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Assessment of puberty in children with chronic kidney disease and end-stage renal disease undergoing hemodialysis

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Abstract

Background: Growth and pubertal retardation are one of the most visible comorbidities in children with chronic kidney disease (CKD) and end-stage renal disease (ESRD) under regular hemodialysis. This study evaluated pubertal development in children and adolescents with CKD and ESRD on regular hemodialysis.

Methods: This study was carried out on 40 children with CKD and 20 with ESRD under regular hemodialysis. All patients and controls were subjected to a thorough clinical examination pubertal assessment.

Results: There was a statistically significant difference in the breast or testicular stage of the three groups ($P < 0.001$). Most cases of ESRD were either stages 1 or 2 (50.0%, 45.0%, respectively). The CKD cases were also stages 1 and 2 (35.7%, 52.4%, respectively). The controls were in stages 3 and 4 (44.3 and 29.5%, respectively), which showed normal development for age. There was a statistically significant difference in the pubic hair stage and axillary hair stage of the three groups ($P < 0.001$). Most cases of ESRD were either stages 1 or 2 (55.0%, 40.0%, respectively). The CKD cases were also between stages 1 and 2 (38.1%, 52.4%, respectively), with a higher level in stage 2. Of the control group, 39.3% was stage 3, and 36.1% was stage 4, with a higher level in stage 3 proving normal development for age.

Conclusion: Pubertal growth and sexual maturation in children with CKD and ESRD are markedly affected. It is necessary to regularly follow up with children with ESRD for early detection of endocrinal complications.

Keywords: Pubertal development, CKD, ESRD

Background

Puberty is a period of dramatic physiologic transformation of children into young adults. Chronic kidney disease (CKD), like many disorders, may delay or blunt the onset and outcomes of puberty [1].

Maintaining optimal pubertal growth and normal sexual maturation is challenging problems in the management of children with chronic kidney disease (CKD); approximately, 50% of children requiring renal replacement therapy (RRT) before their 13th birthday show delayed puberty and have a final height below the normal range [2].

The onset of puberty in CKD patients is associated with a delay of 2 years. This delay also includes the onset of menarche and genital maturation and the incidence of secondary characteristics [3].

Pubertal delay and reduced pubertal growth spurts are characteristic findings of long-standing ESRD and probably result from the reduced release of hypothalamic GnRH and decreased circulating levels of bioactive LH due to CKD-related inhibitory factors such as angiotensin II [4].

Delayed puberty and reduced pubertal growth are most pronounced in children with preexisting severe stunting before puberty, requiring long-term dialysis treatment,

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and in transplanted children with poor graft function and high glucocorticoid exposure [5].

Delayed puberty in a patient with CKD should nowadays not be assumed to be "normal." Still, it should lead to a thorough clinical work-up for other causes of pubertal delay, e.g., Ullrich-Turner syndrome and other gonadal disorders. It has to be kept in mind that specific underlying kidney diseases are frequently associated with gonadal insufficiency/dysgenesis, e.g., syndromes related to mutations in the Wilms tumor gene (WT1) as Denys-Drash syndrome, Frasier syndrome, and nephropathic cystinosis [6].

This study aims to evaluate the pubertal development in patients with CKD and ESRD on regular hemodialysis.

Methods

This cross-sectional study included 40 CKD and 20 ESRD patients aged between 12 and 16 years old who were attending the nephrology clinic and unit of Children's Hospital, Cairo University. Growth and pubertal evaluation were performed at the endocrine outpatient clinic. The laboratory tests were performed at the Diabetes Endocrine Metabolic Pediatric Unit (DEMPU) laboratory in the Center for Social and Preventive Medicine (CSPM). The study was done after being approved from the institutional ethical committee, Cairo University. Informed consent was obtained from the patients and their parents.

Study populations included the following: group A: 40 CKD patients, who were attending the nephrology clinic, group B: 20 ESRD patients who were attending the hemodialysis unit, and group C: 61 normal children aged between 12 and 14 years who were attending the general clinics of Children's Hospital.

