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Demographic, Clinical, and Laboratory Characteristics of Children with Renal Tubular Acidosis

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Abstract

This study included patients followed up for primary renal tubular acidosis (RTA) between 1991 and 2012. Clinical characteristics at presentation, physical examination findings, laboratory test results, and treatments were recorded. The patients' laboratory results, drug doses, height, and weight were recorded every 3 months for the first year of follow-up. Standard deviation scores (Z-scores) of height and weight for age were determined and the patients' growth rates were evaluated. Of 50 patients followed up for primary RTA, 31 (62%) had distal RTA and 19 (38%) had proximal RTA. The median age at diagnosis was 3 months (range, 1-174 months) for patients with distal RTA and 10 months (range, 2-33 months) for patients with proximal RTA. The median follow-up times in these two groups were 96 months (range, 6-204 months) and 89 months (range, 6-180 months), respectively. Family history of RTA was more common among patients with distal RTA than those with proximal RTA (p=0.013). Nephrocalcinosis and deafness were detected more frequently in the distal RTA group (p=0.001), while ocular pathologies were more common in the proximal RTA group (p<0.001). In patients with distal RTA, older age at diagnosis was associated with lower weight and height Z-scores (p<0.05). Early diagnosis had a positive effect on the growth of patients with primary RTA.

Keywords: Renal tubular acidosis, pediatric, growth, nephrocalcinosis, deafness

Introduction

Renal tubular acidosis (RTA) is characterized by normal anion gap metabolic acidosis resulting from reduced bicarbonate absorption by the tubules or impaired hydrogen ion excretion without impaired glomerular filtration.[1] RTA is classified as distal (type I), proximal (type II), and hyperkalemic (type IV), according to the nephron segment in which renal tubular dysfunction occurs. Type III RTA, which is associated with hereditary carbonic anhydrase enzyme deficiency and has some characteristics of type I and type II RTA, has also been defined. RTA can be inherited or may

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develop due to toxic substances or diseases affecting the renal tubules.[2]

In children, 2-3 mmol/kg of hydrogen ions (H^+) are produced per day from the diet, and hydroxyapatites are released from growing bones.[3] Net acid excretion from the body is achieved through the prevention of the loss of bicarbonate (HCO_3^-) ions and excretion of ammonium ions and titratable acids. Approximately 85% of the filtered HCO_3^- ions are reabsorbed through the proximal tubules.[4] Transport in the proximal tubule occurs via the sodium (Na^+)-dependent transport system and megalin/cubilin-mediated endocytosis. Impaired HCO_3^- absorption causes low intracellular Na^+ concentration, disrupting the absorption of other solutes via the Na^+-dependent transport system. This general dysfunction of the proximal tubule is called Fanconi syndrome (FS). Proximal RTA can occur as isolated proximal RTA or as FS.[4,5] Congenital causes of FS in children include galactosemia, Lowe syndrome, cystinosis, mitochondrial diseases, Dent disease, hereditary fructose intolerance, Fanconi-Bickel syndrome, glycogen storage disease type 1, Wilson disease, and tyrosinemia type 1.[5,6] In distal RTA, H^+ secretion into the tubular lumen is impaired.[7] Distal RTA may be congenital or acquired. Congenital distal RTA shows autosomal dominant (type 1a) or autosomal recessive (type 1b, type 1c) inheritance.[8]

Highlights

- Early diagnosis of patients with RTA positively affected their growth
- Early diagnosis should reduce exposure to malnutrition, hypokalemia, hypophosphatemia, and metabolic acidosis and prevent potential adverse consequences by enabling the provision of necessary treatment.
- Early diagnosis was found to have a positive effect on the growth of patients with primary RTA.

