Original Article

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Growth Impairment and Nutritional Status in Children with Chronic Kidney Disease

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Abstract

Objective: Malnutrition is closely linked to chronic kidney disease (CKD) in adult patients with poor outcome. But data on pediatric patients is inadequate. The aim of this study was to describe the prevalence of growth failure and malnutrition in pediatric CKD patients and explore the relationship of these parameters to each other and to other clinical parameters.

Methods: This study included 42 patients and 29 healthy children matched for age and gender. Patients were classified firstly in age group and secondly in therapy modalities. Nutritional evaluations were performed according to the Kidney Disease Outcomes Quality Initiative guidelines, and we performed adjustments using values from children with the same chronological age as reference.

Findings: In pubertal group, the mean height SDS was lower than in pre-pubertal period while it was higher than in early childhood (P=0.4 and P=0.03 respectively). In all groups, 45% of patients had malnutrition: 20 patients on predialysis, 22 patients with end stage renal disease (14 on hemodialysis, and 8 on peritoneal dialysis). The mean weight SDS was lower in end stage renal disease groups (P<0.001). The height SDS was lower in end stage renal disease groups (P<0.001).

Conclusion: Growth failure and malnutrition remain a significant clinical problem as age and therapy modalities are dependent in children with CKD.

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Key Words: Chronic Kidney Disease; Renal Replacement Therapy; Malnutrition; Growth

Introduction

Chronic kidney disease (CKD) in the pediatric population has become an important issue. CKD represents a spectrum of conditions, which result in renal impairment varying from mild renal insufficiency to end stage renal disease (ESRD).

Growth failure is a significant problem in pediatric patients with CKD. Fivush et al[1] reported that half of patients with ESRD in childhood attain adult's height below the 3rd centile. The cause of growth failure in CKD is multifactorial with linear impairment being a final common pathway of

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various factors including malnutrition, anemia, metabolic acidosis and persistent micro-inflammations [2].

CKD can result in impairment in each phase of development from in-utero to adolescence, which can subsequently result in growth retardation, with studies suggesting that the degree of height deficit worsens with duration of disease[3]. The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) reported that more than one–third of children with CKD exhibited significant growth failure[4]. Although a correlation between renal function and growth impairment existed, significant short stature was seen at all levels of renal function [4].

Optimal growth requires adequate nutrition. Malnutrition is a common and significant clinical problem in children with CKD. There is an association between malnutrition and poor outcomes in CKD patients [5]. Affected children display serious medical complication as well as increased mortality [4-8]. Wong et al [9] explored a potential association of serum albumin and mortality in children with ESRD. Also in children protein-energy malnutrition is highly widespread. While malnutrition can be seen in pre-dialysis period, it can also be developed by factors such as increased catabolism, loss of nutrients and anti-oxidants, and aggressive dietary restrictions during dialysis [10]. Serum albumin has been identified as a surrogate marker for nutritional status and morbidity/mortality in patients with CKD. Patients <18 years of age initiating dialysis with hypoalbuminemia are at a higher risk for death [9].

The objective of this study was to describe the prevalence of growth failure and malnutrition in pediatric CKD patients according to age group. We also aimed to explore the relationship between growth parameters and treatment modalities in the patients.

Subjects and Methods

This was a cross-sectional and observational study that included pediatric CKD patients in stages 1-5, followed by peritoneal dialysis (PD), hemodialysis (HD) and pre-dialysis (Pre-D) in Ege University Faculty of Medicine, Department of Pediatric Nephrology in Turkey from October 2007 to May 2008.

This study was approved by the local ethic committee. Patients' clinical characteristics were retrieved from medical interview, physical examination and careful analysis of patients' records.

This study included 42 patients (23 males and 19 females) and 29 healthy children matched for age and gender. Patients were grouped according to treatment modalities: 20 patients on pre-D (5 at stage I, 8 at stageII, 2 at stage III, and 4 at stage IV), 22 patients in stage V CKD (end stage renal disease, ESRD); 8 patients in this group were treated with PD, and 14 patients were treated with HD. The duration of renal replacement therapy (RRT) ranged from 6 to 139 (average 50.6±36) months. Also, we divided the patients into three groups according to the age onset of disease as early childhood (3-6 years), pre-pubertal (7-10 years), and pubertal (11-17 years).

CKD was defined according to Schwartz formula as: stage 1 (renal injury) Estimated glomerular filtration rate (eGFR) of >90 ml/min per 1.73 m^2, stage 2 (mild) eGFR of 60-89 ml/min per 1.73 m^2, stage 3 (moderate) eGFR 30-59 ml/min per 1.73 m^2, stage 4 (severe) eGFR of 15-29 ml/min per 1.73 m^2, stage 5 (ESRD) eGFR of <15 ml/min per 1.73 m^2.

