Research Article / Araştırma Makalesi

Evaluation of the Factors Affecting Disease Progression in Children with Predialysis Chronic Kidney Disease

Prediyaliz Kronik Böbrek Hastalığı Olan Çocuklarda Hastalık İlerlemesini Etkileyen Faktörlerin Değerlendirilmesi

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Abstract: Chronic kidney disease (CKD) is an important health problem that can progress to end-stage renal disease (ESRD). In our study, it was aimed to evaluate the factors affecting disease progression in children with the diagnosis of predialysis CKD. In our study, the data from 25 patients with predialysis CKD were retrospectively reviewed. The laboratory findings were evaluated at the time of admission, at the second and fourth years. The mean follow-up period of the patients was 6.6 ± 2.27 years. Thirteen patients showed progression in the CKD stage. There was a statistically significant difference between the GFR at admission and the GFR at the fourth year follow-up (p=0.043). In patients with a significant decrease in GFR, serum uric acid levels at admission was statistically significantly higher than in patients without a decrease in GFR (p=0.015). Serum uric acid levels had predictive value for the decrease in GFR (area under curve: 0.82, cut-off value:6.1±0.89 mg/dL, sensitivity:83.1%, specificity:67.4%, p=0.028). The frequency of hypertension was higher in patients with a decrease in GFR compared to patients without a decrease in GFR (p=0.001). In Cox regression analysis, significant correlations were found between the serum uric acid levels and the presence of hypertension at admission and a decrease in GFR (hazard ratio:1.536, 95%confidence interval:1.214-1.903, p=0.032, Hazard ratio:1.873, 95%confidence interval:1.164-2.287, p=0.041, respectively).Identification of the factors that cause the progression of chronic kidney disease and treatments to prevent these factors may slow the progression to ESRD in children.
Keywords: Predialysis chronic kidney disease, progression, childhood

Özet: Kronik böbrek hastalığı (KBH), son dönem böbrek hastalığına (SDBH) ilerleyebilen önemli bir sağlık sorunudur. Çalışmamızda prediyaliz KBH tanısı alan çocuklarda hastalığın seyrini etkileyen faktörlerin değerlendirilmesi amaçlandı. Çalışmamızda prediyaliz KBH olan 25 hastanın verileri retrospektif olarak incelendi. Başvuru anında, ikinci ve dördüncü yıldaki laboratuvar bulguları değerlendirildi. Hastaların ortalama takip süresi 6,6 ± 2,27 yıldı. On üç hastada KBH evresinde ilerleme görüldü. Başvuru anındaki glomerul filtrasyon hızı (GFH) ile dördüncü yıl takipteki GFH arasında istatistiksel olarak anlamlı fark vardı (p= 0,043). GFH'de anlamlı azalma olan hastaların başvuru anındaki serum ürik asit düzeyleri, GFH'de azalma olmayan hastalara göre istatistiksel olarak anlamlı derecede yüksekti (p= 0,015). Serum ürik asit düzeyleri GFH'deki düşüş için öngörücü değere sahipti (eğri altındaki alan: 0,82, eşik değer: 6,1 ± 0,89 mg/dL, duyarlılık: %83,1, özgüllük: %67,4, p= 0,028). GFH'si azalan hastalarda, GFH'si düşmeyen hastalara göre hipertansiyon görülme sıklığı daha yüksekti (p= 0,001). Cox regresyon analizinde serum ürik asit düzeyi ile başvuru sırasında hipertansiyon varlığı ve GFH'de azalma arasında anlamlı korelasyonlar bulundu (sırası ile hazard oranı: 1,536, %95 güven aralığı: 1,214-1,903, p= 0,032, hazard oranı: 1,873). , %95 güven aralığı: 1,164-2,287, p= 0,041). Kronik böbrek hastalığının ilerlemesine neden olan faktörlerin belirlenmesi ve bu faktörlerin önlenmesine yönelik tedaviler çocuklarda SDBH'nin ilerlemesini yavaşlatabilir.
Anahtar Kelimeler: Prediyaliz kronik böbrek hastalığı, progresyon, çocukluk çağı

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1. Introduction

Chronic kidney disease (CKD), defined as irreversible decrease in glomerular filtration rate (GFR), is an important health problem that can cause serious morbidity and mortality in children. Chronic kidney disease usually develops in children due to congenital disorders of the kidney and urinary system or various hereditary and metabolic diseases. The prognosis of CKD may vary depending on the systemic complications that may develop. Regardless of the underlying cause, CKD progresses to end-stage renal disease (ESRD) over time(1-3).

