Decreased Rate of CKD Stage V at Admission Among Children: A Single-Center Experience from the Western Part of Turkey

Başvuru Zamanında Çocuklarda Evre 5 KBH Oranının Azalması: Türkiye' nin Batısında Tek Merkez Deneyimi

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ABSTRACT

OBJECTIVE: Chronic kidney disease (CKD) is an important problem in children worldwide. Clinical outcomes of CKD could be improved with early referral. In this study, we aimed to emphasize changing clinical and laboratory features of stage III and advanced CKD in children in the last 15 years at our clinic.

MATERIAL and METHODS: The medical data of pediatric patients who had estimated glomerular filtration rates (eGFRs) of ≤60ml/min/1.73m^2 treated at our hospital from January 1995 to December 2011 were retrospectively reviewed. Data were evaluated in three separate observation periods; period 1: January1995 to December 1999, period 2: January 2000 to December 2005, period 3: January 2006 to December 2011. Statistical analysis was conducted using chi-square and t-tests as well as Pearson correlation analysis in SPSS 20.0.

RESULTS: A total of 242 patients (107 females; mean age 8.56±4.74 years) were included in the study. The leading cause of CKD was urologic diseases (136 patients, 56.2%). Recognizing the CKD children in late stages decreased over time. The number of children diagnosed and managed in a pre-dialysis program significantly increased during period 3. The rate of patients who required urgent dialysis was greater in period 1 (76.5%) than in period 2 (46.1%) and period 3 (27%),(p<0.05).

CONCLUSION: Based on our results, the frequency of urological abnormalities did not change significantly overtime. On the other hand, the need for urgent dialysis significantly decreased over time.

KEY WORDS: Chronic kidney disease, Pediatric, End-stage renal disease

ÖZ

AMAÇ: Kronik böbrek hastalığı (KBH) çocuklarda dünya çapında önemli bir problemdir. KBH'nin erken yönlendirme ile klinik sonuçları iyileştirebilir. Çalışmada, merkezimizde son 15 yıl içerisinde evre 3 ve daha ileri KBH tanısı alan çocuklarda tanı anındaki klinik ve laboratuvar özelliklerinin gösterdiği değişimi vurgulamak amaçlanmıştır.

GEREÇ ve YÖNTEMLER: Hastanemizde Ocak 1995 ile Aralık 2011 tarihleri arasında tahmini glomerüler filtrasyon hızı (eGFH) ≤60 ml/min/1,73m^2 olarak hesaplanan çocuk hastalar retrospektif olarak incelendi.Veriler 3 ayrı gözlem döneminde değerlendirildi; dönem 1: Ocak 1995-Aralık 1999, dönem 2: Ocak 2000–Aralık 2005, dönem 3: Ocak 2006–Aralık 2011. İstatistiksel analizler SPSS 20.0 yazılımı kullanılarak ki-kare ve t-testi yanısıra Pearson korelasyon analizi ile yapıldı.

BULGULAR: Yaş ortalaması 8,56±4,74 yıl olan 107'si kız toplam 242 hasta çalışmaya dahil edildi. Ürolojik nedenler KBH'nın önde gelen nedeni olarak saptandı (136 hasta, %56,2). KBH'nın son evrede tanınması oranlarının zaman içerisinde azaldığı görüldü. Dönem 3'te tanı alan ve koruyucu olarak prediyaliz programında izlenen çocuk sayısının anlamlı ölçüde arttığı saptandı (p<0,05). Acil diyaliz ihtiyacı gelişen hasta oranı, dönem 1'de (%76,5), dönem 2 (%46,1) ve dönem 3'e (%27) göre daha fazla bulundu (p<0,05).

SONUÇ: Bizim sonuçlarımıza göre, ürolojik nedenleri sıklığında zaman içerisinde önemli ölçüde değişiklik saptanmadı. Diğer taraftan, zaman içerisinde acil diyaliz ihtiyacı anlamlı olarak azaldı.

