Pediatric Nephrology

Long-term complications of primary distal renal tubular acidosis

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Corresponding Author:	Fernando Santos Hospital Universitario Central de Asturias Oviedo, Asturias SPAIN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Hospital Universitario Central de Asturias
Corresponding Author's Secondary Institution:	
First Author:	Fernando Santos
First Author Secondary Information:	
Order of Authors:	Fernando Santos
	Helena Gil-Peña
Order of Authors Secondary Information:	
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Abstract:	The clinical manifestations of primary distal renal tubular acidosis usually begin in pediatric age, but the disease is caused by a genetic defect that persists throughout life. This review focuses on the complications of distal tubular acidosis that occur or remain long-term such as nephrocalcinosis and urolithiasis, growth impairment, bone mineralization, severe hypokalemia, kidney cysts, and progressive kidney failure, as well as other persistent manifestations that occur independent of acidosis but are associated in some inherited forms of the disease. The pathogenic factors responsible for kidney failure are discussed in particular because it is a complication to which different publications have recently drawn attention and which affects a high percentage of adults with primary distal renal tubular acidosis. The need to maintain optimal metabolic control of the disease and scheduled clinical follow-up throughout life and the importance of organizing protocols for the transition of patients to adult nephrology services are emphasized.
Response to Reviewers:	Reviewers' comments: The manuscript is almost ready for acceptance. please address these final points: The authors appear convinced that hypokalaemia causes kidney cysts. While they are entitled to their opinion, a review should properly acknowledge that this is highly controversial opinion. There is a plethora of data against this hypothesis, not least the low prevalence of kidney cysts in patients with Gitelman syndrome, even though they usually have more profound hypokalaemia than those with dRTA. While kidney cysts are common in disorders with hyperaldosteronism, it is typically those also associated with hypercalciuria. The possibility of cyst development from obstructing intratubular calcium deposits should at least be mentioned and discussed! Statements of causality, such as on top of page 12 (“…hypokalemia, causing the appearance of kidney cysts…”) should be modified, as it is an association, at best. - We agree with the reviewer that hypokalemia may not be the only factor responsible for cyst formation in patients with dRTA. However, it is also true that many patients with hypercalciuria and/or urolithiasis do not develop cysts. We have added the following

	sentence to the manuscript "However, not all diseases with chronic hypokalemia have an elevated prevalence of kidney cysts [3]. Other factors might increase the risk of cyst formation in patients with dRTA, i.e., elevated intratubular pressure resulting from obstruction by calcium oxalate intraluminal deposits" - The statement “causing the appearance of kidney cysts” has been deleted. As well as “hyperaldosteronism and kidney cysts” a few lines further down in the same paragraph. Language is still a problem and review of the manuscript by a native speaker is highly recommend. Selected issues below, but there are numerous more. 1. Page 5, last line: please replace “completely good” with “adequate” 2. page 7, line 36ff: please change “may disclose..” to “may prompt the initial diagnosis” 3. page 9, line 13: replace “clinical meaning” with “clinical relevance” - We are grateful for the changes recommended by the reviewer, which have been introduced in the text. As for the manuscript’s language, please, see below. Editorial Office comments: Please consider using a professional language editing service, as outlined in the Journal's website here: https://www.springer.com/journal/467/submission-guidelines#Instructions%20for%20Authors_English%20Language%20Support The website also has links to a 'Free online grammar check' and an 'English language tutorial'. - Following this recommendation, we used the AJE’s free grammar check which “can help you determine whether your document could benefit from revisions”. We got the following report “This paper scored a 6.5/10 which is in the 79th percentile of papers submitted to AJE. After editing by AJE, papers improve on average to a score of 8.7 and move into the 95th percentile of research papers submitted to journals. Congratulations! Your document is well written and does not need language editing.” The free online grammar check does not provide the revised version of the manuscript, only the grammatical report, but we understand that according to it the English quality of our manuscript is satisfactory. We also understand that if accepted, the manuscript will be checked by Springer’s copyeditors for spelling and formal style before publication. We thank Springer for this editorial service.