CKD management in childhood should be based on a multidisciplinary approach that includes slowing down the progression to ESRD, increasing the quality of life, ensuring normal growth and development and gaining cognitive abilities, rather than eliminating the factor involved in the etiology. In our study, it was aimed to evaluate the factors affecting disease progression in the predialysis period in children followed up with the diagnosis of CKD on predialysis.

2. Materials and Methods

In our study, the file data of the patients who were followed up with the diagnosis of predialysis CKD in our Pediatric Nephrology Department between 2009 and 2014 were examined. The CKD staging of the patients was performed according to The Kidney Disease Improving Global Outcomes (KDIGO 2012) guideline (1). From the files of the patients, complete blood count, GFR, degree of proteinuria, blood urea nitrogen, creatinine, calcium (Ca), phosphorus, parathormone (PTH), sodium, potassium, protein, albumin, uric acid, vitamin D and lipid levels, blood gas analysis results, and iron parameters were evaluated. Complications such as malnutrition status, change in the severity of proteinuria, decrease in GFR, renal osteodystrophy that developed during the follow-up, metabolic acidosis, secondary hyperparathyroidism, hyperphosphatemia, hypoalbuminemia, anemia, and hypertension were determined. The factors affecting CKD progression were investigated during the four-year follow-up of the patients. GFR values of the patients were calculated using the Schwartz formula. Those who have undergone renal replacement therapy, have a history of surgical intervention related to the urinary system and/or kidney, have systemic diseases other than kidneys, had a history of drug use such as calcinorin inhibitor or non-steroidal anti-inflammatory drugs that might affect kidney functions at the time of admission, and had a follow-up period of less than four years, data of patients with GFR less than 15 mL/min/1.73m2 at the time of admission were not included in the study. The file data of the patients who had a history of being followed up in another center with the diagnosis of predialysis CKD before they were admitted to our hospital, who did not attend regular outpatient follow-ups, and who had missing electronic file records were excluded from the study.

Anemia was defined as Hb value below the 5th percentile adjusted for age and sex. Iron deficiency anemia was defined as a transferrin saturation of <20% and a serum ferritin level of <100 ng/mL in serum samples taken in the morning after a 12-hour fasting at night (4). The patients were followed up at 1-3 month intervals in our Pediatric Nephrology Department. Detailed physical examination, height and weight measurement, and blood pressure measurements were performed during each control in our outpatient clinic. During the routine outpatient examination, venous blood gas and complete blood count were examined, and serum blood urea nitrogen, creatinine, sodium, potassium, chlorine, calcium, phosphorus, albumin and PTH levels were measured. Treatment and follow-up of patients with acidosis, renal osteodystrophy, and malnutrition were performed according to the standard recommendations recommended for pediatric patients with stage 2-4 CKD (5). Antihypertensive treatment was started in line with the recommendations made for patients with blood pressure above the 95th percentile (6). Patients receiving antihypertensive treatment at the time of admission were not included in the data.

Body weight for height below 2 standard deviations was considered as malnutrition (7). In a sitting and resting child, with a cuff of

appropriate size, blood pressure measurement at or above the 95th percentile for age, height, and gender was accepted as HT (8). Patients with serum albumin levels below 3 g/dL were considered to have hypoalbuminemia (2). A spot urine protein/creatinine ratio above 0.2 was defined as proteinuria. A serum phosphorus level above the normal value for age was considered as hyperphosphatemia. PTH levels higher than normal according to CKD stage were considered as hyperparathyroidism (9).

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 06, Date: 13.03.2018).

The data of the patients were evaluated in the SPSS 11.5 program. The conformity of the data in the study to the normal distribution was evaluated with the Shapiro-Wilk test and descriptive statistics were given as mean ± standard deviation. Data that were not normally distributed were expressed as the median (interquartile range). Chi-square test was used to compare categorical variables between groups. The GFR values of the patients during the follow-up were compared with the paired sample test. A COX regression analysis was used to determine the factors affecting the decrease in GFR. Receiver operating characteristic curve (ROC curve) analysis was used to determine the threshold value of serum uric acid level showing a decrease in GFR. A p value less than 0.05 was considered statistically significant.