ANAHTAR SÖZCÜKLER: Kronik böbrek hastalığı, Çocuk, Son dönem böbrek hastalığı

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INTRODUCTION

Chronic kidney disease (CKD) is a general term for heterogeneous disorders originating from structural and/or functional abnormalities of the kidney (1). Contrary to popular belief that CKD affects a small partition of the population, a newly-developed disease staging system and conceptual model in the last decade has uncovered the real disease burden which is a global health issue (1-5). Initial kidney damage often progresses slowly over a long period of time and is irreversible in nature (5-7). Children with early-stage CKD generally do not exhibit any signs of kidney damage even if kidney function has declined. Therefore, some children with CKD remain undiagnosed. Hence, early detection can help decelerate the progression of kidney disease to end-stage renal disease (ESRD). This life-threatening and progressive disease has now become an important global cause of health and economic problems (4, 8). As CKD develops over time, creating awareness among primary care practitioners and encouraging parents to get their child's kidney function checked regularly may allow early diagnosis and slowing down the progression of the disease and perhaps even prevent ESRD (4,6,8-10).

In this retrospective study, we tried to determine the changing characteristics of stage III-IV-V CKD at our center within the last 15 years.

MATERIALS and METHODS

Our study group comprised 242 patients evaluated between January 1995 and December 2011 at the Pediatric Nephrology unit of a tertiary training and research hospital in Izmir (a city of in the Aegean Coast of Turkey). At our Pediatric Nephrology department, we have designed a pre-dialysis intervention program (including eGFR<60 mL/min/1.73m^2) with the aim of improving CKD outcomes or preparing patients for dialysis and kidney transplantation. CKD Stage III (eGFR between 30-60 mL/min/1.73m^2), IV (eGFR between 15-30 mL/min/1.73m^2), and V (eGFR <15 mL/min/1.73m^2) patients or those who need renal replacement treatment were defined according to KDIGO Classification (3) definition. This population was switched from routine outpatient follow-up to this specialized pre-dialysis outpatient follow-up. The eGFR levels of all patients were recorded after admission to this unit and during follow-up. The eGFR values were retrievable as part of the medical record system throughout the study periods. Patients and their medical records were evaluated in three separate observation periods; period 1: January 1995 to December 1999, period 2: January 2000 to December 2005, period 3: January 2006 to December 2011. Gender, initial age, height, weight, serum creatinine, serum albumin and hemoglobin values as well as patient outcomes were recorded using standard charts in all patients. The patients were also subgrouped according their age group at the time of diagnosis as 0-4 years, 5-9 years, 10-14 years and 15-18 years. Glomerular filtration rates were calculated using the Schwartz formula (GFR= k x Height/Serum creatinine) (the k value used was 0.45 for < 1 year old, 0.55 for child or adolescent girl, and 0.7 for adolescent boy) (11). The proportion of patients with ESRD who presented late and required urgent initiation of dialysis was also recorded. Pre-dialysis, dialysis and kidney transplantation durations in their related periods were also calculated.

The underlying diseases were subclassified into urologic and non-urologic causes. The final visits of the patients were also recorded. Patients with inadequate initial or last visit clinical and laboratory values were excluded. We received an approval from our Institutional Review Board for data collection. Statistical analysis was conducted using SPSS 20.0 software. Data were presented as mean ± SD, median (minimum-maximum), and n (%), as appropriate. Comparison of categorical data was with the Binomial and Pearson chi-square tests. Appropriate parametric and non-parametric tests were used for comparison of continuous variables between groups. The statistical significance was defined as a p value of ≤0.05.

RESULTS

A total of 252 patients were included in the study. However, 10 patients (6 in period 1, 4 in period 2) who had inadequate medical records were excluded. Gender, age at diagnosis, number of children by age group and the number distribution of children by time periods are given in Table I. Overall, the mean age at diagnosis was 8.56±4.74 years and showed no difference between genders (p=0.73). There was a significant male predominance in 0-4 and 15-18 year age groups (p=0.02). There was no statistically significant gender difference between the study periods.

The distribution of the underlying disease in 242 patients is given in Table II.

Distribution of underlying diseases in CKD patients according to time periods is given in Table III. Urologic diseases were the most common underlying pathology in all periods (p<0.05). Cystic kidney diseases showed an increasing pattern in period 3 (p=0.04).

Patient characteristics and laboratory features between time periods are given in Table IV. Mean serum creatinine levels gradually decreased (p<0.05) and mean eGFR levels increased over time (p<0.05). Also, the hemoglobin levels of the patients increased (p <0.001). The rate of end-stage renal failure decreased from 66.7% in period 1 to 22.5% in period 3 (p=<0.001). The rate of patients who needed acute dialysis in periods 1, 2 and 3 was 76.5%, 46.1%, 13.5%, respectively (p=<0.001). Median times between diagnosis and starting of dialysis in the 3 time periods were 0 months, 4.18 months and 29.4 months, respectively (p=<0.001). Overall, 30.6% of the patients underwent kidney transplantation.

