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Assessment of Pubertal Status in Children and Adolescents with End-Stage Renal Disease on Hemodialysis

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ABSTRACT

Background: Hormonal dysregulation caused by renal dysfunctions and associated pathophysiological pathways, particularly hemodialysis, will naturally cause growth anomalies and even postpone puberty in adolescents. **Objective:** The aim of the current study was to determine the relationship between serum testosterone and estradiol levels and pubertal development in children and adolescents with end-stage renal disease (ESRD) who receive regular hemodialysis. **Patients and methods:** A case control study was conducted at the Pediatric Nephrology Department and Out-patient Clinics of Zagazig University Children Hospital. The study included 54 participants divided into two groups; 27 Children and adolescents with chronic hemodialysis for ESRD who was identified from the juvenile nephrology unit at the hospital and 27 healthy children and adolescents. All participants underwent a full history taking process, clinical examination, pubertal assessment using Tanner staging, routine laboratory testing, in addition to throughout the course of the trial, serum levels of girls' and boys' estradiol and total testosterone were measured. **Results:** Delayed puberty according to age development was found among ESRD patients by Tanner staging. Patients' weight and height were significant lower in ESRD when compared to control group. Total testosterone in ESRD males and serum estradiol in ESRD females were significant low in comparison to controls and were associated with tanner staging. **Conclusion:** When compared to the general population, children with ESRD receiving regular hemodialysis experience significant impairments in pubertal growth and sexual maturation. Pubertal development is typically postponed, as demonstrated by lower serum levels of the hormones male testosterone and female estradiol.

Keywords: *Testosterone, Estradiol, Children, Hemodialysis, Case control study, Zagazig University.*

INTRODUCTION

The clinical condition known as chronic kidney disease (CKD) is characterized by a long-term, gradual deterioration in kidney function. For example, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines describe CKD as abnormalities in the structure or function of the kidneys that have existed for >3 months and have a negative impact on health. End-stage renal disease (ESRD), which affects 5–10 children per million annually, is a serious health issue for kids. Hemodialysis is the most widely used type of medications to replace the kidneys in this sickness. ESRD patients typically die from cardiovascular problems rather than renal illness **(1).**

While adolescence is the period from puberty until full maturity, puberty is the time when the reproductive organs begin to function. Puberty begins when gonadotropin-releasing hormone production and secretion rise in the hypothalamus and it is transported to the anterior pituitary's gonadotrophs. Pulsatile gonadotropin-releasing hormone, which in turn regulates ovarian and testicular activities, causes the gonadotrophs to secrete luteinizing hormone and follicle-stimulating hormone **(2)**.

Chronic renal failure can cause pathophysiological changes in the sex hormones that might delay or block pubertal maturation. Over 50% of the girls had evidence of pubertal axis delay and one-third of the boys with ESRD, as these endocrine diseases cause the difficulties of the transition from childhood to adulthood are made more difficult by growth failure. These kids' delayed puberty was attributed to a number of reasons, including neuroendocrine dysfunction in the pituitary-gonadal, peripheral changes brought on by uremia, gonadal injury, and poor control of gonadotropin secretion **(3).**

CKD is linked to a change in sex hormones. Teenagers and adults with chronic uremia have been found to have total and free blood levels of testosterone and dihydrotestosterone that are low or low to normal as a result of decreased production and/or increased metabolic clearance. Reduced testosterone conversion to dihydrotestosterone as a result of decreased 5- reductase activity may be the reason of the delayed pubertal development observed in some dialysis patients. Similar to how glomerular filtration rate (GFR) declines in tandem with serum estradiol levels in females, some teenage girls exhibit serum estradiol levels that are low to normal or dropping in proportion to pubertal age **(4).**

The aim of the current study was to measure the levels of blood testosterone and serum estradiol in children and adolescents with ESRD who get regular hemodialysis and the relation between serum testosterone and estradiol levels and pubertal development.

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PATIENTS AND METHODS

A case control study was conducted at the Pediatric Nephrology Department and Out-patient Clinics of Zagazig University Children Hospital, from July 2022 to January 2023. The study included 54 participants, between the ages of 10-18 years old, divided into two groups; 27 Children and adolescents with chronic hemodialysis for ESRD who was identified from the juvenile nephrology unit at the hospital and 27 healthy children and adolescents.

Inclusion criteria: Children and adolescents aged from 10 to 18 years with ESRD on regular maintenance hemodialysis (3 days a week, each session lasted for 3 to 4 hours) for a year at least. Both sexes (males and females) are included.