3. Results

Data from 25 patients were analyzed in this study. Thirteen (52%) of the patients were girls and 12 (48%) were boys, and the ratio of girls to boys was 1.08. The mean age of diagnosis of the cases was 7.5 ± 1.67 years, and their ages ranged from 5 to 16 years. The mean follow-up period of the patients was 6.6 ± 2.27 years. Eighteen (72%) of the patients included in the study had congenital anomalies of the kidney and urinary system in the etiology of CKD (Table 1).

Malnutrition was present in 10 patients (40%), HT in 15 patients (60%), proteinuria in 11 patients (44%), hyperparathyroidism in 17 patients (68%), hyperphosphatemia in 22 patients (88%), and hypoalbuminemia in 8 patients (32%) at the time of admission.

At the time of admission, thirteen patients were at stage 4, four patients were at stage 3, six patients were at stage 2, and two patients were at stage 1 CKD. During the four-year follow-up period, thirteen patients showed progression in the CKD stage. It was determined that the CKD stage of 5 patients progressed from 4 to 5, and the CKD stage 4 patients progressed from 2 to 3. It was determined that one patient for each group also progressed from stage 1 to 2, from stage 2 to 4, from stage 3 to 4 and from stage 1 to 5.

The laboratory values of the patients at admission and during follow-up are shown in Table 2 in detail. There was a statistically significant difference between the GFR at admission and the GFR at the fourth year follow-up (p=0.043). Statistically significant differences were found between the creatinine values of the patients at admission and the creatinine values in the second and fourth years during the follow-up (p=0.001 for the second year, p=0.000 for the fourth year, respectively, Table 3).

In patients with a significant decrease in GFR during follow-up, the serum uric acid level at admission was statistically significantly higher than in patients without a decrease in GFR (p=0.015). A ROC analysis showed that uric acid level had predictive value for the decrease in GFR (Area under the ROC curve (AUC): 0.82, cut-off value: 6.1 ± 0.89 mg/dL, sensitivity: 83.1%, specificity: 67.4%, p=0.028). It was determined that the frequency of HT was higher in patients with a decrease in GFR during the follow-up compared to patients without a decrease in GFR (p=0.001, Table 4). In Cox regression analysis, significant correlations were found between the serum uric acid level and the presence of hypertension at admission and a

decrease in GFR (hazard ratio: 1.536, 95% confidence interval: 1.214-1.903, p=0.032, Hazard ratio: 1.873, 95% confidence interval: 1.164-2.287, p=0.041, respectively).were not

There were no significant correlations between the degree of proteinuria, metabolic acidosis, secondary hyperparathyroidism, hyperphosphatemia, hypoalbuminemia, anemia and decrease in GFR (p >0.05).

Table 1. Demographic characteristics of the patients.

Age (years)	15.3 ± 6.71
Gender (girl)	13
Age of diagnosis (years)	7.5 ± 3.67
Follow-up period (years)	6.6 ± 2.27
Etiologies	
-Congenital anomalies	18 (72)
Primary vesicoureteral reflux	9 (36)
Polycystic kidney	1 (4)
Renal agenesis	4 (16)
Ureterovesical obstruction	3 (12)
Posterior urethral valve	1 (4)
-Nephrotic syndrome	2 (8)
-Urolithiasis	1 (4)
-Glomerulonephritis	1 (4)
-Hemolytic uremic syndrome	1 (4)
-Neurogenic bladder	2 (4)

Results were shown as mean ± standard deviation, median (interquartile range), and number (percentage).

Table 2. Laboratory values of the patients at admission and follow-up

	Admission	**Second year**	**Fourth year**
Hemoglobin (g/dL)	10.6 ± 2.41	10.5 ± 2.66	10.5 ± 2.57
BUN (mg/dL)	21.65 (22.21 – 36.61)	21 (16.55 – 23.51)	47.71 (32.51 – 67.54)
Creatinine (mg/dL)	1.05 (0.92 - 2.74)	1.21 (1.07 - 2.99)	1.85 (1.28 - 4.21)
Albumin (g/dL)	4.1 ± 1.04	4.1 ± 0.75	4.2 ± 0.87
Phosphorus (mg/dL)	5.6 ± 2.41	5.5 ± 2.31	4.6 ± 1.01
Calcium (mg/dL)	9.2 ± 1.29	9.3 ± 1.29	9.5 ± 1.07
Alkaline phosphatase (U/L)	654 (425 - 943)	134 (70 - 388)	226.5 (211- 445)
Uric acide (mg/dL)	6.3 ± 1.93	6.2 ± 1.88	5.1 ± 1.61
Vitamin D (ng/ml)	28 (4.53 - 28)	19.8 (3.88 - 38.85)	19.2 (5.06 - 34.15)
Iron level (ug/dL)	138 (62 - 138)	49.2 (32 - 78)	56 (38.75 - 81.75)
Iron binding capacity (ug/ dL)	249.6 ± 83.96	289.4 ± 91.86	270 ± 79.02
Triglyceride (mg/dL)	126	199	167.2