In the distal RTA, metabolic abnormalities cause complications and failure to thrive. Blood test results in patients with distal RTA indicate normal anion gap metabolic acidosis, often accompanied by hypokalemia. Children with distal RTA have acidic blood pH but alkaline urine. Hypercalciuria, nephrocalcinosis, and nephrolithiasis are frequently associated with distal RTA. Autosomal-recessive inherited forms of distal RTA result from mutations in *ATP6V1B1* or *ATP6V0A4*, genes that encode the apical H1-ATPase, which is also found in some structures of the ear. Therefore, these mutations also lead to sensorineural hearing loss.[1,2,8]

In proximal RTA, defective proximal tubular HCO_3^- reabsorption leads to normal anion gap metabolic acidosis due to loss of HCO_3^- in the urine. As with distal RTA, proximal RTA may also be accompanied by hypokalemia. Unlike in distal RTA, however, in proximal RTA, the distal nephrons retain their capacity to acidify the urine; therefore, proximal RTA patients have a urine pH of 5.5 or lower when plasma HCO_3^- concentrations are below the tubular reabsorption threshold.[1] Compared with patients with distal RTA, patients with isolated proximal RTA are less likely to develop nephrocalcinosis and nephrolithiasis because the alkaline luminal pH inhibits proximal citrate reabsorption, ensuring adequate citrate excretion in the urine.[1,4,5] Nevertheless, nephrocalcinosis can be observed in some subgroups of proximal RTA patients who develop hypercalciuria, such as patients with Dent's disease.[9] The increased urinary calcium excretion caused by both acute and chronic metabolic acidosis directly impacts bone growth.[1,4,5]

The treatments for this patient group aim to ensure adequate growth as well as prevent bone abnormalities, nephrocalcinosis, and nephrolithiasis.[1] Proximal RTA patients require alkali therapy more than distal RTA patients, given their limited capacity for proximal HCO_3^- reabsorption, and increasing the filtered load of HCO_3^- will cause the increased urinary loss.[10]

Typical complaints of patients with RTA at admission include growth retardation and episodes of recurrent vomiting and dehydration. Growth retardation is a result of malnutrition, hypokalemia, hypophosphatemia, and metabolic acidosis.[11] In light of this information, this study was carried out to evaluate the demographic, clinical, and laboratory characteristics of children followed up with the diagnosis of RTA in our hospital between 1991 and 2012.

Material and Method

The population of this retrospective study consisted of children followed up with the diagnosis of RTA in the nephrology outpatient clinic of Ankara Children's Hematology Oncology Training and Research Hospital between 1991 and 2012. Patients with RTA secondary to diseases such as vesicoureteral reflux, nephrolithiasis, and medullary sponge kidney were excluded from the study. In the end, 50 children with primary RTA were included in the study sample. The patients' height and weight data, laboratory results, and drug doses were recorded every three months during the first year of follow-up. Based on these data, patients' standard deviation scores (SDS) (Z-scores) of height- and weight-for-age and growth rates were calculated. Height and weight data were expressed as SDS in line with National Center for Health Statistics standards. Values between +2 SD and -2 SD were accepted as normal lower and upper limits. In addition, delta SDS values were calculated by comparing the weight and height SDS of the patients at admission with their last measured weight and height SDS.[12] Z-scores were calculated as below:

Z = (subject's height-mean height)/standard deviation of mean

Urinalysis was performed using an Iris Q 200 device. Based on urinalysis results, patients' urine pH, protein and calcium levels, and glucose presence were recorded. A Roche Hitachi P800 device was used to study patients' biochemistry. Potassium levels of <3.5 mmol/L (normal range 3.5-5.5 mmol/L), phosphorus levels of <2.7 mg/dL (normal range 2.7-6 mg/dL), and calcium levels of <8.5 mg/dL (normal range 8.5-10.5 mg/dL) were deemed to indicate hypokalemia, hypophosphatemia, and hypocalcemia, respectively. Blood gas analysis was performed using an ABL 735 radiometer. Low

serum HCO_3^- concentrations (<18 mEq/L) and pH values <7.35 were deemed to indicate metabolic acidosis.[13] RTA types were determined based on clinical assessment and laboratory data, i.e., blood and urine pH values, blood and urine electrolyte levels, metabolic assessment, and kidney imaging findings. Accordingly, hypokalemic hyperchloremic metabolic acidosis, hypercalciuria, nephrocalcinosis, and spontaneous acidemia with inability to lower urine pH below 5.5 were deemed to indicate distal RTA, whereas normal to mildly low serum potassium levels and hyperchloremic metabolic acidosis with spontaneous acidemia in which urine pH can be lowered below 5.5 were deemed to indicate isolated proximal RTA.[4,14] Additionally, proximal RTA accompanied by the urinary loss of glucose, protein, phosphate, and amino acids was deemed to indicate renal FS.[15] Renal FS accompanied by corneal cystine crystal accumulation and/or elevated leukocyte cystine levels was deemed to indicate cystinosis,[16] renal FS accompanied by ocular anomalies (congenital cataracts) and central nervous system anomalies was considered to indicate Lowe syndrome.[17] Furthermore, renal FS accompanied by developmental delay, baby face appearance, hepatomegaly, nephromegaly, severe rickets, hypoglycemia, and galactose tolerance disorder was deemed to indicate Fanconi-Bickel syndrome, whereas renal FS accompanied by symptomatic hypoglycemia and vomiting after fructose, sucrose, or sorbitol intake, growth retardation, hepatomegaly, jaundice, hepatic cirrhosis, and nephrocalcinosis with prolonged exposure was deemed to indicate hereditary fructose intolerance.[15] Lastly, RTA associated with osteopetrosis and intracranial calcification was deemed to indicate marble brain disease.[18]

