

Research Article

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Assessment of Serum Testosterone and Estradiol levels in a sample of Arab Pediatric Patients with Chronic Renal Failure

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Abstract

Background: The Testosterone and Estradiol sex hormones are susceptible to significant pathophysiological alterations in children with chronic renal failure under regular hemodialysis, leading to delayed pubertal maturation.

Aim of the work: is to evaluate the plasma levels of Testosterone and Estradiol hormones in children and adolescents with End Stage Renal Disease (ESRD) under regular haemodialysis.

Subjects and Methods: This study was carried out on 40 children with ESRD under regular hemodialysis. Forty children, age- and sex-matched were chosen and served as controls. All patients and controls were subjected to history taking, clinical examination, Pubertal assessment according to Tanner's classification, laboratory investigation: including measurements of plasma levels of follicular stimulating hormone (FSH) and luteinizing hormone (LH), serum total Testosterone levels in boys and serum Estradiol levels in girls.

Results: The mean values of weight, height, body mass index and mid arm circumference of patients group was significantly lower than that of control group. There were significantly lower FSH, LH, testosterone and estrogen levels in Group I compared with Group II. Mean FSH level was 1.36 ± 0.22 mIU/mL in Group I vs. 2.64 ± 0.81 mIU/mL in Group II with. Mean LH level was 0.98 ± 0.25 mIU/mL in Group I vs. 1.91 ± 0.42 mIU/mL in Group II. The mean total male serum testosterone level in the male patients group was 76.87 ± 36.53 mIU/mL in Group I vs. 232.23 ± 137.37 mIU/mL in Group II and mean estrogen level was 26.69 ± 21.59 pg/mL in Group I vs. 51.03 ± 26.50 pg/mL in Group II. There was significant positive correlations between the age development and the Tanner's stage development, male total serum Testosterone level and female serum Estradiol levels in both patients and control groups.

Keywords: Testosterone – Estradiol – Chronic Renal Failure - Children - Adolescents

Introduction:

Background:

Chronic renal failure (CRF) is used to describe a patient who has residual renal function of less than 30%, defined as progressive and irreversible deterioration in renal function; a situation in which recovery of renal function is not likely^[1].

The sex hormones are susceptible to pathophysiological alterations in chronic renal failure, which may lead to delayed or arrested pubertal maturation.^[1] These endocrine disorders result in growth failure^[2] and increase the difficulties of transition from childhood to adulthood^[3] and thus sexual dysfunction is followed.^[4] Puberty delay was reported in more than half of the girls and one third of boys with ESRD. Variable mechanisms were attributed to delayed puberty in these children^[1] including neuroendocrine impairment

in the pituitary gonadal axis, peripheral alterations due to uremia^[5], gonadal damage and impaired regulation of gonadotropin secretion.^[6]

The aim of the work: To evaluate the plasma level of Testosterone and Estradiol hormones in children and adolescents with chronic renal failure under regular haemodialysis.

Subjects and Methods:

Sample size & sampling

The sample size was calculated taking in consideration a significance level of 95%, power 80% and effect size 30%. Resulting in 86 children to be selected. A sample frame which consists of the files of all unit attendants who fulfill the selection criteria was con-

structured from which the target population were chosen randomly, where only 80 children participated in our study (Six patients refused to participate), then they were randomly allocated into two groups 1:1 (Dialysis group and a control group)

Measurement of total serum testosterone in adult men: Comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. J Clin Endocrinol Metab 89: 534-543.

This study was carried out upon 40 children and adolescents with ESRD under regular hemodialysis .Their ages ranged from 10-18 years with a mean value of 14.63 + 2.66 years. They were 20 males and 20 females who were attending the Pediatric Nephrology Unit of Pediatric Department of Tanta University Hospitals in the period from May 2015 to May 2016. Forty children, age- and sex-matched were chosen and served as controls (20 males and 20 females). The study was conducted after approval from the ethical committee of the Faculties of Medicine, Tanta University and informed written parental consents.

All patients were undergoing regular HD, Dialysis was started when GFR is equal or less than 15ml/min/1.73m³. three times per week, with each dialysis session lasting for three to four hours. Patients were dialyzed on Fresenius 4008- B dialysis machine (Germany) at blood flow rate = 2.5 x weight (kg) + 100ml/min., using polysulphane hollow fiber dialyzers suitable for the surface area of the patients (Fresenius F3 = 0.4 m², F4 = 0.7m², F5 = 1.0m² and F6 = 1.2m²). Bicarbonate dialysis solutions were used. All patients were receiving supportive therapy in the form of subcutaneous erythropoietin in a dose of 50 IU/Kg/session, IV iron dextran 100 mg/Kg/week, oral folic acid 1 mg/day, oral calcium 1000 mg/day, oral vitamin D (one alpha) in a dose of 0.01-0.05 µg/Kg/ day and oral antihypertensive medications for hypertensive patients.