	(126 - 532.5)	(77 - 278.5)	(87 - 246)
HDL (mg/dL)	38.9 ± 9.80	52.6 ± 13.86	42.1 ± 18.36
LDL (mg/dL)	88 ± 30.8	107.8 ± 18.56	89.4 ± 26.67
Cholesterol (mg/dL)	195.1 ± 95.78	180.5 ± 38.77	158.8 ± 22.94
GFR (mL/min/1.73 m²)	26.5	32.0	25
	(19.3 - 75.3)	(21 - 71.5)	(18 - 43)
Bicarbonate (mmol/L)	16.1 ± 5.34	18.9 ± 5.41	21.40 ± 4.21
Ferritin (ng/mL)	80.50	44.0	52.50
	(73 - 88)	(23.30 - 144.05)	(29.25 - 120.40)
Spot protein/creatinine	2.85	1.41	3.02
	(0.70 - 5)	(0.27 - 17.80)	(1.91 - 21.32)
24-hour urine protein	97.75	42.49	34.32
(mg/m^2/hour)	(18 - 177.50)	(5.99 - 79)	(14.32 - 67.54)
Parathormon (pg/mL)	288	427	167.60
	(180 - 325)	(187 - 667)	(89.0 - 322.0)

Results were shown as mean ± standard deviation and median (interquartile range). BUN; blood urea nitrogen, HDL; high-density lipoprotein, LDL; low-density lipoprotein, GFR; Glomerular filtration rate.

Table 3. Differences between the laboratory values of the patients at the time of admission and at the second and fourth years.

Mean	Standard deviation	95% CI	p	
GFR 0-2	11.65	27.91	-1.411 - 24.710	0.077
GFR 2-4	4.59	14.73	-2.307 - 11.471	0.180
GFR 0-4	16.24	33.48	1.565 - 31.905	0.043
PTH 2-4	30.45	263.14	-100.406 - 161.303	0.630
Creatinine 0-2	-1.447	1.632	-2.211 - -0.682	0.001
Creatinine 0-4	-1.532	1.434	-2.204 - -0.861	0.000
Creatinine 2-4	-0.086	1.306	-0.696 - 0.52564	0.773
BUN 0-2	-8.305	36.533	-25.403 - 8.793	0.322
BUN 0-4	-3.479	28.241	-16.696 - 9.73738	0.588
BUN 2-4	4.825	19.905	-4.490 - 14.141	0.292

CI: Confidence Interval, GFR; Glomerular filtration rate, PTH; Parathormon, BUN; blood urea nitrogen, A p value of less than 0.05 was considered statistically significant.

Table 4. Characteristics of patients with and without a decrease in glomerular filtration rate.

Decrease in GFR (+)	Decrease in GFR (-)	p	
Hemoglobin (g/dL)	10.6 ± 2.54	10.6 ± 2.26	0.998
Blood urea nitrogen mg/dL)	27.6 (22.45 – 38.5)	34.3 (19.6 -64.25)	0.659
Creatinine (mg/dL)	1.41 (0.85 – 3.38)	1.36 (0.99 – 2.61)	0.968
Albumin (g/dL)	3.9 ± 0.87	4.2 ± 1.45	0.685
Phosphorus (mg/dL)	5.1 ± 0.81	5.85 ± 2.21	0.137
Calcium (mg/dL)	8.9 ± 1.45	9.6 ± 0.72	0.325
Uric acide (mg/dL)	67.3 ± 1.71	4.99 ± 1.67	0.015
Parathormon (pg/mL)	159 (54.8 – 326.5)	217 (86.5 - 368)	0.494
GFR at admission (mL/min/1.73 m²)	45 (20.8 - 72)	29.3 (22.3 - 51.2)	0.659
Hypertension	6 (75)	3 (17.6)	0.001
Proteinuria	3 (37.5)	7 (41.2)	0.551
Follow-up period (year)	6.2 ± 2.29	6.5 ± 1.51	0.466

Results were shown as number (percentage), mean ± standard deviation and median (interquartile range). GFR; Glomerular filtration rate.A p value of less than 0.05 was considered statistically significant.

