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Prevalence of Failure to Thrive in Iranian Children with Chronic Kidney Disease

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Introduction: Malnutrition and inflammation are considered risk factors of morbidity, hospitalization, and mortality in chronic kidney disease (CKD) children. The aim of this study was to determine the prevalence and severity of failure to thrive (FTT) in children with moderate to severe CKD.
Materials and Methods: This cross-sectional study was conducted in 84 children with CKD (30 female, 54 males) aged 2-16 years old from June 2014 to June 2015.The inclusion criteria were eGFR less than 90 ml/min/1.73m^2, being healthy in the month before the visit, and lack other chronic diseases except CKD. Anthropometric data including the body mass index, height, weight, and mid upper arm circumference were collected. Protein wasting energy was scored and the severity of failure to thrive was estimated using Gomez and Jelliffe classifications. P-values less than 0.05 were considered significant
Results: Glomerulopathy and hereditary tubulopathy were the main causes of underlying disease. About 79% of CKD children had FTT and the rate increased with a decline in the renal function (p-value< 0.05). Using modified PWE, 65.5% were identified to score ≥2, which was more frequent in eGFR less than 30 (P>0.05). A quarter of the patients with FTT were classified as no PWE and vice versa.
Conclusion: The majority of the children with moderate to severe chronic kidney disease had failure to thrive and protein wasting energy. There was no correlation between inflammatory markers and the severity of CKD or the presence of failure to thrive.

Keywords: Failure to Thrive; Renal Insufficiency; Chronic; Child.

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Running Title: Failure to Thrive in Chronic Kidney Disease

Introduction

Children with chronic kidney disease (CKD) are at risk of energy-protein malnutrition which is the strongest predictor of mortality. It increases the risk of hospitalization and mortality [1]. Failure to thrive (FTT) is a multi-factorial condition and may result from malnutrition, inflammation, and catabolic state.

The reported prevalence of malnutrition or failure to thrive in CKD children ranges from 5% to 65% as a result of inconsistent criteria worldwide [2-4].

A limited number of epidemiological studies have investigated children with CKD in Iran. However, end stage renal disease (ESRD) has an increasing trend in the Iranian adult population [5].

The trend of ESRD in Iranian patients below 20 years of age remained constant from 1996 to 2005 (around 10.2 and 8.6%) [6]. A recent survey in school age children in Isfahan revealed the annual incidence of CKD stage 3- 5 is 14.5 in one million [7]. Our previous study showed dialysis children with FTT had short a survival time [8]. Few studies have investigated the rate of malnutrition in Iranian children suffering from CKD [9].

The aim of this study was to screen different stages of CKD for malnutrition and failure to thrive using the conventional criteria.

Materials and Methods

This cross-sectional study was conducted in 84 children with CKD aged 2-16 years who were visited at Ali-Asghar Children Hospital, affiliated with Iran University of Medical Sciences from June 2014 to June 2015. CKD was defined by eGFR less than 90 ml/min/1.73m^2. Serum creatinine was measured by the Jaffe method and eGFR was calculated using the Schwartz formula [(Height (cm) x 0.55)/ Plasma creatinine (mg/dl)] [10]. Failure to thrive was considered if the growth parameters of a child fell beyond two or more percentiles or remained persistently below the third or fifth percentile. Then, we used Gomez and Jelliffe classifications to classified the severity of protein energy malnutrition in CKD children. Based on the Gomez classification, FTT was classified to mild (grade 1) if the expected percentage of weight for age (WFA) was between 75 to 90%, moderate (grade 2) if it was between 60-74%, and severe (grade 3) if it was below 60% [11].

Arm circumference was measured around upper two third of right arm by a centimeter at time of outpatient visit. According to Jelliffe classification, normal nutrition is defined as an arm circumference (AC) above 12.5 cm, mild to moderate malnutrition is present if it is 11.5-12.5 cm, and an AC below 11.5 cm indicates severe malnutrition [12].