Inclusion criteria: All children with ESRD and treated by regular maintenance haemodialysis.

Exclusion criteria: Patients of primary endocrinal diseases(e.g. Type 1 Diabetes mellitus) using drugs known to affect Testosterone or Estradiol hormone levels, Children who already get full puberty before onset of ESRD.

All patients and controls were subjected to:

Full history taking: including age and sex. Child's previous growth and development , the precise timing and sequence of the physical and behavior changes of puberty , timing of appearance of axillary and pubic hair ,onset of menarche (the onset of menstruation) for females and onset of first ejaculation for males .

Thorough clinical examination: including :

1. Anthropometric measurements: for assessment of nutritional and developmental status [7] which include:

-Weight: which was recorded with minimal clothing using electronic weight scale in Kilograms

-Height : Measuring the distance from the vertex to the base of the heel in centimeters by using a stadiometer in standing position

-Body mass index (BMI): which was calculated by Formula:

$$\text{BMI} = \text{weight (kg)} / [\text{height (m)}]^2 \quad . [8]$$

Mid arm circumference (MAC): Measurement of the circumference of the left upper arm at the mid-point between the tip of the shoulder (olecranon process) and the tip of the elbow (the acromion process) in centimeters

2. Vital signs: Especially arterial blood pressure which was measured by auscultatory method using a mercury sphygmomanometer, in the semi setting position after 10 minutes of rest, in the non fistula arm using an appropriate sized cuff and was taken as the mean value of 3 successive readings in 3 different days.

3. Pubertal assessment: Rating of genital development were assessed according to Tanner's classification [9] which assess:

In both sexes: Pubic and axillary hairs.

In male only:

-The length and width of the the left and right testicles was measured by metered tape.

- The stretched penile length in the flaccid state was measured with a rigid tape from the pubopenile skin junction to the top of the penis, excluding the prepuce under maximal but not painful extension.

-The penile circumference was measured at the base of the penis "close to the pubis" with a measuring tape.

-For obese males, the abdominal adipose tissue was shifted manually to one side to measure penile length and circumference). [10]

In females only:

- Bras are labeled with letter indicating the depth of the cups which cradle the breasts

- Breast volume measurement by using graduated cylinder and elevation and areola is determined. [11]

Puberty is preceded by adrenarche (the early appearance of axillary and pubic hair) between ages 6–10.. which can be transient and disappear before the onset of true puberty. [12]

On average, girls begin puberty at age's 10–11 years. and usually complete puberty by ages of 15–17, while boys begin puberty at ages of 11–12 years., and usually complete puberty by ages of 16–17 years. [13] Onset of menarche for females between ages of 12–13 years while onset of the first ejaculation for males at age of 13 years. [14]

Delayed puberty is defined as the absence of pubertal onset by the expected age or once puberty has commenced failure of appropriate progression. [15] Boys are considered to have delayed puberty if they reach the age of 13 years without evidence of pubertal changes. [16]

Laboratory investigation: including :

Complete Blood Count (CBC): by an automated analyzer .

Blood urea ,Blood Urea Nitrogen (BUN), and serum creatinine . Serum albumin and serum electrolytes (Ionized calcium , Potassium and Phosphorus).

Measurements of plasma levels of FSH and LH:to assess hypothalamic pituitary gonadal axis.

Measurements of Serum total Testosterone levels: in boys .

Measurements of Serum Estradiol levels: in girls .

Specimen collection and handling:

Venous blood morning samples were withdrawn just before dial-

ysis sessions.

5 ml of them were collected using sterile needles through gentle venipuncture of puncture site under complete aseptic technique. The collected samples were divided into the following fractions:

1. 2 ml which was put on 20 uL EDTA solution as anticoagulant for CBC including differential white blood cells count which was done on Leishman stained peripheral blood smear with evaluation using ERMA PCE-210 N cell-counter from Erma, Inc. Japan^[12].

