

Delayed Puberty and Its Association With Hormonal Changes in Children With Chronic Renal Insufficiency

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Received: 11 Jun. 2021; Accepted: 18 Jan. 2022

Abstract- Chronic kidney diseases affect sex hormones, and thus it is now hypothesized abnormal puberty phenomenon in adolescents suffering renal failure. The primary study endpoint was to assess the frequency of disorders related to the clinical incidence of puberty symptoms among children suffering chronic kidney disease, and the secondary endpoint was also to assess the relationship between such manifestations and the serum level of sexual hormones. This cross-sectional study was performed on children with chronic renal failure (more than three months after the onset of the disease). All baseline characteristics were retrospectively extracted from the hospital recorded files. The pieces of evidence of anemia and acidosis also appeared more in those with delayed puberty. Comparing the groups with delayed puberty and normal puberty showed significantly lower mean body weight and lower mean height in the group with delayed puberty as compared to those with normal status. Comparing serum hormonal conditions between the groups with normal and delayed puberty also showed significantly reduced serum levels of FSH, LH, testosterone, and dihydrotestosterone, as well as increased the serum level of prolactin in the group suffering delayed puberty. The main determinants for delayed puberty in patients suffering chronic renal insufficiency included abnormality in serum hormonal status, along with pieces of evidence of anemia or acidosis. Children with chronic renal insufficiency suffer from delayed puberty. Such phenomenon might be closely linked to abnormal changes in sex hormones due to the nature of renal dysfunction and hemodialysis.

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Acta Med Iran 2022;60(4):243-248.

Keywords: Puberty; Renal failure; Sexual hormone; Hemodialysis

Introduction

Delayed puberty has been reported in more than half of girls and one-third of boys with end-stage chronic kidney disease (1). In these children, various mechanisms have been suggested for delayed puberty, including neuroendocrine insufficiency in the pituitary-gonadal axis, peripheral changes due to uremia, gonadal damage, and inability to regulate gonadotropin secretion (2). Maintaining the optimal growth of puberty and normal sexual maturity is one of the controversial issues in the control of children with chronic kidney disease (3). Approximately 50% of children in need of kidney replacement therapy before the age of 13 show puberty and height below normal (4). The most important factors that impair the growth and development of adolescence

in patients with chronic kidney disease include the presence of degrees of short stature before adolescence, the severity of chronic kidney disease, and exposure to steroids in patients with kidney transplantation (4,5). Thus, accurate monitoring of height growth, puberty, testicular volume (boys), and menarche (girls) is essential in diagnosing abnormal growth and development in children with chronic kidney disease (6). As with any chronic disease, chronic kidney disease affects the growth of these patients at a high growth rate. In the years before puberty, secondary sexual traits appear with a delay and cause a significant reduction in growth rate (7). In these patients, the growth spurt of puberty occurs later and leads to a decrease in the patient's height growth. Delay in the onset and progression of puberty is common in children undergoing renal replacement therapy (8).

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Delayed puberty and renal failure in children

Menarche occurs at a higher age in half of the girls with chronic kidney disease undergoing dialysis or kidney transplantation (9).

Today, puberty delay is not considered normal in patients with chronic kidney disease, and clinical interventions are performed to treat other causes related to puberty delay. It should be noted that undiagnosed kidney disease is commonly associated with gonadal insufficiency/dysgenesis (10). In addition, delayed puberty may be due to treatment with glucocorticoids or other drugs that interfere with the production of sex hormones (11). Reduction and disruption of the growth process is one of the most important and complex problems in children with chronic kidney disease (12). Severe growth retardation is highly prevalent among children with chronic kidney disease, occurring in approximately 35% of patients with end-stage renal disease (13). Despite advances in maintenance therapy and kidney transplantation, 30 to 60% of children with end-stage renal disease have short stature in adulthood (14). Children with chronic kidney disease with moderate to severe growth retardation have higher mortality and morbidity rates than children with normal growth, according to the US Child Development Information System (3). Especially in children who start dialysis and are below the first percentile of the height growth curve in relation to age-sex, the risk of mortality is twice as high as in children whose height growth is normal (15). In these patients, poor nutritional status and increased catabolism are associated with increased incidence of infection, hospitalization, and other side effects (16). It also alters mental growth and development in patients with short stature (17). Therefore, the optimization of medical and health care in these children is more important than the growth of these children in the early stages of the disease. The cause of growth failure in these children is multifactorial, including the age of onset of chronic kidney disease, renal adrenal insufficiency, metabolic disorders, renal osteodystrophy, abnormal growth hormone, and insulin-like growth factor-1 (18).