The WHO growth standards chart was used for assessing growth parameters in CKD children [13]. Protein energy wasting was scored according to the modified criteria for children [14]. Short stature was defined as height below the 5th percentile for age and gender and a BMI above 85 was considered overweight.

The patients were routinely followed in the outpatient clinic for anthropometric parameters, lab tests, and clinical findings. The last measurement was used for classification. Before enrollment in the study, the protocol was explained to the parents and informed consent was obtained. The study adhered to the tenets of the Helsinky protocol. The study was approved by Research Committee of Iran University of Medical Sciences (ID number 1794 dated 6.7.2014). Inclusion criteria were a diagnosis of CKD; age 2 - 16 years; being healthy in the month before the visit; no history of admission for chronic lung disease, recurrent pneumonia, cystic fibrosis or bronchiectasis; and no history of documented hypothyroidism in the previous year. Children with severe congestive heart failure defined by an ejection fraction less than 25% and resistant hypertension defined by receiving three different classes of antihypertensive medications including diuretics were excluded from the study.

Weight and height were measured by minimal clothing without shoes using standard scales (mechanical column scale with an eye-level beam, SECA700). Last visit measurements were recorded for this study.

Quantitative and qualitative variables are presented as mean (±SD) and frequency (percentage), respectively. We used chi-square test or Fisher's exact test to compare qualitative variables, and t-test and ANOVA to compare quantitative variables. The level of significance was set at 0.05.

Results

The mean (SD) age of the 84 children (30 female, 54 male) who were enrolled in the study was 7.97 (±4.4) years [median: 8, range: 2-16 years]. Glomerulopathy and hereditary tubulopathy were the main causes of underlying disease. Table 1 shows the demographics of the patients. FTT was detected in 66 children of whom 21 had severe FTT. eGFR was lower and the rate of PWE was significantly higher in the FTT group. Short stature and overweight was seen in 55 65.5%) and 13 (15.5%) children, respectively. Of overweight children, 61.5% had short stature (P>0.05). From 13 children with BMI >85, three (23%) were classified as FTT in contrast to 63 (88.7%) children with BMI below 85 who had some degrees of FTT (p-value<0.001).

The mean (SD) serum creatinine level was 4.62 (±3.82) mg/dl [median 4, range: 0.4-28) mg /dl] in the patients in this study, and the mean (SD) GFR

Table 1. Demographic data of Children with Chronic Kidney Disease

	With FTT n-66 Mean(SD)	Without FTT n-18 Mean(SD)	p-value 95% CI
Age- year	7.9(4.5)	8 (3.9)	NS
Gender, n(%) **Female** **Male**	 27(32.1) 39(46.4)	 6(7.1) 12(14.3)	NS
Weight- kg	19.7(9.6)	31.2 (16)	P<0.001, CI:17.39,-5.49
Z-score Weight	-2 (0.8)	0.7(1)	P<0.001, CI:-3.22,-2.27
Percentile weight	7.5(7.5)	63.8 (22.5)	P<0.001, CI:-62.87,-49.89
Height- cm	109.4(22.5)	122.5 (27.4)	P:0.042, CI:-25.53,-0.50
Z-score Height	-2.1 (0.9)	-0.8 (1.7)	P<0.001, CI:-1.90,-0.64
Percentile height	11(14.8)	31.9 (30.8)	P<0.001, CI:-31.07,-10.66
Short Stature ,n(%)	50(76)	5(28)	<0.001, OR: 8.12(2.5-26.3)
Arm circumference	2.5(0.8)	2.9 (0.2)	P:0.029, CI:-0.81,-0.04
BMI, Kg/H2	15.7(3.2)	19.7(3.5)	P<0.001, CI:-5.73,-2.24
Z-score BMI	-0.9(1.4)	1.5(1.5)	P<0.001, CI:-3.25,-1.68
Percentile BMI	26.2(25.4)	78.6(30.7)	P<0.001, CI:-66.42,-38.21
BMI, n(%) **>85%** **<15%**	 4(6) 34(51.5)	 12(66.7) 1(5.6)	<0.001
SBP-mmHg	125.2 (23.8)	119.5(26)	NS
DBP-mmHg	72.9(16.1)	73.8 (16.1)	NS
Underlying disease-n(%) **GN/NS** **Tubulopathy/Hereditary** **Cystic** **other**	 26(31) 32(38) 6(7) 2(2)	 12(14) 3(4) 1(1) 2(2)	P:0.048
Duration of disease, years, mean(SD)	4.8(3.7)	3.3(2.8)	NS
RRT, n(%) **None** **PD** **HD** **Tx**	 16(19) 28(33) 10(12) 12(14)	 8(10) 7(8) 2(2) 1(1)	P:0.298
eGFR, ml/min/1.73m²	20.1(17)	39.5(29.8)	P:0.001, CI:-30.11,-8.55
S creatinin, mg/dl	4.8 (3.8)	3.8 (3.6)	NS
Hb, g/dl	10(2.9)	12.7(2.1)	P<0.001, CI:-4.22,-1.27
T.protein, mg/dl	6.2 (1.1)	5.7 (1.4)	NS
Albumin, mg/dl	3.5 (0.7)	3.4 (1.4)	NS
CRP, mg/dl	5.4 (5.3)	9.5 (13.5)	P:0.048, CI:-8.29,-0.04
PWE , n(%) **No PWE** **Minimal** **Standard** **Modified**	 16(24) 28(42) 8(12) 14(21)	 13(72) 2(11) - 3(17)	P:0.001