Nutritional evaluations were performed according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [11], and we performed adjustments using values from children with the same chronological age as reference. All subjects' weights and heights were measured, weight and height standard deviation (SD) scores, and body mass index (BMI) calculated. SD score (z score) was calculated by subtracting the mean height of children of the same age and sex from the observed height and then dividing by the SD for children of that age and sex. Body mass index (BMI) was determined by dividing weight in kilograms by square of height in meters. For these calculations, we used the EPI-INFO Program (version 3.3, October 2004) with Centers for Disease Control (CDC) 2000 references. Growth retardation was described when BMI was below percentile 5 for chronological age, and height/age, weight/age were below −2 z scores for

chronological age [12]. Malnutrition was described according to the subjective global nutritional assessment [13].

Blood samples were collected from all patients after 12-h fasting in a standardized manner. Lipid parameters: total cholesterol, high density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides, hemoglobin, hematocrit, creatinine clearance (blood plus peritoneal fluid in the dialysis group), serum albumin, calcium, phosphorus, parathyroid hormone, calcium in phosphorus, lipid levels and C-reactive protein were evaluated in patients. Blood samples were obtained in post dialysis period. The effectivity of dialysis (Kt/V) was evaluated in the ESRD patients.

Normality of data distribution was assessed using Kolmogorov–Smirnov test and values are presented as mean (±SD) or as median (interquartile range) unless otherwise specified. Student's t test, analysis of variance (ANOVA), or Wilcoxon signed ranked test was used to compare differences between numeric values in different groups. Comparisons of prevalence in different groups were assessed by the chi-square test. Calculations were performed with SPSS (version 11.0) and a *P*-value of less than 0.05 was considered as significant.

Findings

We included 42 (23 males, 19 females) patients and 29 healthy children matched for age and gender. According to their treatment, 22 patients were on RRT (14 on HD, 8 on PD) and 20 were followed in pre-dialysis clinic (5 at stage I, 8 at stage II, 2 at stage III, and 4 at stage IV). The mean age at onset of the disease was 11.2±4.4 years (range 3.3 to 17.5 years). The mean duration of chronic renal failure was 64.5±56.9 months (range 1 month to 16 years).

Nineteen patients (45%) had glomerulopathies, 1 (2%) had Alport syndrome, 15 (35%) had reflux nephropathy, 4 (9.5%) had neurogenic bladder, 3 had obstructive uropathy and 3 had hereditary conditions.

Eight (19%) patients were 3-6 years (early childhood), 9 (21%) patients 7-10 years (pre-pubertal), and 25 (60%) patients 11-17 years old (pubertal). The height was most severely impaired during early childhood (under 6 years old), with mean height SDS of -3.36±2.81. In this group, height SDS in 83% of the patients was below -2. In pre-pubertal group mean height SDS was higher than in early childhood group (-0.99±1.58 vs -3.36 ±2.81, *P*=0.04). In pubertal group, mean height SDS was -1.52±1.76. This value was lower than that in pre-pubertal period while higher than in early childhood (*P*=0.4 and *P*=0.03 respectively). Table 1 shows mean height SDS by age cohorts in all patients.

The mean weight SDS was -0.25±1.46 (range -4 to 1.85), -2.58±1.78 (range -5.3 to 0.68) and 0.53±0.95 (range -0.5 to 1.8) in Pre-D group, RRT group and controls, respectively (*P*<0.001). In RRT groups, the mean weight SDS was -2.92±1.71 (range -5.3 to 0.57) and -1.99±1.87 (range -5.0 to 0.68) in HD and PD groups, respectively (*P*=0.2) (Table2).

The height SDS was -0.77±1.88 (range -5.7 to 2.3), -2.65±1.86 (range -6.6 to -0.1) and 1.3±1.5 (range 0.8 to 2.8) in Pre-D, RRT and controls, respectively (*P*=0.00). In RRT groups, the mean

Table 1: Mean and standard deviation (SD) scores for height by age in all patients according to therapy modalities

	Height Mean (SD)			
Therapy modalities	**3-6 years (n=8)**	**7-10 years (n=9)**	**11-17years (n=25)**	***P value***
Pre – dialysis	-2.60 (3.43)	-0.29 (1.59)	-0.33 (0.74)	0.09 [a]
Hemodialysis	-2.32 (1.12)	-2.2 (0.67)	-2.42 (1.29)	0.6 [b]
Peritoneal dialysis	-3.40 (2.16)	-1.5 (1.83)	-2.62 (3.48)	0.7 [c]
Height SD (Total)	-3.36 (2.81)	-0.99 (1.58)	-1.52 (1.76)	0.03 [d]