As mentioned earlier, chronic kidney disease affects sexual maturity. In this regard, there are studies that have examined changes in sex hormone levels in chronic kidney disease and found that chronic kidney disease causes disorders in sex hormone levels in men and women (19). However, based on our research, there is no comprehensive study to investigate the relationship between chronic kidney disease and the incidence of sexual puberty symptoms and sex hormone levels in childhood in Iran and also the relationship between sex

hormone levels and sexual maturity disorders in children with the chronic kidney disease. The aim of this study was to investigate the frequency of puberty disorder related to the clinical symptoms and its relationship with gonadal hormone in children with chronic kidney disease referred to Aliasghar Hospital in 2019 and 2020.

Materials and Methods

This cross-sectional study was performed on children with chronic renal failure (more than three months after the onset of the disease) that referred to Ali Asghar Children Hospital in Tehran, Iran, between 2018 and 2020. The following subjects were excluded from the assessment: 1) parents who did not consent to the participation of their children in the study, 2) children with the primary endocrine disorders such as type 1 diabetes, 3) patients treated with drugs affecting serum testosterone and estradiol levels, 4) completion of puberty before the onset of end-stage renal disease, 5) transient increase in serum creatinine and 6) patients with short stature syndrome.

Before starting the study, a questionnaire was prepared in which demographic information of children, including age, gender, weight, and body mass index BMI were recorded by reviewing the hospital charts. Also, information about the results of Tanner Stage, laboratory tests (blood counts, arterial blood gas analysis, thyroid function test), endocrinological assessments (the serum levels of testosterone, estradiol, FSH, LH, prolactin level), and information on kidney disease and its management (age of onset of disease and dialysis, type of dialysis, or kidney transplantation) were also collected and recorded at the study checklist. The primary study endpoint was to assess the frequency of disorders related to the clinical incidence of puberty symptoms among children suffering chronic kidney disease, and the secondary endpoint was also to assess the relationship between such manifestations and the serum level of sexual hormones.

For statistical analysis, results were presented as mean±standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using t-test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. *P* of ≤0.05 were considered statistically significant. For the statistical analysis, the statistical software SPSS version 23.0 for windows (IBM,

Armonk, New York) was used.

Results

In total, 85 children (63 as hospitalized and 22 as outpatients) were included in the study. Only one case was a 12-year-old girl who was treated with GNRH at the initial diagnosis of precocious puberty, and additional evaluations revealed that she did not have precocious puberty, and the drug was discontinued. Of the above, 32 children in the desired age range (over 13 years) for delayed puberty were studied. Of the 16 boys over the age of 14 years, 11 had delayed puberty and 5 were normal in terms of puberty, and among 16 girls over the age of 13

years, 13 were delayed in puberty, and 3 were normal in terms of puberty. Baseline anthropometric characteristics of the study population are presented in Table 1. Comparing the groups with delayed puberty and normal puberty showed significantly lower mean body weight and lower mean height in the group with delayed puberty as compared to those with normal status. The mean time for dialysis was also longer in those with delayed puberty. In this regard, the pieces of evidence of anemia and acidosis also appeared more in those with delayed puberty. However, we showed no difference in some baseline parameters, including gender, average age, or etiologies for renal disease between the groups with normal and delayed puberty.