Clinical findings and laboratory results including serum and urine pH, serum biochemistry, serum HCO_3^-, urinalysis, urine protein, urinary creatinine excretion, urine calcium, tubular phosphate reabsorption, metabolic tests and also imaging findings, and follow-up data were obtained from patient files and electronic records. The study protocol was approved by the Ankara Children's Hematology Oncology Training and Research Hospital Ethics Committee (document no: 135-12/2012).

Statistical Analysis

Data interpretation was conducted using the SPSS 11.5 software (SPSS Inc., Chicago, IL, US, 2002 for Windows). The Shapiro-Wilk test was employed to assess the normal distribution of continuous variables. Descriptive statistics for the data were presented as mean and standard deviation for continuous variables with a normal distribution, median with minimum-maximum range for those without a normal distribution, and as count (n) and percentage (%) for categorical variables. The student's t-test for variables with a normal distribution, the Mann-Whitney U test for those without a normal distribution, and Fisher's exact test for categorical variables were used to determine the significance of differences between groups. Spearman's correlation analysis was utilized to test the relationship between continuous variables. To assess the significant variation in clinical measurements' average values at the end of the 12-month follow-up compared to the initial values, the dependent samples t-test was applied. Moreover, the Wilcoxon signed-rank test was used to evaluate any significant shifts in the median values of clinical measurements after 12 months compared to the initial measurements. A p-value less than 0.05 was considered statistically significant.

Results

In this study, there was 50 children followed up with the diagnosis of primary RTA. Of these children, 31 (62%) had distal RTA, and 19 (38%) had proximal RTA. The median age of the children with distal and proximal RTA at diagnosis was 3 months (range, 1-74 months) and 10 months (range, 2-33 months), respectively. In the proximal RTA group, the median age of the children with cystinosis and Lowe syndrome at diagnosis was 9 months (range, 7-12 months) and 23 months (range, 18-30 months), respectively. The median follow-up time of the children with distal and proximal RTA was 96 months (range, 6-204 months) and 89 months (range, 6-180 months), respectively. The rate of children with a familial history of RTA was significantly higher among the children with distal RTA compared to the children with proximal RTA (p=0.013) (**Table 1**).

Of the 19 children diagnosed with proximal RTA, 8 had cystinosis, 5 had isolated proximal RTA, 3 had Lowe syndrome, and 1 patient each had Fanconi-Bickel syndrome, hereditary fructose intolerance, and marble brain disease.

Nephrocalcinosis, deafness, and ocular findings are important in the differential diagnosis of patients with RTA. As expected, nephrocalcinosis and deafness were significantly more common in the distal RTA group than in the proximal RTA group (p=0.001), whereas ocular findings were more significantly common in the proximal RTA group, where patients with cystinosis predominated patients with other subdiagnoses than in the distal RTA group (p<0.001). There were no significant differences between the patient groups and subgroups in other clinical findings (**Table 2**). RTA was associated with hypotonicity and cognitive delay in two of the three patients diagnosed with Lowe syndrome.

Comparison of the patients with distal and proximal RTA in terms of laboratory measurements revealed

Table 1. Demographic characteristics of the patients by group

	Distal RTA (n=31)	Proximal RTA (n=19)	Total (n=50)	p
Gender, male, n (%)	15 (48.4)	12 (66.7)	27 (55.1)	0.24
Consanguineous marriage, n (%)	20 (71.4)	13 (72.2)	33 (71.7)	0.95
Family history, n (%)	8 (28.6)	0 (0)	8 (17.4)	**0.013**

*Median (minimum-maximum), RTA; Renal tubular acidosis

significantly higher blood pH and lower blood sodium, phosphorus, and urine pH levels at admission in the proximal RTA group than in the distal RTA group (p=0.027, p=0.014, p=0.042, and p=0.010, respectively). There was no significant difference between the distal and proximal RTA groups in other blood or urine parameters (p>0.05) (**Table 3**).