[a] No significant differences between height SDS within the Pre-dialysis groups
[b] No significant differences between height SDS within the peritoneal dialysis groups
[c] No significant differences between height SDS within the hemodialysis groups
[d] Significant differences (*P*<0.05; ANOVA) between height SDS within the age groups are marked

Table 2: Demographic and clinical data, and biochemical characteristics in all groups according to the therapy

Parameters	Predialysis (n=20)	Peritoneal dialysis (n=8)	Hemodialysis (n=14)	Controls (n=29)	*P* value
Male/Female (Frequency)	12/8	5/3	6/8	15/14	-
Age (year) [Mean (SD)]	11.3 (4.8)	9.3 (4.9)	12.2 (3.2)	12.1 (4.4)	0.3
Weight SDS [Mean (SD)]	-0,25 (1.46)	-1.99 (1.87)	-2,92 (1.71)	0.53 (0.95)	<0.001 [a]
Height SDS [Mean (SD)]	-0.54 (1.43)	-2.72 (2.69)	-2.73 (1.58)	1.3 (1.5)	<0.001 [a]
BMI SDS [Mean (SD)]	-0.22 (1.44)	-1.03 (1.56)	-1.57 (1.33)	1.4 (1.7)	0.03 [a]
Serum albumin [Mean (SD)]	3.99 (0.4)	3.27 (1.29)	3.87 (0.45)	4.5 (0.9)	0.04 [a]
Total cholesterol [Mean (SD)]	188.0 (25.0)	193.0 (38.0)	178.0 (17.0)	149.0 (8.1)	<0.001 [a]
HDL cholesterol [Mean (SD)]	51.0 (8.5)	41.0 (6.2)	45.0 (4.7)	66.0 (9.1)	<0.001 [a]
LDL Cholesterol [Mean (SD)]	93.0 (15.1)	94.0 (12.8)	98.0 (18.7)	82.0 (8.7)	<0.001 [a]
Triglyceride [Mean (SD)]	116.0 (24.0)	166.0 (28.5)	102.0 (27.2)	68.0 (17.4)	<0.001 [a]
CRP [Mean (SD)]	1.9 (0.2)	1.8 (0.3)	1.3 (0.4)	1.8 (0.3)	0.1

[a]ANOVA between peritoneal dialysis and hemodialysis parameters within the therapy modalities are marked.
SD: Standard Deviation / BMI: Body Mass Index / CRP: C- reactive Protein

height SDS was -2.66±1.55 (range -6.3 to -0.64) and -2.63±2.43 (range -6.6 to -0.10) in HD and PD groups, respectively (*P*=0.96). Seventeen (40%) patients had short stature (height SDS below -2 SDS). The disease duration was longer in patients with short stature than in other patients (7.1±3.8 vs 3.8±4.4 years). There was statistically significant relationship between duration of disease and short stature (*P*=0.01). In our cohorts growth impairment was related to treatment modalities without age group (*P*=0.09, *P*=0.6, *P*=0.7, Pre–D, HD and PD, respectively) (Table 1).

In Pre-D group, 2/20 patients had short stature (height SDS was below <-2SDS), while 12/22 patients had short stature in RRT group (*P*=0.03).

Significant difference was seen between BMI SDS in Pre-D, RRT and controls groups (*P*=0.03), but in RRT groups, the mean BMI SDS doesn't have significant difference in HD and PD groups (*P*=0.4).

In all groups, 19/42 (45%) (4 on Pre-D, 5 on PD, 10 on HD) patients had malnutrition which was attributed to SGA. Mean albumin was 3.82±0.97 which was below the normal reference values (3.5 mg/dl) in only 14% of patients. In Pre-D group, the mean serum albumin was 3.99±0.4 mg/dl (range 3.4 to 4.8), while it was 3.87±0.45 (range 3 to 4.5) and 3.27±1.29 (range 0.3 to 4.5) in HD and PD group, respectively (*P*=0.04) (Table2). Protein catabolic rate was higher in HD groups than in other patients (0.82±0.10 g/kg/per day) (*P*=0.03). The growth and nutritional status were better in Pre-D group than in RRT group.

