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Sexual maturity of children on regular hemodialysis

Role of testosterone and estradiol, a tertiary multicenter experience

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Abstract

A big problem is the delayed growth and sexual maturity in children with chronic kidney disease (CKD) with the consequent reduction in adults' height. Testosterone and estradiol have significant physiologic changes in children suffering from CKD, resulting in delayed puberty. We aim to assess blood levels of these hormones in patients with CKD-5 on regular hemodialysis.

One hundred-six participants were enrolled in the current study, 56 of whom had CKD on hemodialysis 3 times a week 4 hours per session, and 60 healthy age- and gender-matched children acted as controls. Full history was taken, and a clinical review was performed on both patients and controls. The pubertal assessment was performed according to Tanner's classification and laboratory investigations of total and free serum (s.) testosterone in boys and s.estradiol in girls.

Patients' weight and height were considerably lower than controls. The free and total s.testosterone of patients were significantly reduced. The same applies to s.estradiol levels which were substantially reduced in comparison to controls. In both patients and controls, Tanner staging & male total s.testosterone levels and female s.estradiol levels had significant positive associations. There was a negative association between the sex hormones levels and the disease's and dialysis duration in the patients' group.

S.testosterone and s.estradiol levels were significantly low in CKD patients on dialysis and were positively correlated with delayed pubertal growth observed in those patients.

Abbreviations: CKD = chronic kidney disease, ESRD = end-stage renal disease, GFR = glomerular filtration rates = serum.

Keywords: children, chronic kidney disease, dialysis, estradiol, testosterone

1. Introduction

Chronic kidney disease (CKD) is a clinical state in which the kidney functions gradually deteriorate over time. The Kidney Disease Improving Global Outcomes guidelines, in particular, characterize CKD as abnormalities of kidney structure or function that have been present for more than 3 months and have a health effect. Childhood CKD has clinical characteristics that are unique to the pediatric age group, such as the disease's effect on development.[1] The onset of puberty is initiated following increased synthesis and secretion of gonadotropin-releasing hormone in the hypothalamus and its transport to gonadotrophs within the anterior pituitary. In response to pulsatile Gonadotropin-releasing hormone, the gonadotrophs secrete luteinizing hormone and follicle-stimulating hormone, which in turn regulate ovarian and testicular functions.[2]

CKD is associated with alteration in sex hormones. Low or low to normal, total and free s.testosterone and dihydrotestosterone due to decreased synthesis and/or increased metabolic clearance have been reported in adolescents and adults with long-standing uremia. Reduced testosterone conversion to dihydrotestosterone as a result of decreased 5-reductase activity may contribute to the delayed pubertal development observed in some dialysis patients. Similarly, s.estradiol levels in females tend to decrease in parallel with glomerular filtration rate (GFR) reduction, and some adolescent girls show low to normal or decreased s.estradiol levels in relation to pubertal age.[3]

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Ethical Approval and Consent to participate: the study was approved by the research and ethical committee of the participating hospitals. All parents of enrolled children signed written informed consents for the participation of their children in the current study.

All parents of enrolled children signed written informed consents for publication of the current study.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1.1. Study goal

The primary goal of the current study is to assess children and adolescent on maintenance hemodialysis for s.testosterone and s. estradiol levels and study their possible relation to pubertal development.

2. Patients & methods

A case-control study involving 106 children and adolescents was conducted. This was split into 2 categories: ***Group (I):*** fifty six children and teenagers (28 boys and 26 girls), ranging in age from 12 to 18 years, with end-stage renal disease (ESRD) and hemodialysis on a regular basis (3 days a week, each session lasted for 3 to 4 hours) in the Pediatric Nephrology units of the Benha Specialized Children Hospital, Benha University, Egypt, and Alhada Armed Forces Hospital, Taif, Saudi Arabia. Hemodialysis was initiated when the GFR was under 15 mL/min/1.73 m^3. Inclusion criteria: Participants must be 12 to 18 years old and have been on hemodialysis for a year at least. Both sexes were illegible. Exclusion criteria include; CKD patients with a primary endocrine disorder, such as diabetes mellitus, cases on medications that influence the sex hormones levels, and children who achieved full puberty before developing ESRD. ***Group (II):*** A comparison control group of 60 healthy children and adolescents (30 boys and 30 girls) of matched age.

