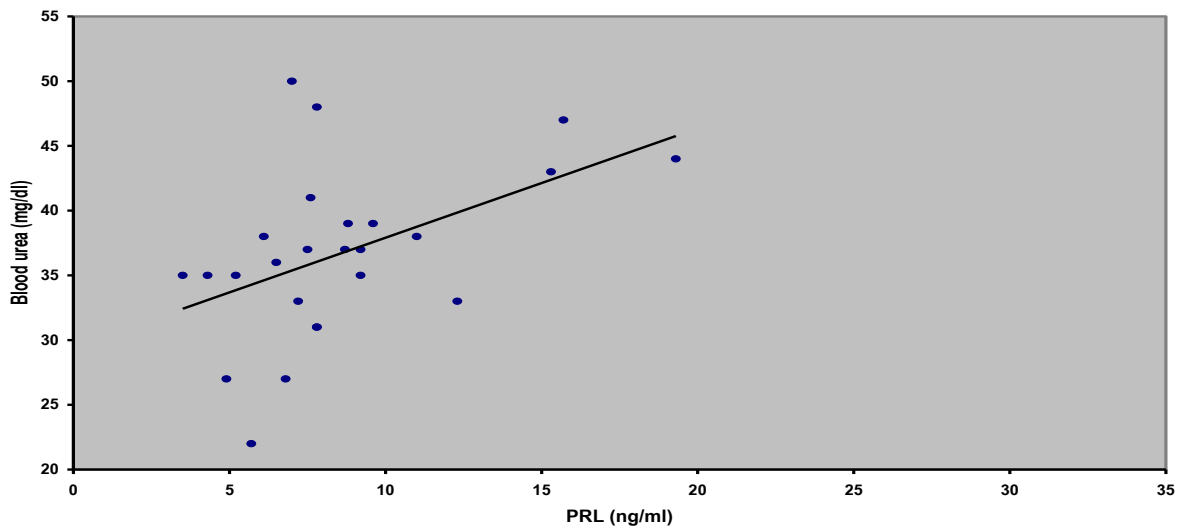
#### Correlation between Reproductive Hormones and Renal Function Tests in Men Patients

The correlation between levels of the reproductive hormones and renal function tests in men patients indicated a significant negative

correlation ( $r = -0.48$ ,  $P < 0.05$ ) was found between level of FSH and serum creatinine (Fig.(1)). While a significant positive correlation ( $r = 0.48$ ,  $P < 0.05$ ) was found between level of PRL and blood urea (Fig.(2)).



*Fig.(1) Correlation between levels of serum FSH and serum creatinine in men patients ( $r=-0.48$ ,  $P<0.05$ ).*

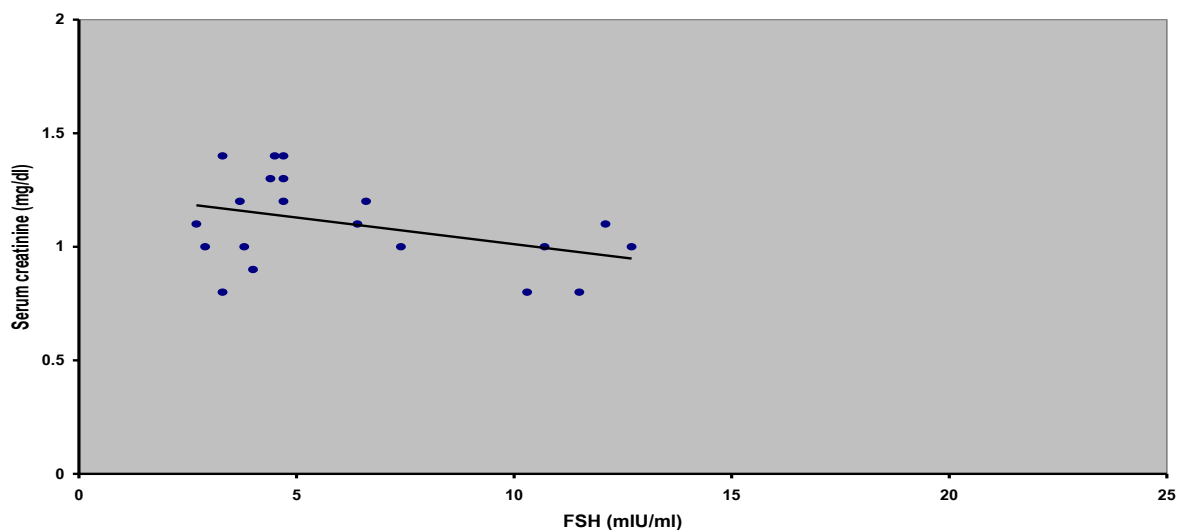


*Fig.(2) Correlation between levels of serum PRL and blood urea in men patients ( $r=0.48$ ,  $P<0.05$ ).*