Pediatric post-renal transplant recipients and patients receiving hormonal replacement therapy for endocrinopathies (e.g., hypothyroidism) and cases with any other chronic systemic illness were excluded from the study.

All cases were subjected to the following:

1. Entire history taking including the following: age, sex, age of onset of puberty, menstrual history in females, age of diagnosis of primary kidney disease, the onset of renal replacement therapy, duration on regular dialysis, family history, and pubertal history (whether failure to start puberty or arrested puberty or failure to complete all the pubertal stages, in girls older than 13 years and boys older than 14 years)
2. Clinical examination with particular emphasis on growth assessment (height, weight, and body mass index), blood pressure [7], signs of puberty, and whether puberty has started, arrested, or completed according to Marshell and Tanner classification [8] and pubertal stage (Tanner staging and testicular volume in males using Prader orchidometer). Height and dry weight were plotted on standard growth charts for the Egyptian population. Delayed puberty: This is defined as an absence of signs of secondary sexual development in a girl aged 13 years or a boy aged 14 years. A more practical definition is a delay in the onset, progression, or completion of puberty sufficient to cause concern to the adolescent, parents, or physician. Delayed puberty in females is defined as the absence of breast development by 13 years and in males by the lack of testicular enlargement (testicular volume < 4 ml) by 14 years. Pubertal failure: Puberty that either fails to begin or has begun but fails to complete (in which case the term mid-pubertal arrest is often used). Primary amenorrhea is defined as the absence of menarche by 16 years of age, and secondary amenorrhea is defined as absence of menses for 6 months after having regular menses [9].
3. Body mass index was calculated using the following equation: BMI = body weight/(height in meters)^2
4. Laboratory investigations including complete blood picture using automated hematology Coulter counter (Cell Dyne 3700, Abbott Laboratories, North Chicago, USA), kidney function test (blood urea nitrogen and serum creatinine), fasting blood glucose, and serum electrolytes (potassium, sodium, calcium, and phosphorus) using multichannel Autoanalyzer, Hitachi, Japan. Urine was centrifuged, and dipsticks and direct microscopy examined the supernatant.

Statistical analysis

All collected data were tabulated and statistically analyzed. Quantitative data were presented as a minimum, maximum, mean, and standard deviation (SD) values. Qualitative data were presented as frequencies and percentages. Statistical tests were applied according to the variables under study. The significance level was set at P-value ≤ 0.05. Mann-Whitney test was considered where distributions were not normal to investigate different levels of associations.

Results

Age was significantly lower in CKD and ESRD than controls, and age on menarche was significantly higher in CKD group than the other two groups. There was a statistically significant difference between the CKD and ESRD regarding the age of onset of the original disease, being older in the ESRD group ($P = 0.027$). Most cases of CKD (76.2%) and about half of ESRD (55%) were males, while 23.8% of CKD and 45.0% of ESRD were females. There

was a statistically significant difference between the three groups regarding weight percentiles ($P < 0.001$). Most cases of ESRD (70.0%) and about half of the instances of CKD (45.2%) have their weight below the 3rd percentile compared to the control group (3.3%). There was a statistically significant difference between the heights of the three groups ($P < 0.001$). Most cases of ESRD (80.0%) and 59.5% of CKD cases have their height below the 3rd percentile compared to the control group (8.2%). There was also a statistically significant difference between the BMI of the three groups ($P = 0.020$), as 9.5% of CKD patients and 10.0% of ESRD have their BMI below the 3rd percentile compared to and control group (0.0%) (Table 1).