In patients with distal RTA, there was a significant increase in body weight (ΔZ-score) at the 12th month of follow-up compared to before the treatment (p<0.05), but no significant change in height (p>0.05) (**Table 4**). Delayed diagnosis was associated with worse Z-scores of height-for-age and weight-for-age in patients with distal RTA. There were significant correlations between age at diagnosis and Z-scores of weight-for-age (r=-0.618 and p<0.001) and Z-scores of height-for-age (r=-0.648 and p<0.001) in the negative direction. On the other hand, there were no significant correlations between Z-scores of height-for-age and weight-for-age and HCO_3^-, potassium, or phosphorus levels at admission (p>0.05) (**Table 5**).

The median Z-scores of weight-for-age and height-for-age of five patients with isolated proximal RTA at admission were -3.89 (range, -6.36 to -1.57) and -3.37 (range, -6.97 to 0.04), respectively. The median Z-scores of weight-for-age and height-for-age of five patients with isolated proximal RTA at the 12th month of follow-up were -2.49 (range, -2.83 to -1.81) and -2.1 (range, -3.03 to -0.6), respectively. These results indicated an improvement in patients' clinical conditions; however, a statistical

Table 2. Patients' hospital admission complaints and clinical findings by group

	Distal RTA (n=31)	Proximal RTA (n=19)	Total (n=50)	p
Growth retardation	5 (16.1)	7 (38.9)	12 (24.5)	0.13
Anorexia	2 (6.5)	3 (16.7)	5 (10.2)	0.31
Polyuria	3 (9.7)	2 (11.1)	5 (10.2)	0.54
Polydipsia	3 (9.7)	2 (11.1)	5 (10.2)	0.54
Rickets	4 (12.9)	5 (27.8)	9 (18.4)	0.26
Bone fractures	0 (0)	1 (5.6)	1 (2)	0.23
Nephrocalcinosis	23 (74.2)	3 (16.7)	26 (53.1)	**0.001**
Deafness	7 (22.6)	0 (0)	7 (14.3)	**0.001**
Ocular pathologies	0 (0)	8 (44.4)	8 (16.3)	**<0.001**
Weight loss	3 (9.7)	2 (11.1)	5 (10.2)	0.54
Failure to gain weight	8 (25.8)	1 (5.6)	9 (18.4)	0.09
Fever	8 (25.8)	3 (16.7)	11 (22.4)	0.37
Respiratory distress	3 (9.7)	0 (0)	3 (6.1)	0.19
Abdominal distention	3 (9.7)	1 (5.6)	4 (8.2)	0.46
Diarrhea	3 (9.7)	2 (11.1)	5 (10.2)	0.54
Constipation	3 (9.7)	3 (16.7)	6 (12.2)	0.44
Agitation	3 (9.7)	3 (16.7)	6 (12.2)	0.44
Malaise	6 (19.4)	3 (16.7)	9 (18.4)	0.51
Vomiting	9 (29)	8 (44.4)	17 (34.7)	0.35

Data expressed in n (%). RTA; Renal tubular acidosis. Statistically significant results (p<0.05) shown in bold

Table 3. *Patients' laboratory data at hospital admission by group*

	Distal RTA (n=31)	Proximal RTA (n=19)	p
HCO_3	**10.9 (3.4-20.4)**	11.8 (6.1-20)	0.26
Blood pH	7.28 (6.95-7.38)	7.34 (7.11-7.6)	**0.027**
Na	138 (125-157)	135 (121-153)	0.014
Cl	110 (95-126)	104 (98-140)	0.19
K	3.1 (1.7-6.2)	2.9 (1.4-5.5)	0.78
P	4.8 (1.6-7.7)	3 (0.3-10.1)	0.04
Ca	9.4 (6.1-13.8)	9.3 (8.5-11.3)	0.96
Urea	27.5 (8-178)	19.5 (9.4-96)	0.24
Creatine	0.4 (0.19-1)	0.43 (0.2-0.94)	0.78
Alkaline phosphatase	296 (9-3,363)	542 (222-2,420)	0.11
Urine density	1,010 (1,001-1,024)	1,010 (1,003-1,030)	0.75
Urine pH	7 (6-8)	5.5 (5-8)	**0.01**
Spot urine Ca/Cr	0.41 (0.01-4.4)	0.41 (0.04-1.5)	0.91