BMI: Body Mass Index, SBP: systolic blood pressure, DBP: Diastolic blood pressure, GN: Glomerulonephritis, NS: nephritic syndrome, RRT: renal replacement therapy, PD: peritoneal dialysis, HD: hemodialysis,eGFR: estimated glomerulr filtration, PWE: protein wasting energy.

was 24.3±21.77 ml/min/1.73m^2 [median 14, range 4.5-9 ml/min/1.73m^2].

Overall, 66 (78.5%) CKD children had FTT and the rate increased with deterioration of the renal function (p-value: 0.005). Using modified PWE, 55 children (65.5%) had a score ≥2 and it was more frequent in eGFR less than 30 (P>0.05). (Table 2)

The Z score of weight and height in children with CKD stage 3 was worse than CKD stage IV in contrast to the Z score of BMI. There was no

Table 2. The severity of Failure To Thrive and Protein Wasting Energy in different classes of eGFR

Classifications ml/min/1.73m^2		FTT				P-value
		No N=18	Mild N=16	Moderate N=29	Severe N=21	
eGFR	<15	5 (20%)	12(28.6%)	12(28.6%)	13(31%)	0.014
	15-30	4(21%)	3(16%)	10(52.6%)	2(10.5%)	
	30-60	4(25%)	1(6%)	6(38%)	5(31%)	
	>60	5(71)	-	1(14)	1(14)	
Classifications ml/min/1.73m^2		PWE				P-value
		No N=29	Minimal N=30	Standard N=8	Modified N=17	
eGFR	<15	14 (33%)	17(40.5%)	2(5%)	9(21%)	NS
	15-30	5(26%)	8(42%)	3(16%)	3(16%)	
	30-60	7(44%)	5(31%)	2(12.5%)	2(12.5%)	
	>60	3(43)	-	1(14)	3(43)	

Table 3. the mean (SE) of anthropometric data in children with different level of eGFR