Final status of the patients is given in Table V. As shown, 83 patients (34.3%) are still on follow-up in our clinic, 16 patients

Table I: Age, age groups, and number of patients at different time periods according to gender of patients.

	Female(%)	Male (%)	Total (n)	*P*
General	107 (100)	135 (100)	242	0.08
Diagnosis age (year)				
Mean (mean±SD)	8.68±4.36	8.47±5.04	8.56±4.74	NS
Median	9.48	9.24	9.35	
Min-Max	0-17.8	0-17	0-17.8	
Distribution of numbers of children by age group (year)				
0-4	22 (20.56)	41 (30.37)	63	0.02
5-9	43 (40.18)	39 (28.88)	82	NS
10-14	38 (35.51)	40 (29.62)	78	NS
15-18	4 (3.7)	15 (11.11)	19	0.02
Diagnosis at time periods				
1995-1999 (Period 1)	26 (24.29)	25 (18.51)	51	NS
2000-2005 (Period 2)	38 (35.51)	64 (47.4)	102	NS
2006-2011 (Period 3)	43 (40.18)	46 (34.07)	89	NS

SD: Standard deviation, **Min:** Minimum, **Max:** Maximum, **NS:** Non-significant.

(6.6%) were transferred to adult clinics whereas 40 patients (16.5%) changed their follow-up clinics due to various issues.

DISCUSSION

This single-center retrospective study showed that diagnosis of CKD stage III and IV rather than stage V demonstrated an increasing pattern in more recent time periods. Diagnosis of CKD at an earlier stage was associated with better pattern of biochemical variables; and it decreased the need for urgent RRT start over the studied 15-year time period, from 1995 to 2011.

Studies from Italy, Spain and Serbia that defined CKD as eGFR<75 ml/min/1.73m^2, eGFR<90 ml/min/1.73m^2 and eGFR<90 ml/min/1.73m^2 for 3 months have reported that the mean glomerular filtration rate (GFR) at presentation was 47.1±20.5, 52±2 and 39.6 ml/min/1.73m^2, respectively (12-14). In our study of 242 children, overall mean eGFR was 27.1±17.4 ml/min/1.73m^2. However, compared with baseline, mean creatinine levels gradually decreased and mean eGFR levels gradually increased at presentation over the studied time period. Children with CKD were more likely to present with advanced CKD in period 1 than in periods 2 and 3.

Bek et al. (15) showed that mean age at diagnosis was 8.05±5.25 years. For our study population, the overall mean age at diagnosis was calculated as 8.56±4.74 years. There was no gender domination and the prominence of urologic diseases and underlying etiology were nearly the same. Thus, our study is a reflection of nation-wide study of Bek et al. (15).

Some studies report a high prevalence of anemia in children with CKD at presentation (12, 15). Our results are comparable to the limited literature. In our study, overall mean hemoglobin value was 9.65±2.3 gr/dl at presentation. However, mean hemoglobin values showed a statistically significant improvement over time.

The percentage of children diagnosed and managed conservatively in our pre-dialysis follow-up program also significantly increased during the period of 2000 to 2011 (from 23.5% in period 1 to 53.9% in period 2 and 68.5% in period 3). Also, the median time between diagnosis to starting of dialysis treatment significantly increased in our study population.

Our study has certain limitations, such as the low number of patients and the retrospective nature and single-center design that limits the generalization of the findings and sub-group analysis. The increasing number of CKD patients in a pre-dialysis follow-up program over time most likely reflects the improvement in the health care system in our region, and in Turkey, as well. However, the lack of reliable data about the number of referred patients and the undetermined number of primary care practitioners make it inconclusive. Longitudinal and analytic prospective studies are therefore needed to delineate whether awareness of CKD and early referral affects prognosis in children with CKD.

In conclusion, the need for urgent dialysis decreased significantly over time though the frequency of urological abnormalities did not change.

Table II: The distribution of the underlying diseases in the study group.