Data expressed as median (min-max). RTA; Renal tubular acidosis, Ca/Cr; Calcium/creatinine ratio, statistically significant results (p<0.05) shown in bold

Table 4.
Z-scores (presenting and ΔZ-score) for weight and height at presentation and after 12 months of treatment

Variable	Presenting Z-score	Month-12 Z-score	ΔZ-score	p
Weight	-2.90±1.10	-1.39±1.41	1.51±1.38	**<0.001**
Height	-1.70±1.38	-1.75±1.24	-0.05±1.44	0.899

Statistically significant results (p<0.05) shown in bold

Table 5.
Relationship between weight-for-age and height-for-age Z-scores and age at diagnosis, HCO_3, potassium, and phosphorus in distal RTA

	Weight-for-age Z-score		Height-for-age Z-score	
	Correlation coefficient	p	Correlation coefficient	p
Age at diagnosis	-0.618	**<0.001**	-0.648	**<0.001**
HCO_3	-0.047	0.762	-0.076	0.626
K	0.140	0.352	0.084	0.585
P	0.053	0.740	0.106	0.508

Statistically significant results (p<0.05) shown in bold, RTA; Renal tubular acidosis

evaluation could not be made due to the insufficient number of patients in the respective subgroups. The median Z-scores of weight-for-age and height-for-age of three patients with Lowe syndrome at admission were -3.83 (range, -4.98 to -2.68), respectively. The median Z-scores of weight-for-age and height-for-age of three patients with Lowe syndrome at the 12th month of follow-up were -3.94 (range, -5.56 to -2.32) and -4.83 (range, -5.2 to -4.47) at 12 months, respectively. Additionally, the median Z-scores of weight-for-age and height-for-age of three patients with cystinosis at admission were -2.89 (range, -5.53 to -1.6) and -3.08 (range, -5.63 to -0.04), respectively. Two of these patients developed kidney failure during follow-up. The median Z-scores of height-for-age of five patients at the last follow-up visit before they developed renal failure were -4.1 (range, -4.99 to -2.85).

The mean HCO_3^- dose required to achieve HCO_3^- >20 mEq/L was 3.39 mEq/kg/day in the distal RTA group and 12.4 mEq/kg/day in the proximal RTA group. Required alkali doses could not be statistically compared between the two groups due to the varying follow-up durations of the patients.

Nephrocalcinosis was detected in 23 of the 31 patients with distal RTA (74.2%) at admission compared to 3 of the 19 patients with proximal RTA (16.7%). Nephrocalcinosis resolved during the follow-up period in 6 patients with distal RTA. On the other hand, one of the two patients without nephrocalcinosis at admission developed nephrocalcinosis during the follow-up period. Nephrocalcinosis persisted in other patients with distal RTA. Nephrocalcinosis regressed during the follow-up period in all affected proximal RTA patients. The relationship between the resolution of nephrocalcinosis and alkali therapy could not be statistically evaluated due to the varying follow-up durations of the patients.

Discussion

RTA is a disorder resulting from impaired bicarbonate absorption or urinary hydrogen ion excretion without impairment of glomerular filtration. Early diagnosis of RTA, effective treatment of acidosis, and electrolyte balancing with supportive therapies positively affect the growth and development of patients with RTA.[19-21] This study was carried out to investigate the demographic, clinical, and laboratory characteristics of children followed up with the diagnosis of RTA, including subdiagnoses, treatments received, and growth development. The median age at diagnosis of our patients [3 months, range: 1-174 months in the distal RTA group (n=31); and 10 months, range: 2-33 months in the proximal RTA group (n=18)] was relatively younger compared to that of the patients investigated by Bajpai et al.[22] [1.8 years, range: 3 months-7.5 years (n=18)]. Bajpai et al.[22] emphasized that earlier diagnosis of RTA, i.e., within the first two years of life, which is a phase of growth acquisition, led to better height and weight gains during the follow-up period.