eGFR ml/min/1.73 m2	ZWT	% WT	ZHT	% HT	ZBMI	% BMI
<15	-1.64(0.21)	14.6(3.3)	-2.21(0.14)	10.4(2.2)	-0.43(0.29)	33(5)
15-30	-1.53(0.22)	19.5(5.6)	-1.37(0.28)	19.8(5.2)	-0.95(0.35)	32.6(6.4)
30-60	-1.56(0.36)	16.6(6)	-2.13(0.29)	11(3)	-0.25(0.37)	40.3(8.3)
p-value	***0.009***	***0.001***	***<0.001***	***<0.001***	***NS***	***0.04***
RRT	**ZWT**	**% WT**	**ZHT**	**% HT**	**ZBMI**	**% BMI**
No dialysis	-0.96(0.28)	25.6(5.8)	-1.33(0.32)	24.6(5.3)	-0.41(0.3)	38.5(7.4)
CAPD	-1.54(0.28)	20.5(4.8)	-2(0.2)	13.5(3.45)	-0.14(0.3)	42(6.1)
HD	-1.66(0.3)	12.5(5)	-2.16(1.2)	12.2(5.1)	-0.92(0.5)	28.7(8.5)
Transplant	-1.84(0.78)	12.3(5.4)	-2(0.25)	7.3(1.6)	-0.84(0.4)	31(8)
p-value	***NS***	***NS***	***NS***	***NS***	***NS***	***NS***

correlation between the severity of FTT and gender, age, or underlying disease (Table 3). In this study, 25% of patients with FTT had no PWE, whereas 25% of the patients with no FTT have PWE.

There was no correlation between FTT or PWE and gender, age, underlying disease, duration of CK, or RRT. Multivariate analysis showed a significant correlation between eGFR and FTT (p-value: 0.004) but not with PWE (p-value=0.56).

Discussion

Children with CKD are at risk of energy-protein malnutrition. Growth disorder is one of the main complications in children with CKD. Failure to thrive has a significant correlation with CKD in the children [15]. In this study, we found that more than 80% of children with moderate to severe CKD had FTT and about 66% had PWE. This rate is too high when we compare it with the report of CKD children around the world. Apostoulu et al reported that 20-40% of children with CKD stage III or higher have malnutrition [2]. A report from Abraham et al showed of 528 children with mild to moderate CKD, 7-20 % had PWE. The rate of hospitalization was also twice as high in these patients [16]. Our study included moderate to severe CKD children and mild CKD was a minority. We detected a higher rate of PWE in these patients. In a previous study of 174 children on chronic renal replacement therapy, weight of 35% of patients was under third percentile. That study showed two times higher mortality rate compared to those with normal weight [17]. Our previous study revealed a high rate ofmortality in young children and those with severe malnutrition on peritoneal dialysis [8]. In a nationwide study of more than 21000 school aged children, Koleishadi et al found a small number of children and adolescent were overweight while the rate of overweight among our CKD children was two times as high as the general population [18]. However, a more recent study on 3582 school children in Zahedan revealed 20% of the cases had BMI over 85% [19]. Javedan et al found the prevalence of overweight was 20% in 17484 preschool children in Tehran. Precisely two thirds of our study group had a short stature and 16% of the children with height below 5% had BMI over 85% [20]. Therefore, BMI may not be a good determinant of FTT in CKD children. Anthropometric measurements of 1949 children with end stage renal disease (ESRD) by Wong et al showed extreme BMI and decreased height SDS were correlated with a higher risk of death in these children [21]. As markers of inflammation, mean CRP was higher in children with no FTT but mean albumin was similar in our study group. Sylvestre et al showed that despite a wide prevalence of 5 to 65% for malnutrition in children with CKD, HD, and PD patients, there is no consistent correlation between inflammation and malnutrition in children [3]. CKD impairs ghrelin activation that has been suggested to be a cause of poor appetite in advanced CKD patients [22]; however, it was not the subject of our study.

The limitations of our study were its small sample size, lack of control group, considering single measurements of anthropometric indexes and inflammatory markers, lack of information about appetite, medication and recall chart of intake, and lack of details of echocardiography results. We suggest a multicentric study with a larger sample size by considering nutritional interventions in order to improve the quality of life and decrease the mortality rate.

Conclusions

This study showed a high rate of failure to thrive and protein energy wasting in children with moderate to severe chronic kidney disease. We found no correlation between inflammatory markers and the severity of CKD or the presence of failure to thrive.

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Conflict of Interest

None declared

Financial Support

None declared

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