Underlying disease	**Female n (%)**	**Male n (%)**	**Total n (%)**	P	P_2
Urologic	**59 (54.87)**	**77 (56.98)**	**136 (56.2)**	NS	NS
VUR± Dysplasia /atrophy/hypoplasia	23 (21.39)	31 (22.94)	54 (44.33)		
Obstructive uropathy	8 (7.44)	19 (14.06)	27 (11.2)		
Neurogenic bladder	16 (14.88)	14 (10.36)	30 (12.4)		
Stone disease	2 (1.86)	7 (5.18)	9 (3.7)		
Pyelonephritis	9 (8.37)	5 (3.7)	14 (5.8)		
Horse-shoe kidney	1 (0.93)	1 (0.74)	2 (0.8)		
Non-urologic	**30 (27.9)**	**48 (36.26)**	**78 (32.2)**	0.09	NS
Primary glomerulonephritis	**15 (13.95)**	**21 (15.54)**	**36 (14.9)**		
FSGS	8 (7.44)	15 (11.1)	23 (9.5)		
MPGN	5 (4.95)	4 (2.96)	9 (3.7)		
MGN		1 (0.74)	1 (0.4)		
RPGN	2 (1.86)	1 (0.74)	3 (1.2)		
Cystic kidney disease	**6 (5.58)**	**8 (5.92)**	**14 (5.8)**		
Polycystic kidney disease		5 (3.7)	5 (2.1)		
Glomerulocystic disease	1 (0.93)		1 (0.4)		
Nephronophthisis	5 (4.65)	2 (1.48)	7 (2.9)		
FHUN		1 (0.74)	1 (0.4)		
Secondary glomerulonephritis	**4 (3.72)**	**9 (6.66)**	**13 (5.4)**		
Amiloidosis		2 (1.48)	2 (0.8)		
SLE	1 (0.93)		1 (0.4)		
Wegener granulomatosis		1 (0.74)	1 (0.4)		
HSV/IgAN	1 (0.93)	2 (1.48)	3 (1.2)		
HUS/TTP		3 (2.22)	3 (1.2)		
Alport syndrome	2 (1.86)	1 (0.74)	3 (1.2)		
Tubular diseases	**7 (6.51)**	**8 (5.92)**	**15 (6.1)**		
TIN	1 (0.93)	2 (1.48)	3 (1.2)		
Cystinosis	1 (0.93)	2 (1.48)	3 (1.2)		
Oxalosis	1 (0.93)	1 (0.74)	2 (0.8)		
Bartter syndrome		1 (0.74)	1 (0.4)		
RTA	1 (0.93)	2 (1.48)	3 (1.2)		
Hypercalciuria	1 (0.93)		1 (0.4)		
Other	**4 (3.72)**	**6 (4.44)**	**10 (4.2)**	NS	
Unknown	**12 (11.16)**	**6 (4.44)**	**18 (7.4)**	NS	
Total	**107 (100)**	**135 (100)**	**242 (100)**		

VUR: Vesicoureteral reflux, **FSGS:** Focal segmental glomerulosclerosis, **MPGN:** Membranoproliferative glomerulonephritis, **MGN:** Membranous glomerulopathy, **RPGN:** Rapidly progressive glomerulonephritis, **FHUN:** Familial hyperuricemic nephropathy, **SLE:** Systemic lupus erythematosus, **HSV:** Henoch-Schönlein vasculitis, **IgAN:** Immunoglobulin A nephropathy, **HUS:** Hemolytic uremic syndrome, **TTP:** Thrombotic thrombocytopenic purpura, **TIN:** Tubulointerstital nephritis, **RTA:** Renal tubular acidosis.

P_2: Comparison between urologic and non-urologic disease groups by gender.

NS: Non-significant.

Table III: Distribution of underlying diseases in CKD patients according to time periods.

Underlying disease	**Period 1 1995-1999 n (%)**	**Period 2 2000-2005 n (%)**	**Period 3 2006-2011 n (%)**	**Total 1995-2011 n (%)**	**p**
Urologic diseases	26 (51)	60 (58.8)	50 (56.2)	136 (56.2)	*<0.001[a],0.01[b]*
Non-urologic disease	22 (43.1)	31 (30.4)	25 (28.1)	78 (32.2)	*NS*
Primary glomerulonephritis	*13 (25.5)*	*14 (13.7)*	*9 (10.1)*	*36 (14.9)*	*NS*
Cystic kidney diseases	*2 (3.9)*	*3 (2.9)*	*9 (10.1)*	*14 (5.8)*	*0.04[c]*
Secondary glomerulonephritis	*3 (5.9)*	*7 (6.9)*	*3 (3.4)*	*13 (5.4)*	*NS*
Tubulary diseases	*4 (7.8)*	*7 (6.9)*	*4 (4.5)*	*15 (6.1)*	*NS*
Other	0 (0)	4 (3.9)	6 (6.7)	10 (4.2)	*NS*
Unknown	3 (5.9)	7 (6.9)	8 (9)	18 (7.4)	*NS*
Total	51 (21.1)	102 (42.1)	89 (36.8)	242 (100)	

[a]: Urologic abnormalities was significantly the leading cause of CKD in all separate periods and whole study period (Ki-square test, p:0.000).