2. 3 ml was put in a plain tube without adding anticoagulant to allow coagulation of the sample. It was put in a waterbath at 37oC. After coagulation, centrifugation was done at rate of 1500 x g for ten minutes. The separated serum was collected in a tube for the assessment of serum testosterone levels.^[17]

Measurements of plasma levels of FSH , LH and estradiol(in females): to assess hypothalamic pituitary gonadal axis

Separated serum was collected in a tube for assessment of FSH, LH, and estrogen serum levels. Samples were collected in puberty girls during the follicular phase of menstrual cycle (From the day 7 to the day 10 from last menstrual period to record the estrogen surge). Kit supplied by (TOSOH Bioscience)^[17]

Principle of the Assay

The AIA-PACK E2 is a competitive enzyme immunoassay, which is performed entirely within the AIA-PACK. Estradiol present in the test sample competes with enzyme- labeled estradiol for a limited number of binding sites on a estradiol-specific antibody immobilized on magnetic beads. The beads are washed to remove the unbound enzyme labeled estradiol and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme labeled estradiol that binds to the beads is inversely proportional to the estradiol concentration in the test sample. A standard curve using a range of known standard concentrations is constructed and unknown estradiol concentrations are calculated using this curve.

Incubation time: 10 minutes

Specimen vol 75 µl

Specimen type: Serum

Assay range: up to 3000 pg/ml

Calibration stability: 90 days

Sensitivity: 25 pg/ml^[17]

Serum total Testosterone levels: in boys.

Measurement of serum total Testosterone levels by Kit supplied by (TOSOH BIOSCIENCE) to assess androgen status of the subjects to distinguish eugonadal from hypogonadal. It included the circulating Testosterone in form of combination of free (unbound) circulating (2%), albumin bound (54%) and sex hormone binding globulin (SHBG) (44%) bound Testosterone. Bioavailable Testos-

terone is the free and albumin-bound Testosterone which is available to tissues for biological action. Serum Total Testosterone measurements in this study were performed by liquid chromatography tandem mass spectrometry in the morning as Testosterone levels exhibit biological variability due to episodic secretion from testes and circadian variation with peak concentrations in the morning.

Principle of the Assay

The ST AIA-PACK Testosterone is a competitive immunoenzymometric assay, which is performed entirely in the AIA-PACK. Testosterone present in the test sample competes with enzyme labeled testosterone for a limited number of binding sites on the testosterone specific monoclonal antibody immobilized on a magnetic solid phase. The magnetic beads are washed to remove unbound enzyme-labeled testosterone and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme-labeled testosterone that binds to the beads is inversely proportional to the testosterone concentration in the test sample. A standard curve is constructed, and unknown sample concentrations are calculated using this curve.

Incubation time: 10 minutes

Specimen volume 70 µl

Specimen type: Serum

Assay range: up to 2200 ng/dl

Calibration stability: 90 days

Sensitivity: 7 ng/dl^[17]

Statistical Methods

Statistical package for social science (SPSS) version 18.0 was used for analysis of data. Normally distributed data was mentioned as mean+standard deviation. For non-normally distributed variable, range and mean were used. Parametric test for analysis was used as student t test. Non-parametric test (Mann-Whitney) was used for analysis of 2 independent quantitative variables. Pearson's correlation was also done where the r value was considered weak if < 0.25, mild if > 0.25 - < 0.5, moderate if > 0.5 - < 0.75 and strong if > 0.75. P value was considered significant if < 0.05.^[18]

Results

Table (1) summarize demographic data of the studied patients and control groups as regard age , sex, weight

The age ranged from 10-18 years with mean 14.63 + 2.66 in patients group and 14.25+2.64 in control group. Duration of dialysis in patients group ranged from 13-144 months with mean 57.15 +37.18. The mean values of anthropometric measurements including weight, height, body mass index and mid arm circumference of patients group was significantly lower than that of control group. Both systolic and diastolic blood pressures of the patients group were significantly higher than that in control group. (P < 0.05).

Table (1): Demographic data of the studied patients and control groups.