Ref.: Ms. No. PNEP-D-21-00779R2
Long-term complications of primary distal renal tubular acidosis
Pediatric Nephrology

Dear Prof. Flynn,

Thank you for the revision of our manuscript and for the reviewers' and editorial office's comments and recommendations.

The manuscript has been reviewed.

The responses to the reviewers' comments are given below. The corresponding modifications have been made to the manuscript and are highlighted in the files uploaded as Supplementary Material.

In addition to the changes suggested by the reviewers, we have corrected an error in the naming of the WDR72 gene that appeared in the text as WDRT2. We have also added reference 71, which was not included and which we consider important.

Best regards and thank you again,

Fernando Santos

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The manuscript is almost ready for acceptance. please address these final points:
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Editorial Office comments:

Please consider using a professional language editing service, as outlined in the Journal's website here:

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The website also has links to a 'Free online grammar check' and an 'English language tutorial'.

- Following this recommendation, we used the AJE’s free grammar check which “can help you determine whether your document could benefit from revisions”.

We got the following report “This paper scored a 6.5/10 which is in the 79th percentile of papers submitted to AJE. After editing by AJE, papers improve on average to a score of 8.7 and move into the 95th percentile of research papers submitted to journals. **Congratulations**! Your document is well written and does not need language editing.”

The free online grammar check does not provide the revised version of the manuscript, only the grammatical report, but we understand that according to it the English quality of our manuscript is satisfactory. We also understand that if accepted, the manuscript will be checked by Springer’s copyeditors for spelling and formal style before publication. We thank Springer for this editorial service.

Long-term complications of primary distal renal tubular acidosis

[1]Fernando Santos, M.D., Ph.D.; [1]Helena Gil-Peña, B.S., Ph.D.

Author affiliations

[1]Pediatrics, Hospital Universitario Central de Asturias. Department of Medicine, University of Oviedo. Oviedo, Asturias, Spain

Corresponding author

Professor Fernando Santos

Email fsantos@uniovi.es

Conflict of interest The authors disclose no conflict of interest related to the content of the manuscript.

Keywords: Distal renal tubular acidosis. Metabolic acidosis. Kidney failure. Growth. Hypokalemia.

Abstract

The clinical manifestations of primary distal renal tubular acidosis usually begin in childhood, but the disease is caused by a genetic defect that persists throughout life. This review focuses on the complications of distal tubular acidosis that occur or remain long-term such as nephrocalcinosis and urolithiasis, growth impairment, bone mineralization, severe hypokalemia, kidney cysts, and progressive kidney failure, as well as other persistent manifestations that occur independent of acidosis but are associated with some inherited forms of the disease. The pathogenic factors responsible for kidney failure are discussed in particular because it is a complication to which different publications have recently drawn attention and which affects a high

percentage of adults with primary distal renal tubular acidosis. The need to maintain optimal metabolic control of the disease and scheduled clinical follow-up throughout life and the importance of organizing protocols for the transition of patients to adult nephrology services are emphasized.

Introduction

Distal renal tubular acidosis (dRTA) is characterized by chronic normal anion gap metabolic acidosis associated with a urinary acidification defect consisting in the inability to decrease the urine pH up to a value ≤ 5.3 [1]. The majority of dRTA diagnosed at the pediatric age are primary forms, i.e., of genetic cause [2, 3]. Clinical and biochemical features characteristic of primary dRTA are summarized in Table 1 [1, 4, 5].

Once the correct diagnosis is established, patients with primary dRTA usually respond well to sustained alkaline supplementation, so the disease is generally considered to have a good prognosis. This review aims to make the pediatric nephrologist aware of the risk of long-term complications in individuals with dRTA and of the need to ensure an adequate transition of adolescents with dRTA to adult nephrology services, as continued follow-up and treatment of these patients during adulthood are mandatory.