In our study, the rate of children with a familial history of RTA was significantly higher among the children with distal RTA compared to the children with proximal RTA, with no significant difference between the genders. In comparison, Caldas et al.[23] reported that 10 of the 28 patients with primary distal RTA, of whom 15 were male, had a familial history of RTA.

Mutations in *ATP6V1B1*, *ATP6VOA4*, and the newly identified *FOXII* gene reportedly cause neurosensory deafness in autosomal recessive distal RTA patients.[7,8,11] In comparison, in our study, nephrocalcinosis and deafness were more frequent in the distal RTA group than in the proximal RTA group. Caldas et al.[23] reported deafness and nephrocalcinosis in 14 of the 28 patients with distal RTA but did not report mutations in deaf patients. Additionally, Bajpai et al.[22] reported nephrocalcinosis in 8 of 18 patients with distal RTA.

Ocular pathologies associated with RTA can be observed in patients with proximal RTA. One example is cystinosis, where cystine accumulation can lead to photophobia, corneal ulceration, and even blindness if left untreated. Another example is galactosemia, an ophthalmic pathology associated with cataracts in Wilson disease and congenital cataracts in Lowe syndrome.[5,6,11] In our study, ocular pathologies were significantly more common in the proximal RTA group than in the distal

RTA group. Of the eight patients followed up with ocular pathologies (n=8, 44.4%), six had cystinosis, and one each had Lowe syndrome and isolated proximal RTA.

Nephrocalcinosis resolved during the follow-up period in 33% of the affected patients in the distal RTA group and all of the affected patients in the proximal RTA group. Soriano et al.[24] reported nephrocalcinosis in three of the five patients with distal RTA. They emphasized that nephrocalcinosis is a severe complication of distal RTA and that timely correction of hypercalciuria with early alkali therapy is needed to prevent kidney damage.

Malnutrition, hypokalemia, hypophosphatemia, metabolic acidosis, and delayed diagnosis are causes of growth retardation associated with RTA. Hypokalemia reduces levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1).[9,22] Appetite suppression and decreased extracellular volume also occur because of hypokalemia. Metabolic acidosis suppresses GH secretion, IGF-1, and GH receptors[25,26] and inhibits osteoblastic activity while increasing osteoclastic activity.[19] The release of Ca^{+2}, as well as Na^{+}, K^{+}, and $CO3^{-2}$ from the soft tissues and bones to buffer acidosis, reduces bone mineral density.[27] Early diagnosis, effective treatment of acidosis, and electrolyte balancing with supportive therapy reportedly improve growth and development in RTA patients.[20-22]

In our study, while Z-scores of weight-for-age showed a significant improvement at the 12th month of follow-up compared to before the treatment, the Z-scores of height-for-age did not show a significant improvement. The lack of a significant improvement in the Z-scores of height-for-age may be due to the relatively short follow-up period. Bajpai et al.[22] reported the median Z-score of height-for-age of 18 patients with distal RTA as -5.2 (range, -7.5 to -0.4) at the time of diagnosis and -2.7 (range, -4.8 to -1.1) at the last follow-up visit. Compared to our study, the patients in the study by Bajpai et al.[22] were diagnosed late and had worse Z-scores of height-for-age at the time of diagnosis. Bajpai et al.[22] 22 also noted that poor Z-scores at the time of diagnosis attenuated the improvement that could otherwise be observed in Z-scores of height-for-age during the follow-up period. They emphasized that concomitant bone deformity, rickets, and genetic potential also influence growth. Caldas et al.[23] divided 28 patients with distal RTA into two different groups according to their time of diagnosis and observed that patients who were diagnosed early had better Z-scores of height-for-age at the time of diagnosis and during the follow-up period compared to those of distal RTA patients who were diagnosed late. Similarly, in our study, Z-scores of weight-for-age and height-for-age of distal RTA patients who were diagnosed early were better than those of distal RTA patients who were diagnosed late. In our study, bicarbonate, potassium, and phosphorus levels at admission were not found to be associated with Z-scores of weight-for-age and height-for-age. In contrast, Caldas et al.[23] reported a negative correlation between serum HCO_3^- level and Z-scores of height-for-age at the time of diagnosis. Soriano et al.[24] reported that early diagnosis of primary RTA and early initiation of alkali therapy to treat primary RTA had a positive effect on the growth of the affected patients. Hsu et al.[28] evaluated the growth of 21 patients with proximal RTA (n=15) or FS (n=6) and found that treating metabolic acidosis significantly contributed to the growth in the positive direction in patients with proximal RTA, but did not produce a significant impact on the growth of patients with FS. It has been reported that early diagnosis and early initiation of treatment in patients with FS, especially early treatment of hypophosphatemia, positively affects growth. Haffner et al.[29] did not find any significant correlation between the Z-score of height-for-age and serum potassium and phosphorus levels in 9 patients with FS. In comparison, in our study, we could not separately analyze the impact of potassium, bicarbonate, and phosphorus levels on growth due to the insufficient number of patients in the subgroups of the proximal RTA group.