The following assessments were conducted for all the study participants:

Full medical history including; age and sex, growth and developmental history, the precise timing and sequence of the physical changes of puberty, the timing of appearance of axillary and pubic hair, and the onset of menarche (the onset of menstruation) for females.

Thorough clinical examination, including anthropometric measurements to determine nutritional and developmental status, which include bodyweight recorded in kilograms while wearing minimum clothing and the height in centimeters which is measuring the distance from the vertex to the base of the heel in centimeters by using a stadiometer in standing position.

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

The pubertal assessment was assessed according to Tanner's classification[4] which assesses; in both sexes; pubic and axillary hairs. In male-only, the length and width of the left and right testicles were measured by metered tape. The extended penile length in the flaccid condition was measured using a stiff tape from the sub-penile skin junction to the apex of the penis, omitting the prepuce, while extending maximally but not painfully. The penile circumference was measured using a measuring tape at the base of the penis "near to the pubis." To evaluate penile length and circumference in obese individuals, the abdominal fat tissue was manually transferred to one side.[5]

Only in females, Bras are assigned a letter that corresponds to the depth of the cups that cradle the breasts. Breast volume is determined using a graduated cylinder, elevation, and areola.[6]

Adrenarche (the early emergence of axillary and pubic hair) occurs between the ages of 6 to 10 years and may be temporary, disappearing before the onset of genuine puberty.[7]

On average, girls start puberty between the ages of 10 and 11. Girls typically finish puberty between the ages of 15 to 17, whilst males begin puberty between the ages of 11 to 12 and typically complete puberty between the ages of 16 to 17.[8,9] Delayed puberty is described as the absence of pubertal onset at the typical age of 13 years in girls and 14 years in males, or the failure of puberty to continue normally after it has begun.[10,11]

Laboratory examination included; a complete blood count performed by mean of an automated analyzer, s.urea, s. electrolytes, s.creatinine, and s.testosterone levels total & free in males and s.estradiol levels in females.

3. Analytical statistics

SPSS version 16 software (SPSS Inc, Chicago, ILL Company) was used to tabulate and analyze the collected data. Quantitative data were expressed as means, standard deviations, medians, IQRs, and ranges, while categorical data were expressed as numbers and percentages. Categorical variables were analyzed using the Chi-Squared test or Fisher exact test. The Shapiro–Wilks test was used to check for normality in quantitative results, assuming normality at $P > .05$. The Student "t" test was used for comparing 2 separate groups of normally distributed variables. The Man–Whitney "U" test was used for analyzing non-parametric variables. For non-parametric variables, the Kruskal–Wallis test was used to check the differences between 3 independent variables. The correlation coefficient of Spearman has been used to assess correlations (rho). In this study, the agreed level of significance was P value $<.05$.

4. Results

Table 1 summarizes demographic data of studied patients and control groups as regard age, sex, and weight. In both groups, the age ranged between 12 and 18 years, with mean of 14.6 ± 2.3 years in patients and 14.7 ± 2.2 years in healthy children. Regarding the weight in (kilograms) & height (centimeters), the population with weight and height below 5th centile has been closely related to patients' group 43 (77%) & 41 (73%) versus

Table 1

Demographic and anthropometric characteristics of patients & controls.

		Patients N = 56	Control N = 60	Test	*P* value
Age (yr)	Range	12–18	12–18	*t* test 0.098	.92
	Mean ± SD	14.6 ± 2.3	14.7 ± 2.2		
Sex	Male N (%)	30 (53.6%)	30 (50%)	X^2 0.0	1.0
	Female N (%)	26 (46.4%)	30 (50%)		
Weight (kg) below 5th centile N (%)		43 (77.0%)	0 (0%)	FET 29.9	<.001
Height (cm) below 5th centile N (%)		41 (73.0%)	0 (0%)	FET 29.3	<.001

FET = Fisher exact test, N = number, t = student test, X^2 = Chi Square test.

Table 2

Comparison of tanner stages in male patients & controls.