Table 1. Baseline characteristics of the study population

Parameters	Normal puberty (n=8)	Delayed puberty (n=24)	P
Mean age, year	14.58±1.14	14.34±0.55	0.581
Mean age of onset of dialysis, month	47.00±17.63	30.25±20.27	0.046
Mean weight, kg	46.25±5.23	36.65±10.61	0.021
Mean height, cm	159.62±6.48	142.72±14.61	0.004
Mean body mass index, kg/m ²	18.21±1.13	17.42±2.19	0.340
Male gender	5 (62.5)	11 (45.8)	0.685
Type of dialysis, %			<0.001
Hemodialysis	2 (25.0)	17 (70.8)	
Peritoneal dialysis	1 (12.5)	7 (28.2)	
Without dialysis	5 (62.5)	0 (0.0)	
Causes for renal failure, %			0.205
ARPKD	2 (25.0)	4 (16.7)	
UTI	0 (0.0)	5 (20.8)	
Reflux	3 (37.5)	4 (16.7)	
Chronic diarrhea	2 (25.0)	1 (4.2)	
PUV	1 (12.5)	1 (4.2)	
UPJO	0 (0.0)	1 (4.2)	
Unknown	0 (0.0)	5 (20.8)	
The presence of anemia, %	1 (12.5)	14 (58.3)	0.041
The presence of acidosis, %	1 (12.5)	18 (75.0)	0.003
The use of Eprex, %	3 (37.5)	24 (100)	<0.001
Proper supportive care, %	8 (100)	14 (58.3)	0.035

Comparing serum hormonal condition between the groups with normal and delayed puberty (Table 2) also showed significantly reduced serum levels of FSH, LH, testosterone, and dihydrotestosterone as well as increased the serum level of prolactin in the group suffering delayed puberty, while the hormonal status remained normal in

almost all patients with normal puberty status.

In a multivariable logistic regression model and with the presence of baseline variable (Table 3), the main determinants for delayed puberty in patients suffering chronic renal insufficiency included abnormality in serum hormonal status (including FSH, LH, testosterone,

dihydrotestosterone, and prolactin), along with pieces of evidence of anemia or acidosis, the use of Eprex, and

inappropriate supportive cares.

Table 2. Baseline hormonal status in study subjects

Parameters	Normal puberty (n=8)	Delayed puberty (n=24)	P
Prevalence of hormonal disorders, %	2 (25.0)	8 (33.3)	0.700
Serum level of FSH, % (n=32)			0.006
Increased	0 (0.0)	3 (12.5)	
Normal	8 (100)	9 (37.5)	
Reduced	0 (0.0)	12 (50.0)	
Serum level of LH, % (n=32)			0.006
Increased	0 (0.0)	3 (12.5)	
Normal	8 (100)	9 (37.5)	
Reduced	0 (0.0)	12 (50.0)	
Serum level of estradiol, % (n=16)			0.200
Increased	0 (0.0)	0 (0.0)	
Normal	3 (100)	5 (38.5)	
Reduced	0 (0.0)	8 (61.5)	
Serum level of testosterone, % (n=16)			0.026
Increased	0 (0.0)	0 (0.0)	
Normal	5 (100)	3 (27.3)	
Reduced	0 (0.0)	8 (72.7)	
Level of dihydrotestosterone, % (n=11)			0.002
Increased	0 (0.0)	0 (0.0)	
Normal	5 (100)	0 (0.0)	
Reduced	0 (0.0)	6 (54.5)	
Serum level of prolactin, % (n=32)			0.014
Increased	0 (0.0)	12 (50.0)	
Normal	8 (100)	12 (50.0)	
Reduced	0 (0.0)	0 (0.0)	

Table 3. Multivariable logistic regression analysis for determining the main determinants for delayed puberty