[b]: Urologic abnormalities showed significantly increased pattern in following periods (Ki-square test, p:0.01).

[c]: In non-urologic etiologies, cystic kidney disease showed increased pattern in times (Ki-square test, p:0.04).

NS: Non-significant.

Table IV: Patient characteristics according to time periods.

	Period 1 1995-1999 n=51	**Period 2 2000-2005 n=102**	**Period 3 2006-2011 n=89**	**Overall 1995-2011 n=242**	***P***
Gender M/F (%/%)	25/26	64/38	46/43	135/107	*NS*
Features at admission					
Age (mean±SD)	8.72±4.49	8.85±4.58	8.15±5.07	8.56±4.74	*NS*
Weight SD (mean±SD)	-1.31±1.6	-1.59±2.55	-1.29±2.32	-1.42±2.29	*NS*
Height SD (mean±SD)	-1.8±2.14	-1.4±3.54	-1.45±2.28	-1.5±2.85	*NS*
BMI SD (mean±SD)	-0.46±1.8	-0.08±2.34	-0.25±1.81	-0.53±2.06	*NS*
Creatinine (mean±SD) (mg/dl)	5.59±2.84	3.49±2.54	2.7±1.95	3.83±3.92	*<0.001*
GFR (mean±SD) (ml/min)	15.4±11.9	27.9±16.9	32.7±17.6	27.1±17.4	*<0.001*
Albumin (mean±SD) (gr/dl)	3.3±0.98	3.51±0.84	3.68±0.83	3.53±0.87	*0.07*
Hb (mean±SD) (gr/dl)	8.25±0.98	9.98±2.1	10±2	9.65±2.3	*<0.001*
CKD stage n (%)					
Stage III	5 (9.8)	43 (42.2)	46 (51.7)	94 (38.2)	
Stage IV	12 (23.5)	25 (24.5)	23 (25.8)	60 (24.8)	*<0.001*
Stage V	34 (66.7)	34 (33.3)	20 (22.5)	88 (36.4)	
Time to initiation of RRT, (month) median (min - max)	0 (0-7.3)	4.18 (0-29.9)	29.4 (0-5)	5.17 (0-29.9)	*<0.001*
The need for urgent dialysis (yes, n (%))	39 (76.5)	47 (46.1)	24 (27)	110 (45.5)	*<0.001*
Kidney Tx (yes, n (%))	21 (41.2)	41 (40.2)	12 (13.5)	74 (30.6)	*<0.001*
Preemptive n (%)	0 (0)	3 (2.94)	0 (0)	3 (1.24)	
Following dialysis n(%)	21 (41.2)	38 (37.26)	12 (13.5)	71 (29.36)	

SD: Standard deviation, **BMI:** Body mass index, **GFR:** Glomerular filtration rate, **Hb:** Hemoglobin, **CKD:** Chronic kidney disease, **RRT:** Renal replacement treatment, **Tx:** Transplantation, **NS:** Non-significant.

Table V: Patient status at last follow-up visit according to gender.

	Female (%)	Male (%)	Total (n)	p
On follow-up	70 (77.77)	87 (70.73)	157 (73.70)	NS
PreD	29 (32.22)	41 (33.33)	70 (32.86)	
PD	6 (6.66)	4 (3.25)	10 (4.69)	
HD	1 (1.11)	2 (1.62)	3 (1.4)	
Kidney Tx	34 (37.77)	40 (32.52)	74 (34.74)	NS
Transfer to adult clinics	4 (4.44)	12 (9.75)	16 (7.51)	0.09
Transfer to other clinics	16 (17.77)	24 (19.51)	40 (18.77)	NS
Total	90 (100)	123 (100)	213 (100)	

PreD: Pre-dialysis, **PD:** Peritoneal dialysis, **HD:** Hemodialysis, **Tx:** Transplantation, **NS:** Non-significant.

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