Hg, sodium, potassium, urea, and creatinine were significantly lower in the CKD group than ESRD group, while WBC, platelets, calcium, and phosphorus were significantly higher in the CKD group than ESRD group (*P*-value < 0.05) (Table 2)

Systolic and diastolic blood pressure and ultrasound grade were significantly higher in the CKD group than ESRD group (*P*-value < 0.05) (Table 3)

Breast or testicular stage was significantly higher in CKD group in stages 1 and 2 than the other two groups and was significantly higher in controls in stages 3, 4, and 5 than CKD and ESRD groups ($P < 0.001$). Pubic hair stage was significantly higher in CKD group in stages 1 and 2 than the other two groups and was significantly higher in controls in stages 3, 4, and 5 than CKD and ESRD groups ($P < 0.001$). Axillary hair stage was significantly higher in CKD group in stage 1 than the other two groups and was significantly higher in controls in stages 2 and 3 than CKD and ESRD groups ($P < 0.001$). There

Table 1 Comparison between the studied groups regarding their demographic data

		CKD ($n = 40$)		ESRD ($n = 20$)		Controls ($n = 61$)		*p*-value
		No.	%	No.	%	No.	%	
Age (year)	**Mean ± SD**	12.74 ± 1.06		12.85 ± 1.23		13.57 ± 1.09		< 0.001
Menarche age	**Mean ± SD**	12.65 ± 5.89		0.00 ± 0.00		10.28 ± 4.71		< 0.001
Sex	Males	32	76.2	11	55.0	31	50.8	0.031
	Females	10	23.8	9	45.0	30	49.2	
Weight	**Below 3rd percentile**	19	45.2	14	70.0	2	3.3	< 0.001
	Between 3rd to 97th percentiles (normal range)	23	54.8	6	30.0	59	96.7	
	Above 97th percentile	0	0.0	0	0.0	0	0.0	
Height	**Below 3rd percentile**	25	59.5	16	80.0	5	8.2	< 0.001
	Between 3rd to 97th percentiles (normal range)	17	40.5	4	20.0	55	90.2	
	Above 97th percentile	0	0.0	0	0.0	1	1.6	
BMI	**Below 3rd percentile**	4	9.5	2	10.0	0	0.0	0.020
	Between 3rd to 97th percentiles (normal range)	38	90.5	18	90.0	61	100.0	
	Above 97th percentile	0	0.0	0	0.0	0	0.0	

CKD chronic kidney disease, *ESRD* end-stage renal disease

Table 2 Comparison between CKD and ESRD groups regarding laboratory investigations

	CKD ($n = 40$)				ESRD ($n = 20$)				*p*-value
	Mean ± SD	Median	Minimum	Maximum	Mean ± SD	Median	Minimum	Maximum	
Hb	10.80 ± 1.44	11.10	7.70	13.80	11.36 ± 2.38	11.45	6.50	15.30	0.190
WBC	8.62 ± 6.89	7.00	3.90	48.00	6.25 ± 2.50	5.80	2.70	12.80	0.015
Platelets	271.81 ± 60.62	253.50	164.00	440.00	232.50 ± 84.57	203.00	70.00	444.00	0.013
Sodium	139.43 ± 5.91	140.00	113.00	149.00	139.60 ± 6.07	139.00	128.00	150.00	0.922
Potassium	4.48 ± 0.49	4.40	3.40	5.70	4.58 ± 0.50	4.55	3.40	5.30	0.326
Calcium	9.35 ± 1.15	9.50	7.00	12.80	9.05 ± 0.95	8.90	7.70	11.10	0.200
Phosphorus	5.31 ± 0.89	5.20	3.40	6.80	4.75 ± 1.89	4.40	1.40	9.80	0.003
Urea	55.12 ± 43.18	43.5	7.0	181.0	80.45 ± 38.62	83.0	29. 0	180. 0	0.012
Creatinine	2.20 ± 1.80	1.65	0.30	7. 0	4.20 ± 1.84	3.95	1.80	9.0	< 0.001

CKD chronic kidney disease, *ESRD* end-stage renal disease, *Hb* hemoglobin, *WBC* white blood cells

Table 3 Comparison between CKD and ESRD groups regarding the blood pressure and abdominal ultrasound