			Group		
			Patients	Controls	Total
Tanner	Stage 1	N	15	0	15
		% Within group	50%	0%	25%
	Stage 2	N	3	0	3
		% Within group	10%	0%	5%
	stage 3	N	12	6	18
		% Within group	40%	20%	30%
	Stage 4	N	0	6	6
		% Within group	0%	20%	10%
	Stage 5	N	0	18	18
		% Within group	0%	60%	30%
Total		N	30	30	60
		% Within group	100%	100%	100%
Fisher extract test	FET		21.1		
	P value		<.001		

FET = Fisher exact test, N = number

none in healthy controls for weight and height respectively ($P < .001$).

Tables 2 and 3 summarizes patients' and control groups classifications according to tanner's staging in males and females. There was a highly significant statistical difference between the 2 studied groups with all males with tanner stage 1 belonged to the patients' group (15, 50%) compared to none in the healthy group, while all those with tanner stage 5 belonged to the control group (18, 60%) compared to none in the patients' group ($P < .001$), Table 2. In females, there was a major gap between the 2 groups, as female patients in tanner stage 1 were 7 (27%) versus 0 (0%) in the control group, while tanner stage 5 were 0 (0%) in the patients versus 12 (40%) in the control group ($P < .001$), Table 3.

Table 4 clarifies serum levels of sex hormones in studied patients and control groups. Comparing the studied females regarding blood estradiol level (pg/mL), patients had significantly lower serum levels than the control group, median (32.8) in patients versus (115) in controls with ($P < .05$), (Fig. 1) while comparing the studied male patients versus healthy males regarding serum total (ng/mL) as well as free testosterone (pg/mL) levels showed a statistically important low level associated with to male patients rather than healthy males (median total testosterone was 1.1 in patients vs 4.6 in healthy)with ($P < .001$), (Fig. 2)while median blood free testosterone levels were (4.39 in patients vs 86.8 in healthy) with ($P < .001$), Table 4.

Table 5 shows a strong negative association was found (p0.001) between s.estradiol in female patients, s.total testosterone in male patients, and both of the duration of ESRD and the dialysis duration (in years), as well as a positive correlation ($P < .001$) with both age (in years) and tanner staging, Figures 3 and 4.

5. Discussion

Pubertal growth is often delayed or interrupted in children with CKD. Pituitary-gonadal axis deficiency has been linked to both neuroendocrine and peripheral changes caused by uremia.[12]

Table 3

Comparison of tanner stages in female patients & controls.

			Group		
			Patients	Controls	Total
Tanner	Stage 1	N	7	0	7
		% Within group	27%	0%	12.5%
	Stage 2	N	9	0	9
		% Within group	35%	0%	16.1%
	Stage 3	N	10	12	22
		% Within group	38%	40%	39.3%
	Stage 4	N	0	6	6
		% Within group	0%	20%	10.7%
	Stage 5	N	0	12	12
		% Within group	0%	40%	21.4%
Total		N	26	30	56
		% Within group	100.0%	100.0%	100.0%
Fisher extract test	FET		15.9		
	P value		<.001		

FET = Fisher exact test, N = number

Table 4

Comparison of sex hormones levels in patients and controls.

Variable	Patients		Controls		MWU	*P*
	Median	Range	Median	Range		
S.estradiol in females (pg/ mL)	32.8	6.55–63.4	115	22–140	2.49	<.05
S.total testosterone in males (ng/mL)	1.1	0.02–5.3	4.65	2.3–5.4	3.24	<.001
S.free testosterone in males (pg/mL)	4.39	0.25–102	86.8	61–102.5	3.74	<.001

MWU = Mann–Whitney *U* test.