Parameter	P	OR	95% CI for OR	
			Lower limit	Upper limit
Age	0.419	1.04	0.95	1.14
Height	0.014	1.11	1.02	1.20
Weight	0.034	1.13	1.01	1.26
Sex (female vs. male)	0.508	0.51	0.09	2.62
Hormonal disease (yes vs. no)	0.661	1.50	0.25	9.17
FSH level (abnormal vs. normal)	<0.001	27.73	10.76	32.32
LH level (abnormal vs. normal)	<0.001	27.73	10.76	32.32
estradiol level (abnormal vs. normal)	<0.001	10.82	8.42	13.74
Testosterone level (abnormal vs. normal)	0.007	26.72	21.21	30.29
Dihydroestosterone level (abnormal vs. normal)	<0.001	143.72	121.12	202.20
Prolactin level (abnormal vs. normal)	0.005	17.00	15.13	20.24
History of anemia (yes vs. no)	0.046	9.80	1.07	46.45
The presence of acidosis (yes vs. no)	0.009	21.00	21.27	53.34
The use of Eprex (yes vs. no)	<0.001	77.00	2.50	112.00
Proper supportive cares (no vs. yes)	0.012	12.34	6.50	15.09

Discussion

Our study attempted to provide an update on the puberty condition in the presence of chronic kidney failure and also to determine the main correlates of

delayed puberty in such patients. Our retrospective study compromised a population of children referred to a referral children's hospital center in Tehran admitted by the definitive diagnosis of chronic renal insufficiency and managed with respect to clinical and hormonal

conditions. As the first finding, delayed puberty was accompanied by abnormal growth conditions as reduced weight and height were a predictable result. Along with the pointed result, those with delayed puberty faced with some disease-related characteristics such as prolonged dialysis, type of dialysis (hemodialysis), higher prevalence rates of anemia and acidosis, and more using Eprex. In other words, the pathophysiological aspects of delayed puberty in children with renal insufficiency, especially those who underwent dialysis, could be closely linked to the pointed conditions. Some previous studies could demonstrate that longer CKD exposure in patients with congenital disorders or disease-specific interference with growth mechanisms, such as more severe electrolyte and acid-base imbalance in tubulointerstitial disorders or metabolic nephropathies, may lead to more severe growth failure, confirming our obtained result. Thus, pubertal status can be strongly affected by underlying clinical and metabolic abnormalities due to renal abnormalities. It should be noted that delayed pubertal status can be directly associated parallel with delayed anthropometric development. According to some recent pieces of evidence, puberty tends to be delayed by one to two years in chronic kidney disease, leading to substantial heightening delay at an age when growth has already ceased in healthy adolescents. In this regard, some researchers have supported the hypothesis that aggressive enteral feeding in infants with CKD may result in weight gain with rather limited effects on longitudinal growth (20,21). Interestingly, renal failure especially on dialysis could affect height status. It has been previously shown that Patients with end stage kidney disease; in particular, those who started dialysis during the observation period, exhibited the poorest growth rates. This effect persisted after adjustment for markers of metabolic acidosis, hyperparathyroidism, anemia, and inflammation suggesting that other factors associated with the uremic state is more important in inhibiting growth in end-stage kidney disease (22).

As another important result, we showed a close association between delayed puberty and significant changes in sexual hormones. In other words, the potential effects of renal dysfunctions and its related pathophysiological pathways especially hemodialysis on dysregulation of hormonal system is expected leading naturally growth abnormalities and even delaying puberty in adolescents. It has been well previously demonstrated abnormal changes in sexual hormones in the background of renal insufficiency. In this regard, reducing serum testosterone in male patients and serum FSH and LH in female patients has been clearly shown (23). Several

etiologic factors appear to contribute to the described changes. Recently, a circulating LH- receptor inhibitor was suggested, which might contribute to Leydig- cell resistance and impaired feedback mechanism at the hypothalamic-pituitary level (7). Furthermore, less acidic and bioactive LH forms might thus contribute to the decrease in testosterone production (8). Additionally, hyperprolactinemia in renal insufficiency is partially induced by a decreased metabolic clearance but also by autonomic overproduction. At least primary hyperprolactinemia leads to (secondary) hypogonadism that can result in reducing hormonal levels (9). Totally, our study emphasized the fact that the hormonal changes related to renal failure could be effectively associated with delayed puberty, and therefore renal failure can affect hormonal axes and puberty regulation bidirectionally.

Acknowledgements

The authors would like to thank Ali Asghar Clinical Research Development Center (AACRDC) for Editorial/Statistical/Search Assistance through the period of study.

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