		CKD ($n = 40$)		ESRD ($n = 20$)		*p*-value
		No.	%	No.	%	
Systolic BP percentile	**Hypotensive (< 5th)**	3	7.1	0	0.0	0.001
	Normotensive (5th–95th)	30	71.5	7	35.0	
	Pre-hypertensive (95th–99th)	6	14.3	4	20.0	
	Hypertensive > 99th	3	7.1	9	45.0	
Diastolic BP percentile	**Hypotensive < 5th**	1	2.4	0	0.0	0.011
	Normotensive 5th–95th	29	69.0	10	50.0	
	Pre-hypertensive (95th–99th)	10	23.8	4	20.0	
	Hypertensive (> 99th)	2	4.8	6	30.0	
Ultrasound grade	**1**	11	26.2	0	0.0	
	2	22	52.4	14	70.0	0.027
	3	9	21.4	6	30.0	

CKD chronic kidney disease, *ESRD* end-stage renal disease

was no statistical difference between the studied groups regarding other pathological associations with cases (Table 4)

Discussion

Impairment of pubertal growth and sexual maturation resulting in reduced adult height is a significant complication in children suffering from CKD [10].

Nevertheless, the published literature is scarce regarding the growth and pubertal status in children with CKD or ESRD. Therefore, we conducted the present cross-sectional study in order to clinically evaluate the development and pubertal status in Egyptian children with CKD and ESRD.

Regarding demographic characteristics of the included patients, the mean age of CKD and ESRD patients was 12.74 ± 1.06 and 12.85 ± 1.23 years old,

Table 4 Comparison between the three studied groups regarding their pubertal development and associations

		CKD ($n = 40$)		ESRD ($n = 20$)		Controls ($n = 61$)		*p*-value
		No.	%	No.	%	No.	%	
Breast or testicular stage	**1**	15	35.7	10	50.0	1	1.6	
	2	22	52.4	9	45.0	10	16.4	
	3	5	11.9	1	5.0	27	44.3	< 0.001
	4	0	0.0	0	0.0	18	29.5	
	5	0	0.0	0	0.0	5	8.2	
Pubic hair stage	**1**	16	38.1	11	55.0	0	0.0	
	2	22	52.4	8	40.0	9	14.8	
	3	4	9.5	1	5.0	24	39.3	< 0.001
	4	0	0.0	0	0.0	22	36.1	
	5	0	0.0	0	0.0	6	9.8	
Axillary hair stage	**1**	33	78.6	16	80.0	1	1.6	
	2	9	21.4	4	20.0	29	47.5	< 0.001
	3	0	0.0	0	0.0	31	50.8	
Others	**Albinism**	1	2.4	0	0.0	0	0.0	0.142
	Down	1	2.4	0	0.0	0	0.0	
	G6PD deficiency	1	2.4	0	0.0	0	0.0	
	Hydrocephalus	2	4.8	0	0.0	0	0.0	
	No	37	88.1	20	100.0	61	100.0	

CKD chronic kidney disease, *ESRD* end-stage renal disease, *G6PD* glucose-6-phosphate dehydrogenase

respectively. The majority of patients in both groups were males. This male predominance can be attributed to congenital renal diseases being more common in males [11].

Similar to our findings, Clavé et al. [12] studied adolescent patients in French pediatric hemodialysis centers and found that their mean age was 13.9 ± 2.0 years, and the majority of them were males.

In our study, the most common causes of CKD were genetic causes, including neurogenic bladder and hypoplastic and solitary kidney, while other reasons included nephrotic syndrome and glomerulonephritis.

Similar to our findings, Ardissino et al. [13] aimed to assess the epidemiology of childhood CKD and found that the leading causes of CKD were hypodysplasia associated with urinary tract malformations (53.6%) and isolated hypodysplasia (13.9%). In contrast, glomerular diseases accounted for as few as 6.8%.