To assess gonadal dysfunctions in children and adolescents with CKD who were receiving hemodialysis on a regular basis. We used Tanner staging and laboratory testing of sex hormones (Testosterone and Estradiol). Tanner staging showed that pubertal development was delayed in patients suffering from CKD. In the current study, all those in Tanner stages I & II belonged to the patients' group (22 patients, 39% & 12 patients, 22% respectively). None of the controls had Tanner stage 1 or 2. The remaining 22 patients belonged to the tanner stage 3. None of the patients were in Tanner stage 4 or 5. On the other hand, all controls were Tanner stage 4 or 5 apart from 18 who were tanner stage 3. This clearly highlights that healthy children advanced to Tanner stages 4 and 5 while patients remained in Tanner stages 1 to 3. Our findings are in line with those of other researchers who made the assertion that on average, children on dialysis had delayed puberty by 2 to 2 and a half years.[12–15]

While the time onset of puberty is typically delayed in patients who are suffering from CKD, the progression through the pubertal stages is typically normal or a little late.[14]

According to Burke et al., puberty occurs after the upper limit of the usual age range (i.e., 15 years old) in approximately 50% of patients with dialysis or transplantation. Additionally, despite completing pubertal stage IV or V, a sizable proportion of dialysis patients had irreversible impairment of reproductive function.[16]

Delayed puberty in a patient who suffering from CKD should no longer be taken for granted "natural," but should prompt a detailed clinical examination to exclude other pathologies can lead to pubertal delay, such as the syndrome of Ullrich Turner and other gonadal disorders.[17]

In our study, patients had lower s.testosterone and s.estradiol levels than controls, which was consistent with previous researches.[18,19] In females, s.estradiol tends to decrease with

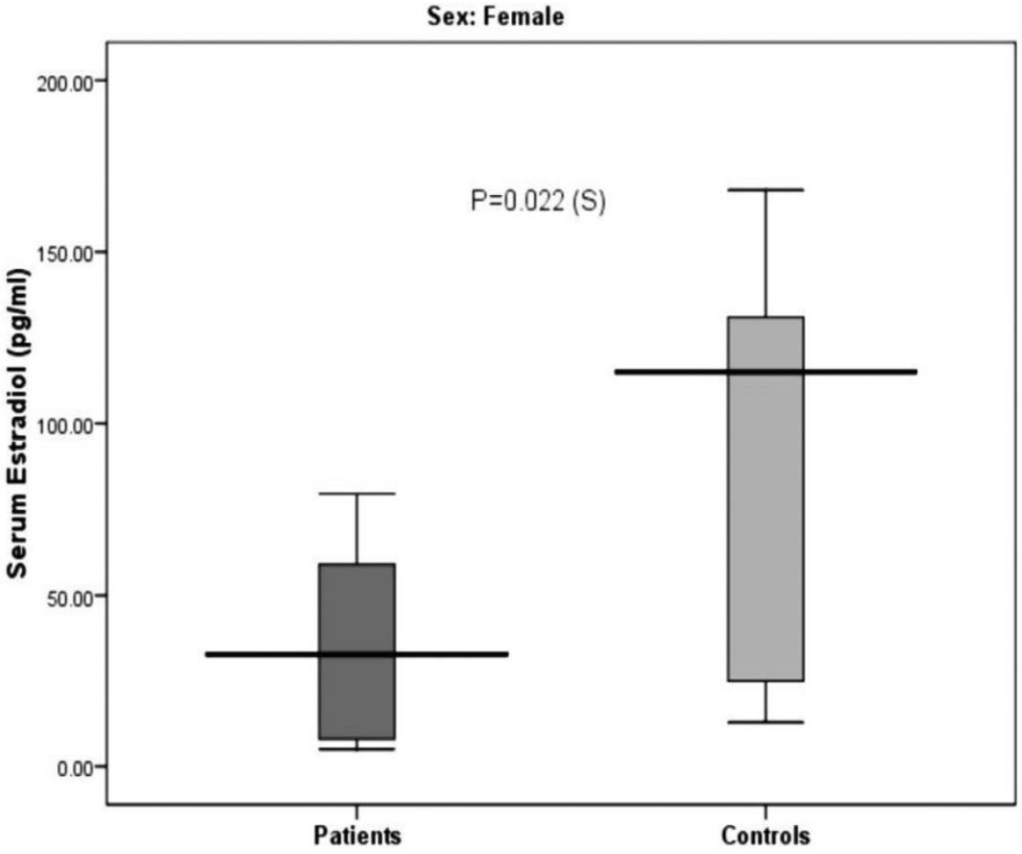

Figure 1. Comparison between the median value of s.estradiol in female patients and controls.