4. Discussion

In this study, the factors affecting the progression in children with predialysis CKD were investigated. It was determined that serum uric acid level and the presence of HT at the time of admission were effective factors in the decrease in GFR.

Although the causes of CKD in childhood differ from country to country, it is reported that it is often related to congenital anomalies of the kidneys and urinary system. Congenital kidney and urinary tract anomalies include structural and functional malformations at different levels of the urinary system such as kidney, collecting duct, bladder or urethra (10). The NAPRTCS, Italkid, and EDTA studies show that CKD and ESRD in children are most commonly associated with congenital anomalies of the kidney and urinary system. These are followed by glomerular diseases, neurogenic bladder and other kidney pathologies (11-13). In our study, similar to the literature, the most common cause of CKD was found to be congenital kidney and urinary system anomaly. It was concluded that close follow-up of children with symptoms suggestive of urinary system anomaly in the antenatal period and childhood and performing necessary examinations in the early period are important in order to reduce the risk of developing CKD in the later period of life.

Renal blood flow is used for the blood supply of the remaining nephron with a decrease in kidney mass as a result of kidney damage for any reason. Thus, the blood supply and filtration pressure of the nephrons increase, and as a result, hypertrophy develops in the nephrons. This hyperperfusion and hyperfiltration cause renin angiotensin aldosterone system activation and HT (14, 15). Many studies have reported that disease progression can be delayed by blood pressure control in children with CKD (16). Chronic kidney disease is one of the most common causes of secondary HT. Hypertension accompanies almost all acquired and congenital types of renal parenchymal disease and is more common as GFR decreases (17). Therefore, treatment of HT is necessary to slow the progression of CKD. In a study involving 385 children with CKD in Germany, it was shown that blood pressure (BP) control reduced the progression to ESRD by 50%. In this study, it was shown that BP control significantly reduced the progression to CKD in children with glomerulopathy or renal hypo/dysplasia in the etiology of CKD, compared to children with other underlying congenital or hereditary nephropathy (18). In a prospective, randomized, 2-year multicenter study, it was shown that HT and proteinuria are independent risk factors for the progression of CKD in 191 pediatric patients (2-18 years of age) with CKD (19). In our study, it was determined that HT was effective on GFR reduction. This result supported that BP regulation might play an important role in slowing or preventing CKD progression.

Although uric acid has antioxidant effects, hyperuricemia triggers kidney diseases, metabolic syndrome, diabetes mellitus, HT, cardiovascular diseases and contributes to the progression of these diseases. The relationship between hyperuricemia and CKD has been known since the 1890s (20). In the vast majority of CKD cases, the cause of hyperuricemia is due to a problem in renal excretion of uric acid. Metabolic acidosis and short/long term salt restriction also cause hyperuricemia (21). Uric acid causes kidney damage by many mechanisms. Renin-angiotensin-aldosterone system activation, inhibition of neuronal nitric oxide synthase, proliferation in vascular smooth muscle cells, and release of cyclooxygenase 2 from the vessel wall are some of these mechanisms (22). In a prospective study examining the relationship between hyperuricemia and CKD progression, including 70 children with CKD aged 3-15 years in Iran, GFR was determined to be 10 mL/min/1.73m2 higher the case group whose serum uric acid level was controlled by allopurinol treatment than in the control group that did not receive allopurinol treatment (23). In another study conducted in adult patients with diabetic nephropathy, the hypouricemic effect of losartan was shown to reduce the risk of kidney disease. According to the results of this study, the risk of kidney disease decreases by 6% for every 0.5 mg/dL decrease in uric acid (24). The results of our

study showed that serum uric acid level at admission was an effective factor in the decrease in GFR.

It is known that proteinuria leads to the progression of kidney damage and is an independent risk factor for the development of ESRD and increased mortality (25). In our study, no significant difference was found between the degree of proteinuria at admission and a significant decrease in GFR. In our study, especially patients with congenital anomalies constituted the largest group. Since the results of follow-up in childhood were evaluated in our study, it was thought that there may not be a significant correlation due to the absence of significant proteinuria in the early period, and studies with larger samples with longer follow-up periods could yield more accurate results.

Our study has several limitations. This study was retrospective and had a small study population.

In conclusion, the close monitoring of serum uric acid level, early and appropriate treatment of hypertension and hyperuricemia may have a slowing effect on the decrease in GFR in children with predialysis CKD.

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Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 06, Date: 13.03.2018).

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