		Patients	Control	T. test	P. value
Age (years)	Range	10 – 18	10 – 18	0.200	0.657
	Mean ± SD	14.63 ± 2.66	14.25 ± 2.64		
Sex	Male (%)	20 (50%)	20 (50%)	X ² =0.0	1.0
	Female (%)	20 (50%)	20 (50%)		
Duration of dialysis (months)	Range	13 – 144	-	-	-
	Mean ± SD	57.15 ± 37.18	-	-	-
Weight (kg)	Range	20 – 55	35 – 78	25.146	0.001*
	Mean ± SD	36.43 ± 10.51	54.85 ± 12.63		
Height (cm)	Range	102 – 162	141 – 180	14.561	0.001*
	Mean ± SD	137.75 ± 17.86	156.75 ± 11.03		
Body Mass Index	Range	13.6 – 32.6	17 – 31	4.664	0.037*
	Mean ± SD	19.14 ± 4.68	21.91 ± 3.31		
Mid Arm Circumference (cm)	Range	13 – 26	21 – 30	33.403	0.001*
	Mean ± SD	19.75 ± 3.71	25.55 ± 2.52		
Systolic blood pressure (mm Hg)	Range	120 – 160	100 – 130	17.366	0.001*
	Mean ± SD	139.25 ± 10.04	114.50 ± 7.59		
Diastolic blood pressure (mm Hg)	Range	80 – 110	60 – 80	20.829	0.001*
	Mean ± SD	95.5 ± 7.42	74 ± 5.98		

X² Chi square test
P. Value < 0.05 significant

Table (2) Summarize routine laboratory data of the studied patients and control groups ,there was significant increase in levels of Blood urea, BUN, Serum creatinine Serum Potassium and serum Phosphorus levels in patients group when compared to control group. (P < 0.05).

Table (2): Investigations of the cases group and the control group..

		Cases	Control	T. test	P. value
Blood Urea (mg/dl)	Range	100.8 – 257	21.7 – 36.7	53.710	0.001*
	Mean ± SD	168.33 ± 50.03	28.99 ± 4.84		
Serum Creatinine (mg/dl)	Range	4.9 – 10.3	0.5 – 1.4	87.349	0.001*
	Mean ± SD	7.76 ± 1.53	0.91 ± 0.27		
BUN (mg/dl)	Range	45 – 115	9.6 – 16.3	59.093	0.001*
	Mean ± SD	76.01 ± 22.30	12.81 ± 2.19		
HB (g/dl)	Range	7.2 – 12.4	11.2 – 13.9	46.311	0.001*
	Mean ± SD	10.45 ± 1.44	12.84 ± 0.74		
HCT %	Range	21.5 – 37.9	33.6 – 42	37.711	0.001*
	Mean ± SD	31.61 ± 4.48	38.37 ± 2.31		
PLT ×1000/cmm	Range	133 – 414	250 – 435	39.727	0.001*
	Mean ± SD	223.05 ± 81.65	357.90 ± 49.89		
WBC ×1000/cmm	Range	3.4 – 9.1	4.1 – 12.5	4.575	0.039*
	Mean ± SD	5.74 ± 1.77	7.05 ± 2.08		
Serum Albumin (g/dl)	Range	2.8 – 4.6	3.6 – 5.5	19.727	0.001*
	Mean ± SD	3.69 ± 0.54	4.52 ± 0.64		
Serum Ionized Ca (mg/dl)	Range	2.44 – 5.2	4.2 – 5.5	21.671	0.007*
	Mean ± SD	4.08 ± 0.69	4.89 ± 0.36		
Serum K (mmol/l)	Range	3.5 – 6.1	3.5 – 5.2	20.841	0.001*
	Mean ± SD	5.14 ± 0.74	4.22 ± 0.52		
Serum P (mg/dl)	Range	4.2 – 8.8	3.5 – 6.1	18.390	0.001*
	Mean ± SD	5.95 ± 1.03	4.71 ± 0.77		

P. Value < 0.05 significant

HB haemoglobin % HCT Hematocrite value
 PLT Platelet count BUN blood urea nitrogen
 Ca calcium P phosphorus
 K potassium

But there was significant decrease in levels of hemoglobin percent, hematocrit values, platelet count total leucocytic count/White blood cells count, serum Albumin and Serum Ionized Calcium in patients group when compared to control group. (P < 0.05).

Table (3) and figure (1) show no statistically significant difference between the patients and the control groups as regard Tanner's stage development (P > 0.05).

Table (3) : Tanner's stage distribution between the patients and control groups.