Exclusion criteria: Primary endocrinal diseases (e.g. type 1 diabetes mellitus), Cases involving drugs that affect the levels of sex hormones. Children who reached puberty and had ESRD before they did.

All patients and controls underwent a clinical examination, including anthropometric measurements, and history taking. A stadiometer was used to measure height while the subject was standing and Weight of the children and adolescents (in kilograms) having only the barest of garments on, the patient was standing. For the dialysis group of children, using a mercury sphygmomanometer and the auscultatory method, arterial blood pressure was measured and ratings of genital development were evaluated in accordance with Tanner's classification.

Complete blood count (CBC), kidney function tests, blood urea, and serum creatinine (mg/dl) are all included in laboratory investigations. Electrolytes, including serum calcium (mg/dl), potassium (mmol/l), sodium (mmol/l), and magnesium (serum) (mg/dl), Serum phosphorus(mg/dl)]. 25OH vit D.

Investigation of sex hormones Basal venous blood early morning samples in fasting condition before dialysis to avoid circadian variation were examined for Serum levels of testosterone in men and estradiol in women. Venous blood samples from both patients and controls were taken. Separated and stored serum at -18°C for analysis.

Ethics Approval:

This study was ethically approved by the Institutional Review Board (IRB # 9556) of the Faculty of Medicine, Zagazig University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS IBM Corp., Armonk, NY: USA) version 23.0 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean, standard deviation (SD) and range. For two groups, independent sample t-test was used for detection of difference between different quantitative variables normally distributed, while nonparametric data was evaluated with Mann-Whitney U test. Spearman's correlation coefficient has been used to evaluate correlations. P value ≤0.05 was considered to be statistically significant.

RESULTS

Table 1 shows that there was no significant difference between diseased group and control group regarding age and sex distribution (P>0.05).

Table (1): Demographic characteristics of the studied groups.

Parameters	ESRD group (n. 27)	Control group (n. 27)	t	P-value
Age per years Mean ± SD Median (range)	13.3 ± 2.2 14 (10-17)	13.92 ± 2.5 14 (10-18)	0.93	0.36
Sex Males Females	16 (59.3%) 11 (40.7%)	14 (51.8%) 13 (48.2%)	**χ 2** 0.3	0.58

t: test of significance. χ2: Chi-square test of significance. P>0.05 insignificant. P<0.05 significant.

Table 2 showed that there was a considerable difference between the groups that were being evaluated, and Tanner 1 participants all belonged to the sick group to none in the control group where regarding tanner 4, 12 participants belonged to the control group and only 5 participants belonged to the patient group.

Table (2): Tanner in both groups.

Parameters	ESRD group (n. 27)	Healthy control (n. 27)	χ2	P-value
Tanner 1	9 (33.3%)	0 (0%)	F	0.002*
Tanner 2	10 (37%)	12 (44.4%)	0.307	0.58
Tanner 3	3 (11.1%)	3 (11.1%)	-	-
Tanner 4	5 (18.6%)	12 (44.4%)	4.2	0.04*

F= Fisher Exact test, χ2 Chi square test, P>0.05 insignificant, *P<0.05 significant, Disease group (ESRD): End-Stage Renal Disease on Hemodialysis.

Table 3 showed that there was significant decrease in testicular volume and serum testosterone hormone level in ESRD group when compared to control group (P<0.05).

Table (3): Testicular volume and testosterone hormone of males in both groups.

Parameters	ESRD group (n. 16)	Control group (n. 14)	P-value
Testicular volume (ml) Mean ± SD	5.2 ± 1.1	13.5 ± 3.1	0.004*
Testosterone hormone (pg/ml) Mean ± SD	2.1 ± 0.15	4.9 ± 0.8	0.001*

SD: Standard deviation, P>0.05 insignificant, *P<0.05 significant.

Table 4 showed that there was significant difference in serum estradiol level in ESRD group when compared to the control group (P<0.05). Also there was significant difference between the two groups as regards onset of menarche; also there was a significant increase in serum estradiol level in ESRD group in females with menarche when compared with those with no menarche.

Table (4): Females in both groups as regards menarche and estradiol level.