The treatment methods to be used in the treatment of RTA are determined according to the type of RTA and the respective etiology. That being said, HCO_3^--replacement is the foundation of treatment in all types of RTA.[30,31] High-dose alkali therapy (5-15 mEq/kg/day) is needed to treat proximal RTA, whereas low-dose alkali therapy (2-4 mEq/kg/day) is sufficient to treat distal RTA. In our study, the bicarbonate dose required to achieve HCO_3^- >20 mEq/L was 3.39 mEq/kg/day in the distal RTA group and 12.4 mEq/kg/day in the proximal RTA group.

Study Limitations

Notwithstanding the study's strengths, including its relatively large sample size considering the rarity of this patient group, there were also some limitations to this study. Its retrospective and single-center design was the primary limitation. The fact that patients' long-term growth outcomes were not presented may be considered another limitation of the study.

Conclusion

This study's findings indicated that early diagnosis of primary RTA in children positively affected their growth compared to late diagnosis. As a reason, early diagnosis reduces exposure to malnutrition, hypokalemia, hypophosphatemia, and metabolic acidosis and prevents potentially adverse consequences that might otherwise occur by ensuring the timely application of the necessary treatments.

Ethical Approval: The study was approved by the Ankara Children's Hematology Oncology Training and Research Hospital Ethics Committee (document no: 135-12/2012).

Informed Consent: Retrospective study.

Author Contributions: Concept: A.Y., N.Ç., Design: A.Y., N.Ç., Data Collection or Processing: A.Y., N.Ç., Analysis or Interpretation: A.Y., N.Ç., Literature Search: A.Y., Writing: A.Y., N.Ç.