Tanner's stage		Patients	Controls	Total
I	N	10	10	20
	%	25.0%	25.0%	25.0%
II	N	14	8	22
	%	35.0%	20.0%	27.5%
III	N	10	10	20
	%	25.0%	25.0%	25.0%
IV	N	4	8	12
	%	10.0%	20.0%	15.0%
V	N	2	4	6
	%	5.0%	10.0%	7.5%
Total	N	40	40	80
	%	100.0%	100.0%	100.0%
Chi-square test	X ²	1.818		
	P-value	0.769		

P. Value < 0.05 significant

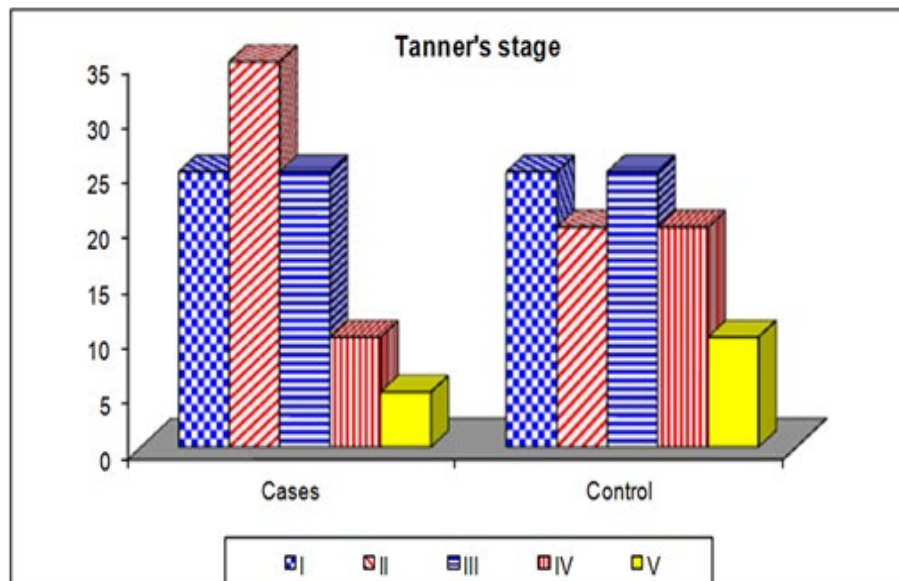


Figure 1 : Tanner staging of the studied groups.

Table (4) clarifies Serum levels of sex hormones in the studied patients and control groups , the total male serum testosterone level in the male patients group was significantly lower than that in the male control group .The female serum estradiol level in the female patients group was significantly lower than that in the female control group ($P < 0.05$). There were significantly lower serum FSH, LH, and estrogen levels in Group I compared with Group II. Mean FSH level was 1.36 ± 0.22 mIU/mL in Group I vs. 2.64 ± 0.81 mIU/MI in Group II with a p value of 0.021. Mean LH level was 0.11 ± 0.006 mIU/mL in Group I vs. 1.78 ± 1.12 mIU/mL in Group II with p value of 0.003.78

Table (4): Serum levels of sex hormones in the studied patients and control groups.

		Patients	Control	T. test	P. value
Serum total male Testosterone (ng/dl)	Range	1.17 – 172.50	2.1 – 614.3	4.465	0.042*
	Mean \pm SD	76.87 ± 36.53	232.23 ± 137.37		
Serum female Estradiol (pg/ml)	Range	1.1 – 57.2	2.7 – 74.6	5.071	0.037*
	Mean \pm SD	26.69 ± 21.59	51.03 ± 26.50		
Serum FSH (mIU/ml)	Range	0.4– 1.68	1.9 – 3.8	3.882	0.029*
	Mean \pm SD	1.36 ± 0.22	2.64 ± 0.81		
Serum LH (mIU/ml)	Range	0.44– 1.5	0.99– 3.6	3.114	0.016*
	Mean \pm SD	0.98 ± 0.25	1.91 ± 0.42		

P. Value < 0.05 significant

Table (5) shows that there was significant positive correlations between the age development and the Tanner’s stage development in both the patients group where (P value = 0.001) (figure 2), and the control group (P value = 0.001), but less significant in cases group.

Table (5): Correlation between the age development and Tanner’s stage development and serum sex hormones levels in both the patents and the control groups.

Correlation with	Age development			
	Patients group		Control group	
	r	p	r	p
Tanner Stage	0.838	0.001*	0.959	0.001*
Male testosterone (ng/dl)	0.765	0.010*	0.851	0.002*
Female Estradiol (pg/ml)	0.947	0.001*	0.938	0.001*