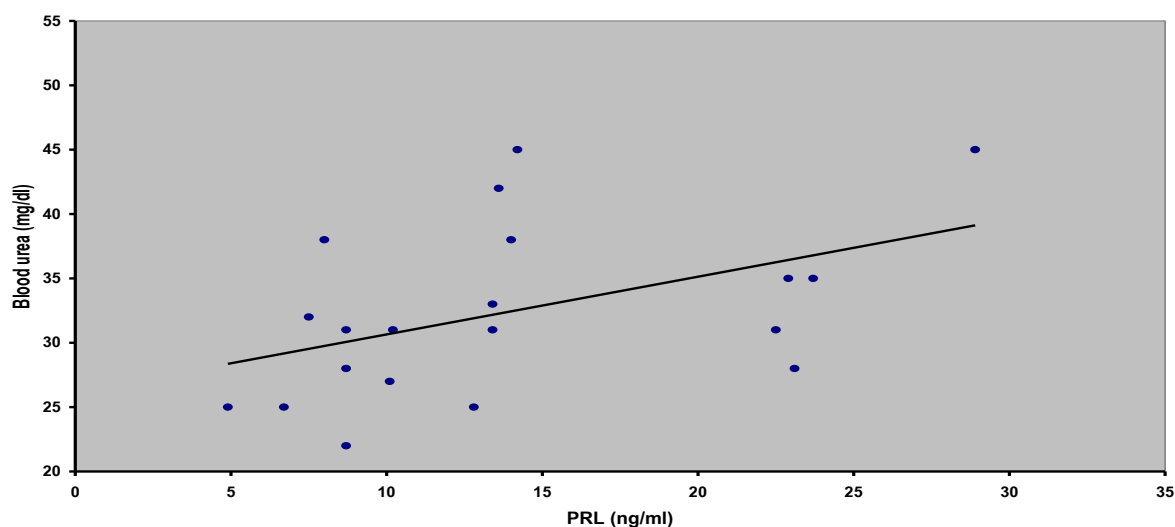
**Correlation between Reproductive Hormones and Renal Function Tests in Women Patients**

Study of the correlation between the level of reproductive hormones and renal function tests in women patients revealed that a highly

significant negative correlation ( $r=-0.74$ ,  $P<0.01$ ) was observed between level of FSH and serum creatinine (Fig.(3)), while a significant positive correlation ( $r=0.49$ ,  $P<0.05$ ) was observed between level of PRL and blood urea (Fig.(4)).



**Fig.(3) Correlation between levels of serum FSH and serum creatinine in women patients ( $r=-0.74$ ,  $P<0.01$ ).**



**Fig.(4) Correlation between levels of serum PRL and blood urea in women patients ( $r=0.49$ ,  $P<0.05$ ).**

## Discussion

Kidney transplantation was reported to restore endocrine function, but study results are discordant. The restoration of hormonal profiles after successful KT is still controversial. The results of a previous study have suggested that KT restores the balance in the HPG axis<sup>(8)</sup>. It has been reported that the HPG axis after KT is mostly influenced by the quality of allograft function, the use of immunosuppressive treatments and general health conditions<sup>(15;16)</sup>. In 2007, Anantharaman *et al.* found that successful KT may restore normal sexual function, especially in younger patients<sup>(17)</sup>. In 2008, Barroso *et al.* stated that kidney transplants improve sexual function of

patients compared with ESRD on hemodialysis<sup>(18)</sup>. These data differed from those of other authors who found persistent abnormalities of the HPG axis function in KT recipients with well functioning allografts<sup>(19;20)</sup>.

In the present study, we investigated level of reproductive hormones in men and women after successful KT. We found increased prolactin levels in transplanted men as compared to controls. These results are in line with those of Exaire *et al.*<sup>(21)</sup> and in contrast to results of Samojlik *et al.*<sup>(7)</sup>. Regarding to the other reproductive hormones (testosterone, LH, and FSH), our finding showed that there were no significant differences in levels of

these hormones between male patients and controls. These results are in line with those of Samojlik *et al.*<sup>(7)</sup> who found that, three months after transplantation, plasma testosterone, LH, and FSH levels were restored toward normal. A trend toward normal levels of these hormones in men after KT suggests improvement of testicular function. The results of a previous study have suggested that a higher GFR indicating better allograft function was associated with higher serum testosterone level<sup>(20)</sup>. Results of the current study revealed no statistical significant difference in circulating levels of LH, FSH and E<sub>2</sub> between female patients and controls, while PRL was significantly higher in the female patients than control group.

Immunosuppressive drugs may influence the restoration of hormonal profiles after successful KT. Tondolo *et al.*<sup>(22)</sup> were able to evaluate the hormonal status of successful renal transplant recipients who were treated with different immunosuppressive agents. They concluded that immunosuppressive therapies may influence the restoration of normal levels of gonadal hormones after KT. In several studies, erythropoietin therapy has been reported to cause normalization of the pituitary gonadal feedback mechanism with reduced plasma concentrations of LH and FSH, increases in plasma testosterone levels, and reductions in elevated plasma PRL levels<sup>(23;24)</sup>. Several aetiologic factors appear to contribute to the elevated PRL levels in the men and women kidney transplanted patients in this study. Hyperprolactinaemia is partially induced by a decreased metabolic clearance and also by autonomic overproduction<sup>(2)</sup>.