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References

1. Alexander RT, Bitzan M. Renal Tubular Acidosis. *Pediatr Clin North Am*. 2019;66:135-157. *[CrossRef]*
2. Kurtzman NA. Renal tubular acidosis syndromes. *South Med J*. 2000;93:1042-1052. *[CrossRef]*
3. Halperin ML, Jungas RL. Metabolic production and renal disposal of hydrogen ions. *Kidney Int*. 1983;24:709-713. *[CrossRef]*
4. Roth KS, Chan JC. Renal tubular acidosis: a new look at an old problem. *Clin Pediatr (Phila)*. 2001;40:533-543. *[CrossRef]*
5. Foreman JW. Fanconi Syndrome. *Pediatr Clin North Am*. 2019;66:159-167. *[CrossRef]*
6. Finer G, Landau D. Clinical approach to proximal renal tubular acidosis in children. *Adv Chronic Kidney Dis*. 2018;25:351-357. *[CrossRef]*
7. Zhang L, Xu B, Niu Y, et al. Familial distal renal tubular acidosis. *J Int Med Res*. 2021;49:3000605211000533. *[CrossRef]*
8. Soares SBM, de Menezes Silva LAW, de Carvalho Mrad FC, et al. Distal renal tubular acidosis: genetic causes and management. *World J Pediatr*. 2019;15:422-431. *[CrossRef]*
9. Sekine T, Nozu K, Iyengar R, et al. OCRL1 mutations in patients with Dent disease phenotype in Japan. *Pediatr Nephrol*. 2007;22:975-980. *[CrossRef]*
10. Kari JA, El Desoky SM, Singh AK, et al. The case | Renal tubular acidosis and eye findings. *Kidney Int*. 2014;86:217-218. *[CrossRef]*
11. Bagga A, Sinha A. Renal Tubular Acidosis. *Indian J Pediatr*. 2020;87:733-744. *[CrossRef]*
12. Hamill PV, Drizd TA, Johnson CL, et al. NCHS growth curves for children birth-18 years. United States. *Vital Health Stat 11*. 1977;i-iv, 1-74. *[CrossRef]*
13. Langlois V. Laboratory evaluation at different ages. In: Geary DF, Schaefer F, eds. Textbook of Comprehensive Pediatric Nephrology: Philadelphia, 2008:39-54. *[CrossRef]*
14. Ouigley R. Renal tubular acidosis. In: Avner ED, Harmon WE, Niaudet P, eds. Textbook of Pediatric Nephrology, 6th ed. Springer: Berlin, 2009:979-1003. *[CrossRef]*
15. Igarashi T. Fanconi sydrome. In: Avner ED, Harmon WE, Niaudet P, eds. Textbook of Pediatric Nephrology, 6th ed. Springer: Berlin, 2009:1039-1067. *[CrossRef]*
16. Gahl WA. Cystinosis. In: Avner ED, Harmon WE, Niaudet P, eds. Textbook of Pediatric Nephrology, 6th ed. Springer, Berlin, 2009.p.1019-1038 *[CrossRef]*
17. Bockenhauer D, Bokenkamp A, van't Hoff W, et al. Renal phenotype in Lowe Syndrome: a selective proximal tubular dysfunction. *Clin J Am Soc Nephrol*. 2008;3:1430-1436. *[CrossRef]*
18. Nicoletta JA, Schwartz GJ. Distal renal tubular acidosis. *Curr Opin Pediatr*. 2004;16:194-198. *[CrossRef]*
19. Morris RC Jr, Sebastian A. Alkali therapy in renal tubular acidosis: who needs it? *J Am Soc Nephrol*. 2002;13:2186-2188. *[CrossRef]*
20. McSherry E. Acidosis and growth in nonuremic renal disease. *Kidney Int*. 1978;14:349-354. *[CrossRef]*
21. Domrongkitchaiporn S, Khositseth S, Stitchantrakul W, et al. Dosage of potassium citrate in the correction of urinary abnormalities in pediatric distal renal tubular acidosis patients. *Am J Kidney Dis*. 2002;39:383-391. *[CrossRef]*
22. Bajpai A, Bagga A, Hari P, et al. Long-term outcome in children with primary distal renal tubular acidosis. *Indian Pediatr*. 2005;42:321-328. *[CrossRef]*
23. Caldas A, Broyer M, Dechaux M, et al. Primary distal tubular acidosis in childhood: clinical study and long-term follow-up of 28 patients. *J Pediatr*. 1992;121:233-241. *[CrossRef]*
24. Rodriguez-Soriano J, Vallo A, Castillo G, et al. Natural history of primary distal renal tubular acidosis treated since infancy. *J Pediatr*. 1982;101:669-676. *[CrossRef]*
25. Flyvbjerg A, Dørup I, Everts ME, et al. Evidence that potassium deficiency induces growth retardation through reduced circulating levels of growth hormone and insulin-like growth factor I. *Metabolism*. 1991;40:769-775. *[CrossRef]*
26. Tsao T, Fawcett J, Fervenza FC, et al. Expression of insulin-like growth factor-I and transforming growth factor-beta in hypokalemic nephropathy in the rat. *Kidney Int*. 2001;59:96-105. *[CrossRef]*
27. Salusky IB, Kuizon BG, Jüppner H. Special aspects of renal osteodystrophy in children. *Semin Nephrol*. 2004;24:69-77. *[CrossRef]*
28. Hsu SY, Tsai IJ, Tsau YK. Comparison of growth in primary Fanconi syndrome and proximal renal tubular acidosis. *Pediatr Nephrol*. 2005;20:460-464. *[CrossRef]*
29. Haffner D, Weinfurth A, Seidel C, et al. Body growth in primary de Toni-Debré-Fanconi syndrome. *Pediatr Nephrol*. 1997;11:40-45. *[CrossRef]*
30. McSherry E, Morris RC Jr. Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. *J Clin Invest*. 1978;61:509-527. *[CrossRef]*
31. Hahn H, Kang HG, Ha IS, et al. ATP6B1 gene mutations associated with distal renal tubular acidosis and deafness in a child. *Am J Kidney Dis*. 2003;41:238-243. *[CrossRef]*