P. Value < 0.05 significant.

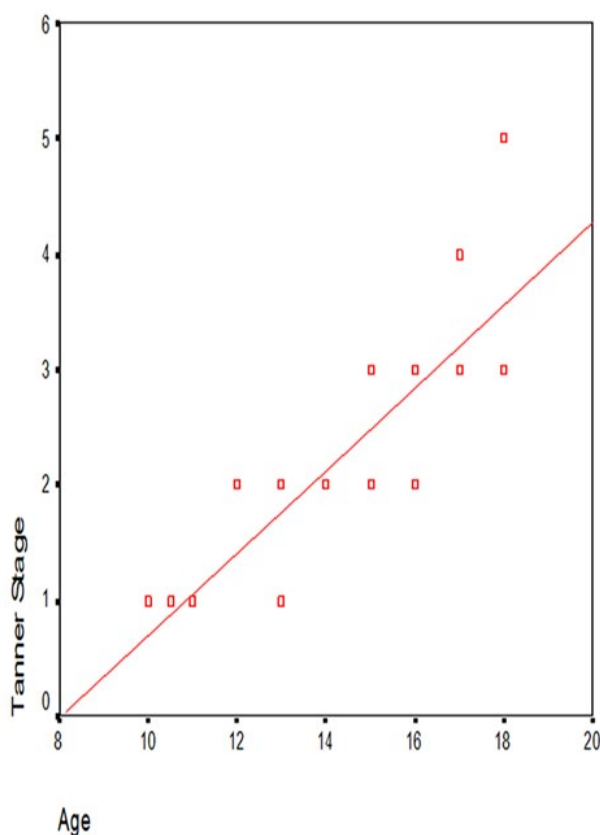


Figure 2: Correlation between ages and Tanner stages of patients.

Also there was significant positive correlation between the age development and male total serum Testosterone level in both male patients group (P value = 0.01) (figure 3), and male control group where (P value = 0.002) but less significant in patients group.

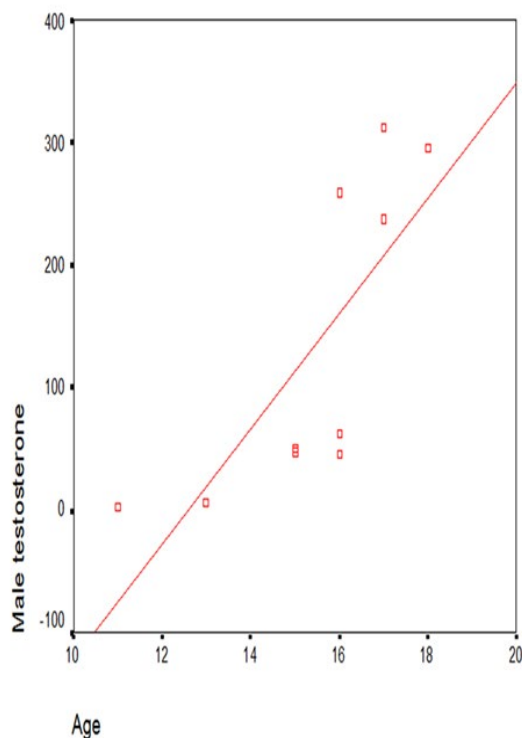


Figure 3: Correlation between ages and serum testosterone of the studied patients

There was also significant positive correlation between the age development and female serum Estradiol level in both female patients group (P value = 0.001)(figure (4), and female control group (P value = 0.001) but less significant in cases group.

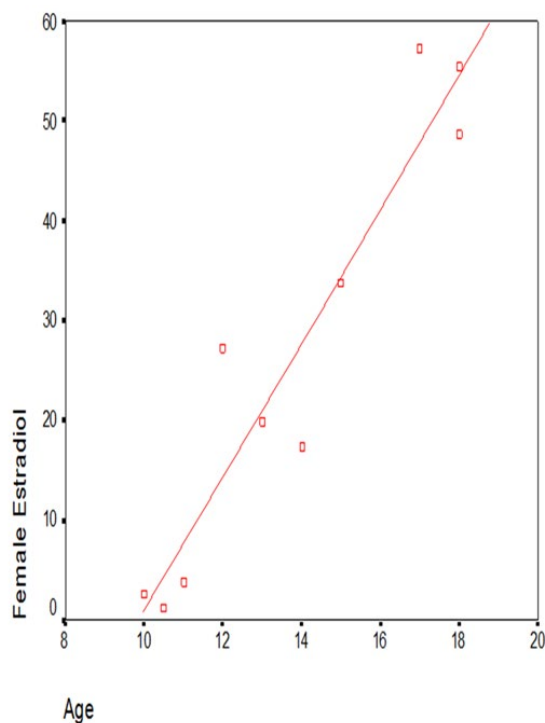


Figure 4: Correlation between ages and serum estradiol of the studied patients

Discussion

Pubertal development is frequently delayed or disordered in children with chronic renal failure. Both neuroendocrine and peripheral alterations due to uremia have been hypothesized to explain the impairment in the pituitary gonadal axis^[5].