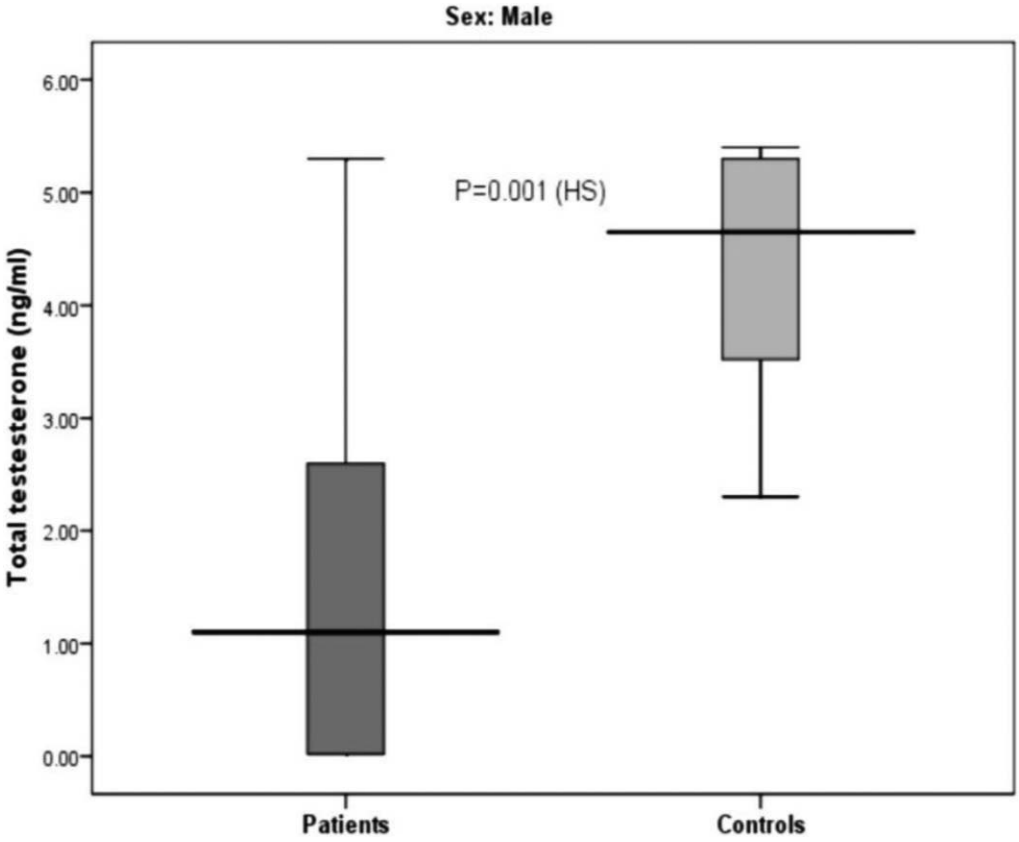

Figure 2. Median values of s.total testosterone in male patients & controls.

GFR reduction, and some adolescent girls have low to normal or decreased levels of s.estradiol in relation to pubertal age.[3] In patients with pre-dialytic CKD, there was an inverse relation between s.creatinine and s.estradiol level.[20]

In 1996 Prem et al, suggested that low serum testosterone & estradiol levels are due to primary gonadal injury caused by a circulant receptor inhibitor of luteinizing hormone could lead to gonadal cell resistance and impaired feedback,[21] in addition to the existence of CKD associated hyperprolactinemia.[22]

Forest and his colleagues suggested that gonadal damage in CKD starts before & during puberty, however since the adrenal cortex is the major site of androgen production before puberty, and even this is also low in children suffering from CKD.[23] Blood levels of testosterone in male patients are average or slightly low.[24] Since synthesis is reduced and/or metabolic clearance increased in adolescents and adults with long-term uremia.[3]

According to Prem and co-workers, disturbances in sex hormone levels seldom return to normal following the starting of dialysis, and some aspects of reproductive function may remain impaired. In contrast, after successful transplantation, the steroidogenic function became almost normal.[22]

The current study assessed growth parameters (weight & height) in all patients were substantially less than controls. That was in accordance with Kretzler and Allred, who reported that growth retardation is one of the most significant complications of children with CKD, and that it was assumed to be multi-factorial, with disrupted insulin-like growth factor-I activity, nutritional status, acid-base balance, and bone demineralisation.[25]

Table 5

Statistical correlation between sex hormones levels and demographic and disease factors.