Menarche and estradiol level	ESRD group (n. 11)	Control group (n. 13)	T	P-value
Menarche Yes No	5 (45.5%) 6 (54.5%)	13 (100%) 0 (0%)	F	0.003*
Onset menarche Mean ± SD	n.5 12.2 ± 1.9	n.13 11.1 ± 0.99	t 1.5	0.14
Estradiol (ng/ml) Mean ± SD	22.8 ± 4.1	39.6 ± 5.2	U 3.3	0.001*
ESRD groups	**ESRD group females (n. 11)**		**U**	**P-value**
	Menarche (n. 5)	**No Menarche (n. 6)**		
Estradiol (ng/ml) Mean ± SD Median (range)	26.2 ± 5.2	19.9 ± 4.4	11.4	0.003

SD: Standard deviation, t: t test of significance, U: Mann-Whitney U test of significance, F: Fisher's exact test, P>0.05 insignificant, *P<0.05 significant. Disease group (ESRD): End-Stage Renal Disease on Hemodialysis.

Table 5 showed that there was significant, lower value of vitamin D in ESRD females who had menarche compared to healthy control children (P<0.05). While there is no significant difference between ESRD females whose menarche not occurred compared to healthy control children (P>0.05).

Table (5): Vitamin D in studied females.

Parameters	ESRD group females (n. 11)		Control group females (n. 13)	U	P-value
	Menarche (n. 5)	No menarche (n. 6)			
25 OH Vitamin D (ng/ml) Mean ± SD	19.5±3.1	25.4±3.8	34.06±6.7	8.9	0.012*

U: Mann-Whitney U test of significance, *P<0.05 significant, P>0.05 no significant.

Table 6 showed that there was positive correlation between Testosterone level and weight, Z score of weight, height, mid arm circumference, age, duration of disease, testicular volume, in renal dialysis males, however no correlation was found between testosterone level and other parameters.

Table (6): Correlation between (Testosterone) and age, anthropometric measures, Vitamin D, duration of disease, duration of dialysis session Testicular volume of males with renal dialysis and healthy males

Variables	males with renal dialysis Testosterone (n. 16)	
	R	P-value
Renal Dialysis		
Age (years)	0.695**	0.003
Weight (kg)	0.840**	0.0001
Z score weight	0.511*	0.043
Height (cm)	0.696**	0.003
Z score height	0.295	0.267
Mid arm circumference (cm)	0.758**	0.001
BMI (kg/m2)	0.333	0.207
z score	0.196	0.466
25 OH Vitamin D (ng/ml)	-0.086	0.752
Duration of disease (years)	0.548*	0.028
Duration session (hours)	-0.096	0.725
Testicular volume (ml)	0.690**	0.003
Healthy Males		
Age (years)	0.703**	0.005
Weight (kg)	0.583*	0.029
Z score weight	0.627*	0.016
Height (cm)	0.695**	0.006
Z score height	0.169	0.563
Mid arm circumference (cm)	0.389	0.169
BMI (kg/m^2)	0.36	0.22
z score	-0.491	0.075
25OH Vitamin D (ng/ml)	0.224	0.441
Testicular volume (ml)	0.566*	0.035

(r) Correlation coefficient ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Table 7 showed that there was positive correlation between Estradiol level and age, weight, Z score of weight, height, Z score of height, mid arm circumference, vitamin D, in renal dialysis females, however no correlation was found between estradiol level and other parameters.

Table (7): Correlation between Estradiol level and age, anthropometric measures, Vitamin D, in renal dialysis females and healthy females.

Variables	Females with renal dialysis Estradiol (n. 11)	
	R	P-value
Renal Dialysis Females		
Age (years)	0.581	0.049
Weight (kg)	0.721*	0.012
Z score of weight	0.672*	0.023
Height (cm)	0.758**	0.007
Z score of height	0.192	0.573
Mid arm circumference (cm)	0.824**	0.002
BMI (kg/m2)	0.314	0.346
z score	0.149	0.663
Duration of disease (years)	0.493	0.123
Duration of session (hours)	-0.209	0.538
25 OH Vitamin D (ng/ml)	-0.2	0.555
Healthy Females		
Age (years)	0.666*	0.013
Weight (kg)	0.536	0.047
Z score of weight	0.206	0.499
Height (cm)	0.748**	0.003
Z score of height	0.620*	0.024
Mid arm circumference (cm)	0.639*	0.019
BMI (kg/m2)	0.418	0.156
z score	0.024	0.938
25 OH Vitamin D (ng/ml)	0.555*	0.046

(r) Correlation coefficient ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

In our research according to the included patients' demographics, the majority of ESRD patients were men, with an average age of 13.3 (SD 2.2). This is in agreement with **Clavé *et al.*** [5] who looked into teenagers who had hemodialysis at French pediatric centers and found that their average age was 13.9 years old and that they were mostly male. Additionally, they found that the mean ages of patients with CKD and ESRD were 12.74 and 12.85 years old, respectively. Male patients made up the bulk of both categories of patients. This male predominance can be related to the higher prevalence of congenital renal disorders in males [6].