Most of the publications cited in this manuscript, describing complications in adults with primary dRTA, correspond to journals of specialties other than nephrology, such as emergency medicine, anesthesia, internal medicine, neurology, etc. This fact could reflect a lack of regular follow-up of these patients by adult nephrology services and indicate the need for greater attention by nephrologists to the complications that occur in adults with primary dRTA, including the following that will be discussed in this

review: nephrocalcinosis and urolithiasis, growth impairment, bone mineralization, severe hypokalemia, kidney cysts, progressive kidney failure, and extrarenal manifestations associated with some types of inherited dRTA but not dependent on acidosis itself.

Nephrocalcinosis and Urolithiasis

Nephrocalcinosis is an early and common finding of primary dRTA. It is already detected by echography at the time of diagnosis in the vast majority of pediatric patients [2, 3, 6]. Nephrocalcinosis is frequently visible in X-ray films and persists into adulthood even if correct treatment is initiated and maintained [7]. Urolithiasis is less frequent in pediatric dRTA patients, so most children do not have stones, however it can be found in approximately 20-40% of adults with primary dRTA [7].

The combination of hypocitraturia and hypercalciuria is thought to be the main factor increasing the risk of calcium phosphate precipitation in dRTA. Hypocitraturia is caused by stimulated proximal tubular reabsorption of citrate [8]. The elevation of calciuria occurs because of the liberation of calcium salts from bone to buffer fixed acid retention and, likely, a decreased tubular reabsorption of calcium as well [9]. Urinary alkalinity can contribute to calcium phosphate precipitation. Although urine calcium excretion rate has been shown to correlate inversely with plasma bicarbonate concentration in pediatric patients with dRTA [4], some children may remain hypercalciuric in spite of being non-acidotic and, vice versa, some patients may be acidotic despite having calciuria within normal reference ranges [9, 10].

Nephrocalcinosis may contribute to the urinary acidification defect, although nephrocalcinosis itself does not cause secondary dRTA, and likely impairs the ability of dRTA patients to maximally concentrate the urine [11], whereas urolithiasis may

cause episodes of kidney colic, urinary obstruction and be related to repeated urinary tract infections [12]. Nephrocalcinosis and nephrolithiasis might play a role in the genesis of kidney failure in patients with primary dRTA (vide infra).

Growth impairment

Growth retardation and failure to thrive are major and common presenting manifestations of primary dRTA in infancy and childhood [2]. Usually, the normalization of blood pH and serum bicarbonate after starting alkaline treatment results in acceleration of growth velocity and catch-up growth [13]. However, a study on growth outcome of early diagnosed and treated primary dRTA pediatric patients prospectively followed-up until reaching final height is not available. Lopez-Garcia et al [7] found that the height SDS mean (± SD) of a large series of adults with primary dRTA was -0.57 (± 1.16), in comparison to the normal population reference values, with no significant difference among the groups classified according to the underlying causal gene. It should be noted that this study was retrospective and on a heterogeneous sample without genetic confirmation in a high percentage of cases. Gómez-Conde et al [14] found that the median SDS height at 20 years follow-up of 16 patients with primary dRTA diagnosed in childhood was −1.23 (IQR −1.71, −0.48), and did not significantly improve from diagnosis. Forero-Delgadillo et al [15] reported that the height SDS mean (± SD) of 25 patients included in the RenalTube database with genetically confirmed primary dRTA was −0.45 (± 0.38) after a median follow-up of 8.8 years.

Thus, the growth retardation characteristically found at the diagnosis of primary dRTA in pediatric patients may not be fully reversed with alkaline treatment despite the initial beneficial effect of alkali treatment on growth velocity. Sustained metabolic

acidosis itself exerts an adverse effect on longitudinal growth and on growth plate structure and dynamics [16], and may interfere with growth hormone secretion and with the production of insulin-like growth factor I and cause resistance to growth hormone action [17, 18]. An unsatisfactory response of growth to treatment likely indicates that the metabolic control of dRTA is not adequate, compromising the full growth potential of the patient. It should be noted that growth impairment and improvement of growth with bicarbonate supplementation have even been reported in children with posterior urethral valves diagnosed as incomplete dRTA on the basis of normal blood pH and bicarbonate concentration and inability to maximally acidify the urine [19]. Although factors other than acidosis might interfere with growth rate in some patients with dRTA, optimal control of metabolic acidosis is mandatory to achieve normal growth.