	S.estradiol		S.total testosterone	
	Female patients (N = 26)		Male patients (N = 30)	
	(*r*)	*P*	(*r*)	*P*
Age (yr)	0.777	<.001	0.705	<.001
Duration of illness (yr)	−0.765	<.001	−0.659	.002
Duration of dialysis (yr)	−0.615	.004	−0.802	<.001
Tanner stage	0.860	<.001	0.889	<.001

r = correlation coefficient.

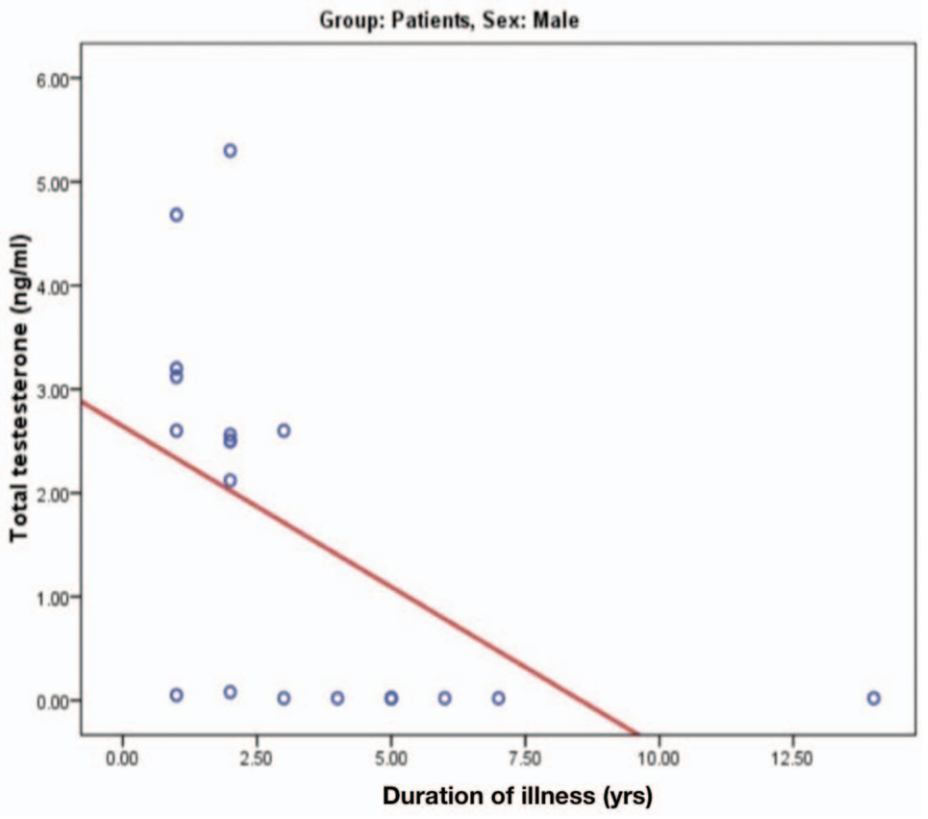

Figure 3. Correlation between male serum total testosterone level (ng/mL) and duration of illness in years.