In our study as regards tanner staging compared to the standard group, which included every patient in Tanner 1's patient group; there was a substantial difference to none in the regarding tanner 4, 12 participant belonged to patient group.

This is in agreement with **Soliman *et al.*** [7] found that pubertal development was delayed in CKD patients who examined the child and adolescent gonadal dysfunction with regular hemodialysis. Tanner stage I patients (22 patients, 39%; 12 patients, 22%; respectively) were included in the patient group. Tanner stage 1 is not contained in any controls. Stage 3 tanner patients made up the final 22 cases. On Tanner's scale, none of the patients were in stages 4 or 5. The controls, nonetheless, all were Tanner stage 4 or 5 with the exception of 18, who were Tanner stage 3. This demonstrates unequivocally even while patients were still in stages 1 to 3 of Tanner, healthy youngsters proceeded to Tanner stages 4 and 5.

Also, **Ghobrial *et al.*** [6] revealed a statistically significant difference in the pubic stage, testicular stage, axillary stage, and breast stage between the patient and control groups. Comparing cases with ESRD to healthy controls, cases had considerably lower stages. Stages 1 or 2 of ESRD comprised the majority of patients.

Systolic and diastolic blood pressure was significantly higher in the study's ESRD group compared to the healthy control group. This is in agreement with **El-Gamasy *et al.*** [8] who noted that the patient group's systolic and blood pressure during the diastole was much higher than it was during the control group ($P<0.05$).

Also, with **Ghobrial *et al.*** [6] the CKD group had considerably greater than the group with ESRD in terms of systolic and diastolic blood pressure as well as ultrasound grade.

In our study, the ESRD group had lower serum levels of testosterone and estrogen than the controls group. This could be brought on by primary gonadal injury, the presence of circulating luteinizing hormone (LH) receptor inhibitor, which may increase gonadal-cell resistance, and a malfunctioning hypothalamic-pituitary level feedback loop [9]**.** This is in agreement with **Parasher *et al.*** [10] who discovered lower levels of serum testosterone and estrogen in CKD patients, indicating that the disease's progression may have a significant impact on these abnormal hormonal levels.

Similarly to **Haffner and Fischer** [11]**,** observed that certain teenage girls have low to normal or lowered estradiol levels in response to pubertal age, and that female plasma estradiol levels tend to decline in conjunction with GFR reduction.

Our results also agree with **Amirkashani *et al.*** [12] revealed a tight connection between postponed puberty and significant alterations in sexual hormones in CKD

patients, who had lower serum testosterone levels, and with **El-Gamasy** [13] who discovered that patients with chronic renal failure had significantly lower serum levels of testosterone and estrogen than controls.

In the current study there was a highly significant association between estradiol, testosterone level and pubertal stages among ESRD patient. Our results agree with **Amirkashani *et al.*** [12] who emphasized that renal failure could affect hormonal axes and puberty regulation because it can cause hormonal changes that are effectively associated with delayed puberty. Bidirectionally demonstrated a strong relationship between postponed puberty and important alterations in sexual hormones.

The pubertal growth phase is frequently delayed in children and adolescents with ESRD. Their levels of s. testosterone and s. estradiol are significantly below average, which causes a gradual delay in pubertal development and sexual maturation [7].

In our study as regards testicular volume there was a significant lower testicular volume and testosterone hormone level in ESRD group when compared to the control group. This agrees with **El-Gamasy** [13] who discovered that the testicular volume and the patient group's total testosterone serum levels were statistically considerably lower than those of the control and study groups ($P<0.05$).

As regards to onset of menarche, there was no significant difference between both groups. This is in agreement with **Kim *et al.*** [14] who discovered that girls with CKD and healthy girls have similar median ages at menarche. Up to 10% of CKD females experience delays in menarche and a potential for small stature.

On contrary to our findings, **Ghobrial *et al.*** [6] discovered that menarche age was considerably older in individuals with CKD and ESRD than in the control group.

CONCLUSION

Comparing children with ESRD on regular hemodialysis to the general population, pubertal growth and sexual maturation are significantly altered, and pubertal development is typically delayed as shown by lower serum levels of male testosterone and female estradiol hormones.

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- **Conflicts of interest:** There are no conflicts of interest, according to the authors.

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