Bone mineralization

Hypercalciuria and acidosis are factors that affect bone mineralization and structure in patients with dRTA. Although rickets may be a presenting manifestation of primary dRTA [3], the first reported systematic evaluation of radiographic findings, assessed by X-ray films, in a large group of patients with various types of renal tubular acidosis found skeletal abnormalities in only one individual out of 42 patients with dRTA diagnosed by clinical and biochemical data [20]. This dRTA patient had radiological signs compatible with osteopenia and kidney failure. There is scarce published information on bone mineralization in patients with dRTA. In a cross-sectional study of 14 Thai adult patients with dRTA and normal glomerular filtration rate (GFR), before starting alkaline therapy, analysis of bone mineral density and bone histology showed that low bone mass was common and bone formation and resorption were suppressed, with osteomalacia not being the predominant lesion [21]. Alkaline

therapy corrected abnormal bone cell function and elevated bone mineral density in 10 of these patients followed for 1 year [22]. It is of note that association of incomplete forms of dRTA, i.e., defective ability to acidify urine with normal blood pH and bicarbonate concentration, and osteopenia or osteoporosis, have been found in adults [23], although the pathophysiological mechanism of this association is not clear.

Severe hypokalemia

Untreated patients with primary dRTA usually have plasma potassium concentrations mildly decreased or in the low range of normality [2, 3, 6]. Although the precise mechanism responsible for hypokalemia in primary dRTA is to a great extent unknown [24, 25], it is generally believed that hypokalemia results from stimulated potassium ion secretion in the collecting duct, caused by (i) hyperaldosteronism secondary to sodium wastage and subsequent extracellular volume depletion, and (ii) a more favorable transtubular gradient (lumen negative) for the potassium secretion in the collecting duct, generated by the uptake of sodium ion via epithelial sodium channel and not balanced by the secretion of protons [25, 26].

Severe manifestations such as paralysis, respiratory arrest, cardiac arrhythmias, musculoskeletal symptoms, and rhabdomyolysis caused by the aggravation of hypokalemia have been reported in individuals with dRTA [27-29] and may prompt the initial diagnosis of the disease [30]. These hypokalemia-related complications have rather been found in adults with dRTA secondary to Sjögren syndrome [31], which is the most frequent cause of acquired dRTA [25], and other autoimmune diseases [32, 33], but they have also been described in patients with primary forms of dRTA [34, 35]. The usual way that dRTA patients get symptomatic hypokalemia is with intercurrent diarrhea/vomiting associated with missing oral

supplements or intolerance to them. Aggravation of acidosis and profound hypokalemia have been reported in females with primary dRTA during pregnancy [36] and in the initial postpartum period [37], likely as a result of metabolic and clinical changes that occur in pregnancy such as an increase in GFR causing increased filtration of bicarbonate, hyperemesis leading to interruption of alkaline treatment and concomitant urinary tract infections.

To correct or ameliorate hypokalemia, dRTA patients are treated with sustained alkali supplementation given as potassium citrate and/or potassium bicarbonate [4, 11]. In patients with persistent hypokalemia, despite well-controlled acidosis [38], oral supplements of potassium as potassium chloride or potassium aspartate may be recommended as well [11].

Kidney cysts

In 1991, Igarashi et al first noticed the formation of kidney cysts as complication of primary dRTA [39] and in 1994 they reported that 71% of 17 patients with dRTA had cysts larger than 5 mm in diameter detected by sonography and/or CT scan at a mean age of 17.9 years (range 7-29) [40]. Cysts were multiple, the number of kidney cysts increased with age, were localized in one or both kidneys, had less than 5 cm in diameter and were not associated with low GFR.

Although there is scarce information on the prevalence of kidney cysts in dRTA [41], the increased occurrence has been confirmed in other cohorts including a greater number of patients with primary dRTA. Thus, Besouw et al [3] detected medullar cysts by ultrasound in nine of 24 children, the first cyst being noted between 3 and 17 years of age.