Contrary to our findings, Hazza [14] reviewed the records of 1018 (56.7% were males, ages ranging from 1 to 19 years) Egyptian patients suffering from CKD and ESRD followed up at the pediatric nephrology units (outpatient clinics and dialysis units) of 11 universities over a period of 2 years. The most common cause of CKD was obstructive uropathy (21.7%), followed by primary glomerulonephritis (15.3%), reflux/urinary tract infection (14.6%), aplasia/hypoplasia (9.8%), and familial/metabolic diseases (6.8%).

In the present study, we found that the mean weight, height, and BMI were significantly lower in patients with CKD and ESRD than in normal children. Most cases of ESRD (70.0%) and about half of the instances of CKD (45.2%) have their weight below the 3rd percentile compared to and control group (3.3%). Similarly, most cases of ESRD (80.0%) and 59.5% of CKD have their height below the 3rd percentile compared to control group (8.2%). A total of 9.5% of CKD patients and 10% of ESRD have their BMI below the 3rd percentile compared to the control group of 0.0%.

In agreement with our findings, Sozeri et al. [15] reported that the mean weight and height standard deviation score (SDS) was lower in CKD and ESRD patients than in healthy controls.

Additionally, Abd El-Monem [16] found that compared with normal children, children with CKD showed a statistically significant short stature, low body weight, anemia, and poor QOL.

Gupta [17] aimed to assess nutritional intake and anthropometry of children presenting with CKD in a developing country. Out of 45 children, 27 (60%) had moderate to severe malnutrition at assessment. The mean weight and height (SDS) were −2.77 ± 2.07 and −2.30 ± 1.38, respectively.

In the present study, we found a statistically significant difference between patients and control groups regarding the breast and testicular stage, pubic hair stage, and axillary hair stage. Cases with CKD and ESRD had significantly lower stages than healthy controls. Most cases of ESRD were either stages 1 or 2. The CKD cases were also stages 1 and 2 with a higher level in stage 2. Thus, pubertal growth was substantially more impaired in dialysis patients than in CKD patients.

In concordance with our findings, El-Gamasy et al. [18] evaluated the development of Egyptian children and adolescents with ESRD under regular hemodialysis. The mean Tanner stages were significantly lower in ESRD patients than in a control group.

Our study found that patients with CKD and ESRD had a significantly older age at menarche than the control group.

Similarly, Ferris [19] reported that approximately half of the children with CKD had delayed puberty and late age at menarche.

Similar to our findings, Noh and Koo [20] investigated the association between the age of menarche and CKD and found that the age of menarche in the CKD group was 16.2 ± 9 years old, which was higher than that in the non-CKD group ($P < 0.001$).

We acknowledge that the present study has several limitations. The sample size of our cohort was relatively small, which may affect the generalizability of our findings. In addition, the study was based only on a single-center experience. Also, the significant differences in age and sex between the groups are considered important factors affecting puberty. Moreover, long-term patient-centered outcomes were not utilized in our research.

Conclusion

In conclusion, pubertal growth and sexual maturation in children with CKD and ESRD are markedly affected when compared to the normal population. This impairment was more notable in patients with ESRD. It is necessary to regularly follow up with children with ESRD for early detection of endocrinal complications. It is an add-on to their daily challenges, and raising awareness of such a problem and the possibility to solve among their nephrology specialists may contribute to a better quality of life.

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Authors' contributions

All authors have contributed significantly, and all authors are in agreement with the content of the manuscript. Authors' contribution and participation were as follows: EEG participates in search in the literatures, follow the results, prepare the final manuscript. REG participates in choice of the issue of the study, follow the results, and prepare the final manuscript. MSG participates in collecting data of the patients, follow the results, and search in the literatures.

YMS participates in choice of the issue of the study, follow the results and prepare the final manuscript and the corresponding author. The authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
This study was approved by the ethical scientific committee in the Cairo University Hospital and was conducted in accordance with the university bylaws for human research. It conforms to the provisions of the Declaration of Helsinki in 2000.

Consent for publication
All participating children and/or legal guardians have given their informed consent to publish their children's data.

Competing interests
The authors declare that they have no competing interests.

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