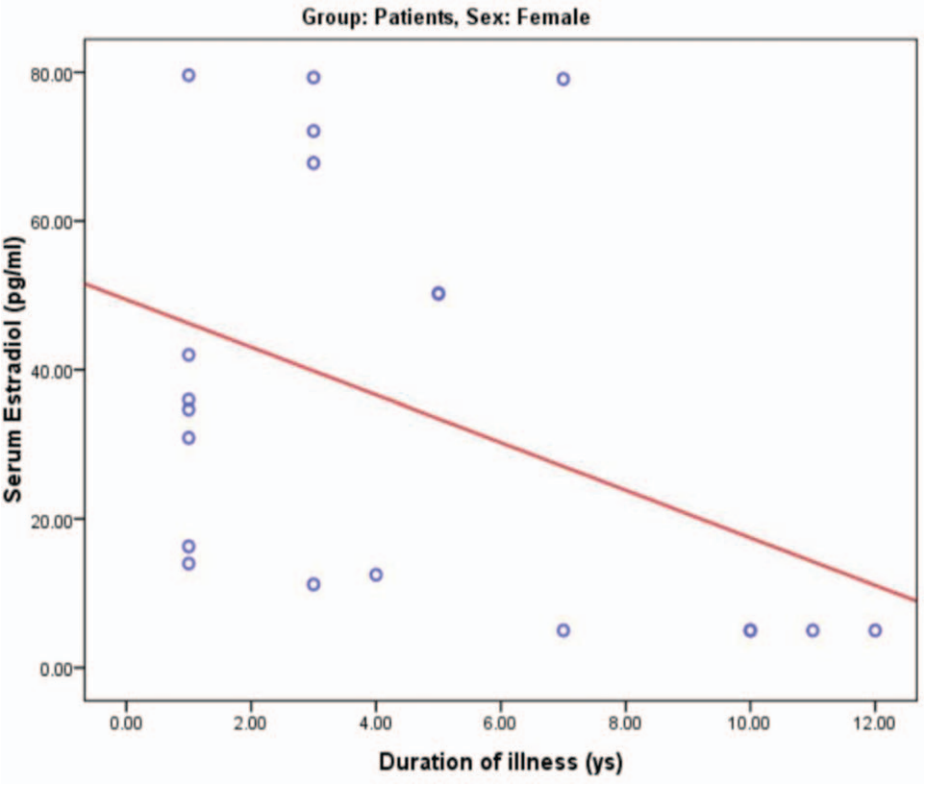

Figure 4. Correlation between female serum estradiol level (pg/mL) and duration of illness in years.

According to Cherry and Shalansky, growth delay in CKD patients is the resultant of a decreased response to growth hormones and insulin-like growth factors, which leads to increased catabolism and promotes protein wasting. Hyperparathyroidism is a common occurrence in these patients, it increases muscle protein metabolism worsening the wasting syndrome. Additionally, metabolic acidosis, which is also common, can increase catabolism, promoting protein breakdown and bone demineralization. Phosphate binders made of aluminium and calcium also interfere with nutrient absorption.[26]

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. 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 pre-spurt 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 pre-pubertal growth phase, resulting from the delayed onset of the pubertal growth spurt.[27]

There is evidence that over the last years, final height post-transplant is improving,[28] this is likely to be due to a combination of factors such as better nutrition, growth hormone therapy pre-emptive transplant thus avoiding dialysis.[29]

There are few reports on the use of sex hormones in children with CKD, Kassmann et al revealed a short-term growth response to low-dose testosterone therapy in prepubertal hemodialysis boys with impaired pretreatment growth, whereas boys with "normal" pretreatment growth rates did not exhibit a short-term growth response.[30]

Low testosterone treatment resulted in a rapid increase in growth velocity and development of secondary sexual characteristics in 4 male ESRD patients aged 19 to 21 years with severe growth delay during puberty; however, bone maturation accelerated disproportionately, at rates of 2 to 4 years of bone age per year of chronological age, resulting in a dramatic loss of predicted height.[31]

Currently, treatment of growth failure in CKD patients with sex steroids must be viewed with caution. The growth plate of patients with chronic kidney disease may be hypersensitive to stimulation by sex hormones, particularly in situations of significant pubertal delay.[3] However, treating hypogonadism in teenage CKD patients with sex steroids appears to be warranted to promote the development of secondary sexual traits and to aid in matching the patients with their peers.[30]

6. Conclusions

Children and adolescents with ESRD typically have delayed pubertal growth. Their s.testosterone and s.estradiol levels are significantly lower than normal, which lead to progressive delay of sexual maturation and final adult height but pre-emptive transplant can avoid this. We recommend larger multi-center studies to validate the possible supportive role of sex hormone therapy in improving sexual functions and final adult height in these patients.

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