The mechanism responsible for the development of kidney cysts has not been specifically studied in dRTA. A high frequency of kidney cysts has been demonstrated in adult patients with chronic hypokalemia and primary or secondary aldosteronism [42, 43]. Experimental studies indicate that hypokalemia stimulates the hypertrophy and proliferation of epithelial cells lining the cysts [44]. Studies in rodents have found that hypokalemia itself causes hyperplasia of the collecting tube cells in the outer medulla that is sufficient to obstruct the tubular lumen and result in tubular dilatation [42]. However, not all diseases with chronic hypokalemia have an elevated prevalence of kidney cysts [3]. Other factors might increase the risk of cyst formation in patients with dRTA, i.e., elevated intratubular pressure resulting from obstruction by calcium oxalate intraluminal deposits.

Likewise, the clinical relevance of the kidney cysts in dRTA is not well defined. Manifestations caused by acquired simple cysts such as hemorrhage, infection or rupture [45] are not usually reported in individuals with dRTA and the cysts have not been found to be associated with reduced GFR or with the extension of nephrocalcinosis in dRTA patients [3, 40]. It is of note that the co-occurrence of primary dRTA and medullary sponge kidney, an entity characterized by cystic dilatation of the renal medullary collecting ducts, has been reported in two pediatric patients with mutations in *ATPV0A4* and *ATPV1B1* genes [46].

Progressive kidney failure

Although primary dRTA is traditionally considered a tubular disease with normal or mildly decreased GFR [1, 4], recent publications have warned of an elevated risk of kidney failure in these patients, particularly in the long term [7]. In the above-mentioned study by Lopez-García et al [7], in a sample of 340 patients with a clinical diagnosis of

primary dRTA, 55.6%, 23.5% and 3.7% of adults had chronic kidney disease (CKD) stages 2, 3 and 4, respectively. Interestingly, the mean estimated GFR in the dRTA cohort at the age of 18 years was already equivalent to CKD stage 2, indicating kidney damage since childhood. Several studies have reported a high occurrence of kidney failure in children and adults with primary dRTA, with variable percentages that ranged in adults from 40% to 100% for stages 2 to 4 [2, 3, 14, 15, 47-49].

The methodological characteristics of the published studies do not allow a precise determination of the mechanisms responsible for the reduction of GFR. It can be stated that the reduction of GFR in primary dRTA does not depend on the type of mutated causal gene and it is already present in a small percentage of children and adolescents, although it is more prevalent after long-term follow-up.

Several factors potentially interrelated may play a pathogenic role in the development of kidney failure (Figure 1). The persistence of poorly controlled metabolic acidosis seems to be of particular relevance as clinical and experimental findings support the deleterious effect of acidosis on kidney function [50]. It has been suggested that patients with poor metabolic control, defined by low bicarbonatemia and hypercalciuria, have an increased risk of kidney failure [7], but this relationship has not been confirmed in other studies [14, 48]. The adverse effect of acidosis on the progression of kidney failure has been suggested in clinical trials in adults with CKD [51, 52] although more trials are needed to demonstrate the beneficial effects of sodium bicarbonate therapy on kidney function [53]. The sustained decrease of interstitial and intracellular pH in the kidney leads to interstitial inflammation and kidney fibrosis through several potential mechanisms recently reviewed [54]. It is of interest for the discussion of the pathogenesis of CKD in dRTA that these mechanisms damaging the kidney may occur not only because of acidemia but also may be

triggered by acid retention even if it does not produce clinically appreciable metabolic acidosis, a situation called eubicarbonatemic acidosis [50]. This situation is likely to occur in untreated or insufficiently treated dRTA in which there is a daily retention of fixed acid equivalent to the net acid excretion.

Repeated episodes of acute kidney injury triggered by intercurrent events of metabolic decompensation induced by drugs, gastrointestinal disorders, lack of treatment or non-compliance, or other stressing conditions may also contribute to CKD.

In addition, urolithiasis and nephrocalcinosis account for a risk of obstructive uropathy and/or pyelonephritis leading to chronic tubulointerstitial nephritis and fibrosis. The impact of repeated infections and obstruction as factors leading to or aggravating CKD should be emphasized. In this regard, a possible correlation between the severity of nephrocalcinosis and the reduction of GFR has not been analyzed in patients with primary dRTA, likely because nephrocalcinosis is almost a universal finding in these patients and the extension and degree of nephrocalcinosis is difficult to quantify reliably.