Furthermore, CRF was found to be associated with gonadal damage and decreased Testosterone and Estradiol levels together with impaired regulation of gonadotropin secretion.^[19]

In the present study laboratory assessment of sex hormones (Testosterone and Estradiol) was done in order to assess gonadal dysfunctions in ESRD children and adolescence on regular hemodialysis therapy.

In pediatric patients with CRF, only a few studies have been performed to evaluate the status of the hypothalamo-pituitary-gonadal axis. Most of these deal with the endocrine changes that occur during adolescence. The problem is unsolved if in CRF hormonal alterations comparable to those of adult patients occur before the onset of puberty or not.^[5]

As far as clinical pubertal assessment of the studied ESRD patients was concerned, delayed pubertal development was found among them. This is in agreement with Giusti et al., 1993, Harold et al 1983 and Castellano et al., 1993 who stated that pubertal progression occurs in dialyzed uremic children, although it is delayed for chronological age.^{[5], [20], [21]}

Sexual dysfunction is common in adolescents with ESRD.^[4] Disturbances of pubertal development are commonly encountered in adolescent patients with chronic renal failure.^[22]

Delayed puberty is also a common finding with CRF, half of the girls and one third of boys with CRF reach sexual maturity later than 95% of the normal population.^[23]

The onset of puberty is usually delayed in adolescents with CKD. At least 50% of adolescents with end-stage renal disease (ESRD) enter puberty later than the normal range and achieve the pubertal milestones beyond the normal age range.^[24]

Late puberty is observed both in children on dialysis and after renal transplantation. In the Cooperative Study for Pubertal Development in CKD the onset of puberty was delayed by 2–2.5 years on average.^[25]

The start of genital maturation was delayed by 1.8 years in uremic and 2.5 years in transplanted boys. Full genital maturation was achieved with a delay of 2.2 and 3.2 years respectively. Thus, once started, puberty appears to proceed at a normal rate. However, in individual patients, particularly on long term dialysis, pubertal maturation may arrest for years. Almost half of the girls treated by dialysis or renal transplantation fail to menstruate before the upper normal age limit of 15 years. Menarche even tends to occur later in transplanted than in dialyzed girls.^[26]

Unlike the development of secondary sexual characteristics, which is delayed but not permanently halted in CKD, reproductive function may be permanently impaired.^[27] These changes do not appear reversible after renal transplantation.^[28]

In the current study, serum levels of LH, FSH, were significantly

lower in Group I compared with Group II. These findings may be explained by uremic deposition in secretory cell of endocrine glands such as gonadotrophin cell of the pituitary gland that leads to the impairment of gonadal hormone secretion including FSH and LH. In our study serum testosterone and estradiol levels was found significantly lower in patients than in controls, which was in agreement with Giusti et al., 1993 and Oertel et al., who stated that testosterone and estradiol levels were lower in cases of CRF with or without dialysis.^{[5], [22]}

Low plasma testosterone and estradiol levels was reported in boys and girls with chronic renal failure.^[29]

In male children with renal failure, plasma testosterone levels are decreased or in the low normal range.^[30]

In 1999, Palmer suggested that hypogonadism and low testosterone and estradiol levels (which agrees with our findings), may be caused by primary gonadal damage, presence of circulating LH receptor inhibitor that might contribute to gonadal-cell resistance and impaired feedback mechanism at the hypothalamic pituitary level, in addition to presence of hyperprolactinemia.^[19]

Secondary gonadal failure due to siderosis of the pituitary gland or primary gonadal failure due to iron deposition in testes and ovaries due to repeated blood transfusion and iron overload.^[31]

In adults with CKD plasma concentrations of testosterone (T) and Estradiol (E2) are usually low or low normal, due to reduced synthesis and, perhaps, increased metabolic clearance rate.^[32]

In prepubertal children with predialytic renal failure, low total and free T and dihydrotestosterone (DHT) plasma concentrations have been reported.^[22] However, since the adrenal cortex is the major site of androgen production before puberty and specific adrenal androgens are also low in children with CKD.^[33] Low prepubertal plasma androgen levels do not provide evidence for gonadal damage before puberty.^[34] In pubertal patients, normal or slightly subnormal plasma Testosterone concentrations are observed.^[35] In late puberty, however, DHT concentrations are significantly reduced in children with CKD compared with healthy or posttransplanted children. Impaired conversion of T to DHT due to decreased 5-reductase activity has been suggested.^[36]