Most patients were receiving the usual medications, such as phosphate binders, antihypertensive agents, vitamins, and nutritional supplements. For patients in HD, mean Kt/V was 1.75, whereas for patients in PD, it was 4.2. Mean CRP concentration was 1.07±1.86 mg/dl (range 0.1–8.41 mg/dl). Sixteen (45.7%) patients presented CRP levels above 0.3 mg/dl and therefore were considered inflamed. A larger proportion of HD patients (59%) were inflamed.

Discussion

Growth failure is a major obstacle for full rehabilitation and may result in severely diminished adult height in childhood with CKD.

Chronic kidney disease can result in impairment in each phase of development from in-utero to adolescence, which can subsequently result in growth retardation, with studies suggesting that the degree of height deficit worsens with duration of disease [3]. In this study we found that a relation exists between disease duration and short stature.

Previous studies have described aspects of growth pattern, either focusing on infancy, pre-puberty or puberty [14-16]. These studies showed that infancy and early childhood represent the most affected growth periods in children with CKD. In this study, our patients under 6 years of

age showed the most severe growth deficit in height (mean height SDS was -2.45). In the age cohort, height SDS in 83% of the patients was below -2.

Zivicnak et al [17] have shown that growth kinetics differed during early and late puberty, beginning with a slowing-down of growth during early puberty. Similarly, we observed the same pattern of height SDS curves in all patients. The mean height z score decreased in early childhood and pubertal groups than in prepubertal group (Table 1).

Growth failure remains a challenging problem of the management of children with CKD. The degree of kidney failure and treatment modalities did significantly influence the severity of growth impairment without age dependence [17]. Despite good progress with regard to both conservative treatment and RRT, 30% to 60% of children with ESRD still grow up to become stunted adults [18-20]. Growth failure is associated with mortality, morbidity and especially psychosocial problems in children with CKD [5,7]. Reduced adult heights have been reported in about 30% to 50% of patients with CKD [15,16,21]. The age at onset of ESRD, the duration of chronic renal failure, gender and primary disease were related to final height [22]. In our cohort, longer duration of chronic renal failure was found to be associated with short stature while gender, age at onset of CRF and primary disease were not related to final height. At the end of the follow up time 17 (40%) patients had short stature (9 patients on HD, 4 on PD and 4 on pre-D). The pre-dialysis patients were found better than RRT patients. In HD group, there was lower mean height SDS, which was not statistically significant. In our cohorts, growth impairment was related to treatment modalities independent of age group. We show the main clinical and laboratory characteristics in Table 2.

The body mass index can be prognostic, because extremes are associated with increased mortality and morbidity. Wong et al [5] demonstrated that the adjusted relative mortality risk of children with ESRD is 60% higher at BMI standard deviations of -2.5 and +2.5 as compared with an ideal BMI standard deviation of 0.5. In our study, 10 patients' BMI SDS was under -2.5 SDS (1 on pre-D, 5 on HD and 3 on PD). The pre-dialysis patients were found to be better than renal replacement therapy patients.

Malnutrition is an important risk factor for mortality and it is too prevalent in adults and children with CKD[10,23,24]. The prevalence of loss of energy and protein in pediatric HD patients is reported to be 56%[25]. Measuring inadequate nutritional status is difficult. However, measurement of nutritional parameters is complicated in CKD because of salt and water imbalance [26]. Anthropometric and nutritional measures are usefully expressed as a score of the number of standard deviations from the mean for a normal population of the same age (e.g. height, weight or body mass index SD scores).

This allows comparison with the normal population and helps follow progress in the individual patient [26].

Serum albumin is surrogate marker for nutritional status in children with ESRD [27]. It is an independent biomarker for increased mortality and morbidity [9]. However, patients on peritoneal dialysis have significant protein and amino acid losses in the dialysate [22]. In our patients, the mean serum albumin level was higher in Pre-D group than HD and PD patients. Peritoneal dialysis patients had lower serum albumin levels as expected in our cohorts. The serum albumin levels were statistically different among groups. Previous studies have shown that hypo-albuminemia is related to inflammation [28,29]. We did not find a correlation between hypo-albuminemia and elevated CRP.

In summary, we investigated growth parameters in children with CKD according to both age groups and therapy. Growth impairment in our patients was age dependent with the most vulnerable period of longitudinal growth being early childhood. Secondly we observed that growth impairment was found more frequently in patients under HD therapy.

Conclusion

Growth failure and malnutrition remain a significant age dependent clinical problem in children with CKD. Growth parameters correlate to the degree of kidney failure and treatment

modalities. We suggest that peritoneal dialysis provides a better growth than hemodialysis does.

Acknowledgment

This study adhered to the principles of the Declaration of Helsinki and was approved by the local Ethics Committee.

Conflict of Interest: There are no financial conflicts of interests.

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