Preliminary data based on 22 Spanish cases of genetically confirmed dRTA [15], indicate that the percentage of low birth weight (LBW), less than 2,500 g, in the group of seven patients who developed low GFR after a median follow-up of 12 years was 29%, higher than that expected in the reference population which is approximately 8% of newborns, although not significantly greater than 20% found in the fifteen cases who kept a normal GFR. The reason for this increased prevalence of LBW in infants with dRTA is not known because it cannot be attributed to acidosis which is not present in fetal life or at birth in these patients. This finding, that might represent an additional

risk factor for the development of kidney failure in adults with pediatric onset dRTA [55], needs to be confirmed in larger series of patients. Moreover, the interference of metabolic acidosis on the catch-up growth in small for gestational age infants might cause small sized kidneys. To our knowledge, there is no available data on the evolution of kidney growth in patients with dRTA in the first years of life. In some patients with primary dRTA, the prolonged effects of hypokalemia and the development of chronic interstitial nephropathy, which is likely mediated by ammonia-mediated complement activation [56], might be another risk factor for kidney failure [57]. However, it is of note that patients with tubulopathies causing higher degrees of potassium depletion usually do not develop kidney failure, although this is found in up to 25% of patients with Bartter syndrome [58].

Extrarenal manifestations not dependent on acidosis

Patients with primary dRTA may have other manifestations that are independent of acidosis but which are caused by the same genetic defect (Table 1). Thus, sensorineural deafness is an almost constant finding in pediatric patients with *ATP6V1B1* gene defect [2, 3, 6], is found in 35-50% of adults with *ATP6V0A4* mutations [2, 7, 62], and is also a characteristic manifestation of the few cases of dRTA caused by *FOXI1* gene that have been described so far [60]. The association of primary dRTA and hearing loss is due to the simultaneous dysfunction of a common set of membrane transport proteins expressed in the epithelia of the inner ear and renal collecting duct [61]. Bilateral enlargement of vestibular aqueduct has also been found in some deaf patients with inherited dRTA [60, 62, 63], the underlying pathophysiologic mechanism of this association being unclear [64]. The timely introduction of hearing aids or cochlear implants is essential for normal intellectual development and social integration of patients.

Patients with dRTA caused by mutations in *SLC4A1* gene may have hemolytic anemia (Table 1) because *SLC4A1* encodes isoforms of the anion exchanger (AE1) protein located in red cells (eAE1, band 3) and kidney (kAE1) [65]. The kAE1 isoform is a truncated protein with 65 amino acids missing the N-terminal cytoplasmic domain. Most *SLC4A1* mutations cause either dRTA or hematological abnormalities but certain *SLC4A1* mutations may result in the association of Southeast Asian ovalocytosis (SAO) or hereditary spherocytosis and dRTA [66-68]. The coexistence of SAO and dRTA is the result of compound heterozygosity and follows an autosomal recessive form of inheritance [65]. Incomplete forms of dRTA, characterized by a urinary acidification defect without spontaneous metabolic acidosis, have been found in patients with hereditary spherocytosis harboring autosomal dominant heterozygous mutations of the *SCL4A1* gene [65]. The association of complete dRTA and severe hereditary spherocytosis has been reported in very few patients with homozygous or compound heterozygous mutations [67, 68].

A very rare form of dRTA of variable severity associated with amelogenesis imperfecta has been reported in a few families with mutations in the *WDR72* gene [69-71]. Mutations in *WDR72* disrupt clathrin-mediated endocytosis in amelocytes, resulting in impaired enamel mineralization. The reason for dRTA is unknown, although the WDR7 protein co-localizes with V-ATPase in kidney tubule cells and may be required for proper proton pump function [72].