Estradiol plasma concentrations in the low normal range are observed in females with CKD.^[37]

In pubertal girls with CKD, estradiol plasma levels were normal or low when related to pubertal stage.^[38]

An inverse correlation between serum creatinine levels and estradiol concentrations was found in patients with predialytic CKD.^[2]

Palmer, 1999 stated that disturbances in pituitary-gonadal axis rarely normalize with initiation of hemodialysis or peritoneal dialysis, moreover, they may progress that matching with our study. This was explained by him that plasticizers in dialysis tubing, such as phytate may play a role in propagating the abnormalities in pituitary-gonadal axis.^[19]

Also Schmidt et al., 2002 stated that impairment of hypothalamo-pituitary-gonadal axis is not reversed by initiation of otherwise effective hemodialysis or peritoneal dialysis therapy.^[30]

Growth parameters were evaluated in the current study revealing that all Anthropometric measurements (Weight, Height, body mass index and mid arm circumference) were significant low in all patients if compared with normal children and adolescents.

These results are supportive of data from multiple centers showing that children with a history of ESRD have poor growth and low BMI compared with children in general population. [39][40][41]

These changes are associated with alteration in body composition. Both primary retention of uremic toxins and the resulting metabolic and hormonal changes may play a role. [42]

The height gain achieved during the pubertal growth spurt is usually reduced. In a longitudinal analysis of the growth curves of 29 adolescents with various degrees of CKD, the growth spurt started with an average delay of 2.5 years. [35] The degree of the delay was correlated with the duration of uremia. Although a distinct acceleration of growth during puberty occurred, the total pubertal height gain was reduced in both sexes to approximately 50% of normal maturing children. This reduction was due to a marked suppression of the late prespurt height velocity, a subnormal peak height velocity, and a shortening of the pubertal growth period by 1 year in boys and 1.5 years in girls. Notably, the prolonged prepubertal growth phase, resulting from the delayed onset of the pubertal growth spurt. [23]

The pathogenesis of growth failure in children with ESRD is clearly multifactorial but recent research by Wong et al., 2000 who has shown that endocrine-related factors might be largely responsible for growth impairment in these children with renal failure. [41]

Growth failure in CKD has been associated with both increased morbidity and mortality. Growth failure in the setting of kidney disease is multifactorial and is related to poor nutritional status as well as comorbidities, such as anemia, bone and mineral disorders, and alterations in hormonal responses, as well as to aspects of treatment such as steroid exposure [43].

The patients in our study exhibit significant low Hb % and Hct. This was in agreement with Harmon and Jabs, 1998 who reported that CRF was followed by renal anemia which has been contributed to several factors as erythropoietin deficiency, decrease erythrocyte survival and increase blood loss. [44]

Chatterjee et al., 2000 explained the association of anemia with disturbed hypothalamo-pituitary-gonadal axis by presence of some metabolic factors including chronic ill health, chronic hypoxia, underweight and low body mass index. In addition, iron overload due to repeated blood transfusion may cause secondary gonadal failure due to siderosis of the pituitary gland or primary gonadal failure due to iron deposition in testes and ovaries. [30] This significant correlation indicates the importance of correcting anemia for a normal pubertal development.

Limitation of this study are small sized sample and non measurement of serum prolactin hormone in our included children.

Conclusions

The pubertal development of children and adolescents with ESRD is usually delayed as proven by decreased serum male total testosterone and female Estradiol hormones levels which suggest a

state of hypogonadism. Nutritional therapy especially optimizing protein intake to prevent hypoproteinemia, adequate dialysis and correction of anemia are clinical trials of controversy and worthy of considering to optimize pubertal development until these patients are transplanted.

Our home message was to highlight effects of hemodialysis on gonadal hormone levels and sexual function of children and adolescents with ESRD.

Recommendations

It is necessary to regularly follow up children with ESRD for early detection of endocrinal complications to improve their quality of life. Improving the efficiency of dialysis play a role in improving sexual function and normalization of sex hormones levels. Improving nutritional status help these patients to attain normal pubertal growth. Keeping Hb level within normal is recommended for normal pubertal development. Patients with delayed puberty in need to be further investigated to measure follicular stimulating hormone (FSH) and Luteinizing hormone (LH) to assess hypothalamic pituitary gonadal axis.

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