It has been reported that the HPG axis function in women is less clear than in men, either before or after KT<sup>(20)</sup>. In the present study, recovery of menses which occurred in the studied women after KT may be due to reversion of hormone aberrations after transplantation, resulting in normal ovulatory cycles and regular menstruation<sup>(1)</sup>. It has been reported that one of the effects of an improved general health state after successful KT in women of reproductive age is recurrence of regular menstrual function. Results of a previous study have suggested that stabilization of graft function resulted in

restoration of normal ovarian hormone metabolism and ovulatory cycles in female kidney transplanted recipients<sup>(25)</sup>.

When a relationship between levels of the reproductive hormones and renal function tests in men and women kidney transplanted patients was studied, the results showed that a significant and a highly significant negative correlation were found between levels of FSH and serum creatinine in men and women patients, respectively. While a significant positive correlation was found between levels of PRL and blood urea in both men and women patients. This negatively significant correlation indicates that increased serum creatinine levels in the studied cases suggest conditions that affect FSH production results in decreased levels of this hormone in the blood of men and women patients. On the other hand, the significant positive correlation indicates that an increased blood urea level is a good indicator for incidence of hyperprolactinaemia in these patients (men and women).

## Conclusions

A normalization of the levels of the reproductive hormones (LH, FSH, testosterone and E<sub>2</sub>) in KT recipients is probably multifactorial, being influenced by immunosuppressive treatments and erythropoietin therapy. This restoration of normal levels of these hormones suggests improvement of testicular function in men and restoration of normal ovarian hormone metabolism and ovulatory cycles in women. The elevated PRL level in men and women after KT was explained mostly by a decreased metabolic clearance and increased production.

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البرولاكتين اعلى بصورة معنوية عالية في المرضى الاناث مقارنة مع السيطرة الاناث. عند دراسة علاقة الترابط بين مستوى الهرمونات التكاثرية واختبارات الوظيفة الكلوية في المرضى، اظهرت النتائج وجود علاقة سالبة معنوية وعلاقة سالبة معنوية عالية بين مستوى الهرمون المحفز للجريب و تركيز كرياتينين المصل في المرضى الرجال والنساء على التوالي. بينما وجدت علاقة موجبة معنوية بين مستوى البرولاكتين ويوريا الدم في جميع المرضى رجالاً ونساءً.

### الخلاصة

صممت الدراسة الحالية لالقاء الضوء على الوظيفة التكاثرية في الرجال والنساء بعد عملية زرع الكلية الناجحة. تضمنت الدراسة ٤٥ مريضاً بالغاً ( ٢٥ رجلاً و ٢٠ امرأة) ممن تتوفر فيهم المعايير المتضمنة (تركيز كرياتينين المصل  $\geq 1.4$  اغم/١٠٠ مل، قيمة معدل الترشيح الكبيبي  $\leq 60$  مل/دقيقة، المدة الزمنية بعد عملية زرع الكلية على الاقل ٣ أشهر). كذلك تضمنت الدراسة ١٢ رجلاً و ١٠ نساء من الاصحاء كمجموعة سيطرة. تم تقييم اختبارات الوظيفة الكلوية (يوريا الدم، كرياتينين المصل، ومعدل الترشيح الكبيبي) وتحديد مستوى الهرمونات التكاثرية (الهرمون اللوتيني، الهرمون المحفز للجريب، والبرولاكتين) في الرجال والنساء، والتستوستيرون والاستراديول في الرجال والنساء على التوالي. كذلك تمت دراسة علاقة الترابط بين مستوى هذه الهرمونات واختبارات الوظيفة الكلوية في المرضى. اظهرت نتائج اختبارات الوظيفة الكلوية ارتفاعاً معنوياً في تراكيز يوريا الدم وكرياتينين المصل وانخفاضاً معنوياً عالياً في قيمة معدل الترشيح الكبيبي عند المرضى مقارنة بمجموعة السيطرة. فيما يتعلق بمستوى الهرمونات التكاثرية، لم تكن هناك اختلافات معنوية في مستويات الهرمون اللوتيني، الهرمون المحفز للجريب، والتستوستيرون في المرضى الذكور والسيطرة الذكور، بينما كان مستوى البرولاكتين اعلى بصورة معنوية في المرضى الذكور مقارنة مع السيطرة الذكور. كذلك لم تكن هناك اختلافات معنوية في مستويات الهرمون اللوتيني، الهرمون المحفز للجريب، والاستراديول في المرضى الاناث والسيطرة الاناث، بينما كان مستوى