Prevention and transition

As can be inferred from the above, there is a need for well-designed prospective studies aimed at clarifying the role that different pathogenic factors may play in the onset and progression of kidney failure in patients with dRTA. Early diagnosis,

adequate treatment and lifelong follow-up appear to be crucial for the prevention of complications from dRTA. Updated recommendations for the clinical management of patients with dRTA have recently been published [11] and provide useful reference guidelines for the physicians that take care of these patients.

The transition to adult nephrology units is a critical point that requires special attention by pediatric nephrologists to ensure adequate monitoring and treatment of these patients not only in childhood but also throughout their lives as well as patient adherence to chronic medication, follow-up visits and regular specialized urology input to eliminate kidney stones and minimize urinary tract infections. A survey conducted within the scope of the Spanish Society of Nephrology in 2019 showed that dRTA is a not well-known entity by nephrologists and that most of them believe that the metabolic control of patients and adherence to treatment are not good [73]. It would be of interest to design and implement a transition protocol aimed at raising awareness among patients and adult specialists of the need for continuous and chronic control of the disease. It is very important to achieve good and continued adherence to treatment.

Raina et al [74] proposed a protocol for cystinosis, named after the acronym RISE, based on the following four areas of competency summarized as follows:

R - *Recognition* of one's disease process, treatment, health-care system, as well as personal goals.

I - *Insight* into short- and long-term impact of the disease, treatment, and non-adherence.

S - *Self-reliance* and self-management of medications and appointments

as well as ability to identify urgent/emergent changes in the health.

E - *Establishment* of healthy lifestyle choices, life-long adherence to medications and follow-up.

This protocol could serve as the basis for adaptation to dRTA in discussion forums formed by specialists involved, patient associations and representatives of the healthcare system.

In summary, physicians and patients should be aware of the high risk of long-term complications in primary dRTA. Lifelong care of the patients including chronic alkaline therapy and appropriate clinical monitoring are essential to prevent and treat these complications. Well-designed clinical studies, as well as other research initiatives, should be performed to clarify the role of the potential pathogenic factors responsible for kidney failure in dRTA.

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Figure legend

Figure 1 Potential pathogenic factors of chronic kidney disease (CKD) with reduced glomerular filtration rate in distal renal tubular acidosis (dRTA). The factors may be largely interrelated, which is represented graphically in the drawing by the double-headed arrows.

Table 1 Typical features of primary distal renal tubular acidosis (dRTA)

GFR, glomerular filtration rate

Genetic basis	• Genes most frequently involved: *ATP6V0A4*, *ATP6V1B1*, *SLC4A1*. • Loss of function mutations in other genes (*FOXI1, WDR72, ATP6V1C2*) described in a very reduced number of patients or families. • No conclusive gene defect found in approximately 25% of cases. • Autosomal recessive transmission. Autosomal dominant inheritance also reported in dRTA linked to *SLC4A1*.
Clinical manifestations	• Early presentation in infancy. Forms caused by *SLC4A1* present later, even in adulthood, and may be detected during family screening. • Episodes of vomiting and dehydration. • Failure to thrive and growth failure. • Early ultrasonographic nephrocalcinosis. • Associated neurosensorial deafness in *ATP6V1B1* and, less frequently, not as early and with less severity, in *ATP6V0A4* gene defects. • Associated hemolytic anemia in some autosomal recessive inherited *SLC4A1* gene mutations found in Asian patients.

Biochemical profile	• Hyperchloremic, normal anion gap, metabolic acidosis. • Normal or mild reduction of GFR. • Inability to decrease urine pH to a value ≤ 5.3. • Normal / low serum potassium. • Hypocitraturia. • Hypercalciuria. • Low urinary ammonium. • Normal fractional excretion of bicarbonate in the presence of normal bicarbonatemia. • Functional tests (furosemide administration, urine minus blood pCO_2 in alkaline urine) may disclose the defective urinary acidification ability.
Chronic therapy	• Good clinical response and correction of metabolic acidosis on chronic treatment with alkaline treatment, 2-3 mEq/kg/day. Sodium bicarbonate and/or potassium citrate are orally given every 4-6 h in infants and children. Slow-release preparations (Sibnayal®) given twice a day are being successfully used in recent years.

Figure 1

Figure 1