The European distal renal tubular acidosis registry: a five-year analysis

Giaccari, Marta[1,2]; Veligratli, Faidra[3] ; Hayes, Wesley [3,4] ; Topaloglu, Rezan[5]; Ozdemir, Gulsah[5]; Ruggiero, Barbara[2]; Boyer, Olivia[6,7]; Knebelmann, Bertrand[7]; Nedelec, Yann[7]; Fila, Marc[8]; Hemery, Floriane[8]; Atmis, Bahriye[9]; Karabay Bayazit, Aysun[9]; Bertholet-Thomas, Aurélia[10]; Lemoine, Sandrine[10]; Papizh, Svetlana[11]; Prikhodina, Larisa[11]; Aksu, Bağdagül[12]; La Scola, Claudio[13,14]; Eid, Loai[15]; Güngör, Tülin[5]; Canpolat, Nur[12]; Trepiccione, Francesco[16]; Decramer, Stéphane[17]; Camilla, Roberta[18]; Yüksel, Selçuk[19]; Girisgen, Ilknur[20]; Schaefer, Franz[21]; Haeberle, Stefanie[22]; Levtchenko, Elena[23,24]; Haffner, Dieter[25,26]; Ariceta, Gema[27]; Claes, Kathleen[24]; Koster-Kamphuis, Linda[28]; Petzold, Friederike[29]; Harambat, Jérôme[30]; Godron-Dubrasquet, Astrid[30]**;** Oh, Jun[31]; Burgmaier, Kathrin[32,33]; Cerkauskiene, Rimante[34]; Longo, Germana[35]; D'Ambrosio, Viola[36]; Konrad, Martin[37]; Lungu, Adrian[38]; Maxted, Drew[39]; Bockenhauer, Detlef[24]; Emma, Francesco[2]

1. Universitá Cattolica del Sacro Cuore, Rome, Italy;
2. Division of Nephrology, Bambino Gesù Children's Hospital – IRCCS, Rome Italy;
3. Department of Paediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust
4. Zurich Children's Hospital
5. Hacettepe University Faculty of Medicine Department of Pediatric Nephrology, Ankara Turkey
6. Néphrologie pédiatrique, MARHEA, Institut Imagine,
7. Hôpital Necker Enfants Malades, APHP, Université Paris Cité, Paris, France
8. CHU Arnaud de Villeneuve – reference center for renal rare disease SORARE – Montpellier
9. Çukurova University, Faculty of Medicine, Department Pediatric Nephrology, Adana Türkiye
10. Rare kidney disease centre - MAREGE - ORKiD network - Lyon – France
11. Veltishev Research Clinical Institute for Pediatrics & Children Surgery, Pirogov Russian National Research Medical University
12. Division of Pediatric Nephrology, İstanbul Faculty of Medicine, Istanbul University
13. Pediatric Nephrology and Dialysis SSD – IRCCS AOU Bologna
14. Paediatric Nephrology Outpatient Clinic –Department of Women's, Children's and Adolescents' Health, Rimini – AUSL Romagna
15. Kidney Centre of Excellence Al Jalila Children's Specialty Hospital, Dubai, UAE

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

© The Author(s) 2026. Published by Oxford University Press on behalf of the ERA. All rights reserved. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site-for further information please contact journals.permissions@oup.com

16. Department of Medical Translational Sciences, University of Campania "L. Vanvitelli", Naples, Italy
17. Pediatric Nephrology, Children hospital Toulouse, Renal Rare Diseases Reference Centre
18. Nephrology Unit; Regina Margherita Children's Hospital, AOU Città della Salute e della Scienza di Torino, Turin, Italy
19. Department of Pediatric Nephrology, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Turkey
20. Department of Pediatric Nephrology, Pamukkale University, Faculty of Medicine, Denizli, Turkey
21. Center for Pediatrics and Adolescent Medicine, Heidelberg University Hospital
22. ERKNet Central Office, Heidelberg University Hospital, .
23. Department of Pediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, Location AMC, Amsterdam, The Netherlands.
24. Department of Paediatric Nephrology, University Hospital Leuven, Heerestrat 49, Louvain, Belgium.
25. Department of Paediatric Kidney, Liver, Metabolic and Neurological Diseases, Hannover Medical, School, Hannover, Germany.
26. Center for Congenital Kidney Diseases, Center for Rare Diseases, Hannover Medical School, Hannover, Germany
27. Pediatric Nephrology. Hospital Vall d'Hebron. University Autonomous Barcelona, Barcelona, Spain.
28. Department of pediatric nephrology Radboudumc Amalia Children’s Hospital Nijmegen the Netherlands
29. Division of Nephrology, University of Leipzig Medical Center, Leipzig, Germany
30. Pediatric Nephrology Unit, Reference center for rare kidney diseases (Sorare), Bordeaux University Hospital, Bordeaux, France
31. Hamburg University Medical Center Hamburg-Eppendorf, Germany
32. Department of Pediatrics, Faculty of Medicine, University Hospital Cologne and University of Cologne, Cologne, Germany
33. Faculty of Applied Healthcare Science, Deggendorf Institute of Technology, Deggendorf, Germany
34. Pediatric Center, Intstitute of Clinical medicine, Medical Faculty, Vilnius university, Lithuania
35. Pediatric Nephrology Unit, University-Hospital of Padova, Italy
36. Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

37. University Children's Hospital Münster, Germany
38. Fundeni Clinical Institute, Bucharest, Romania
39. Nottingham Children's Hospital Renal and Urology Unit

Correspondence to:

Francesco Emma

E-mail: francesco.emma@opbg.net

Detlef Böckenhauer

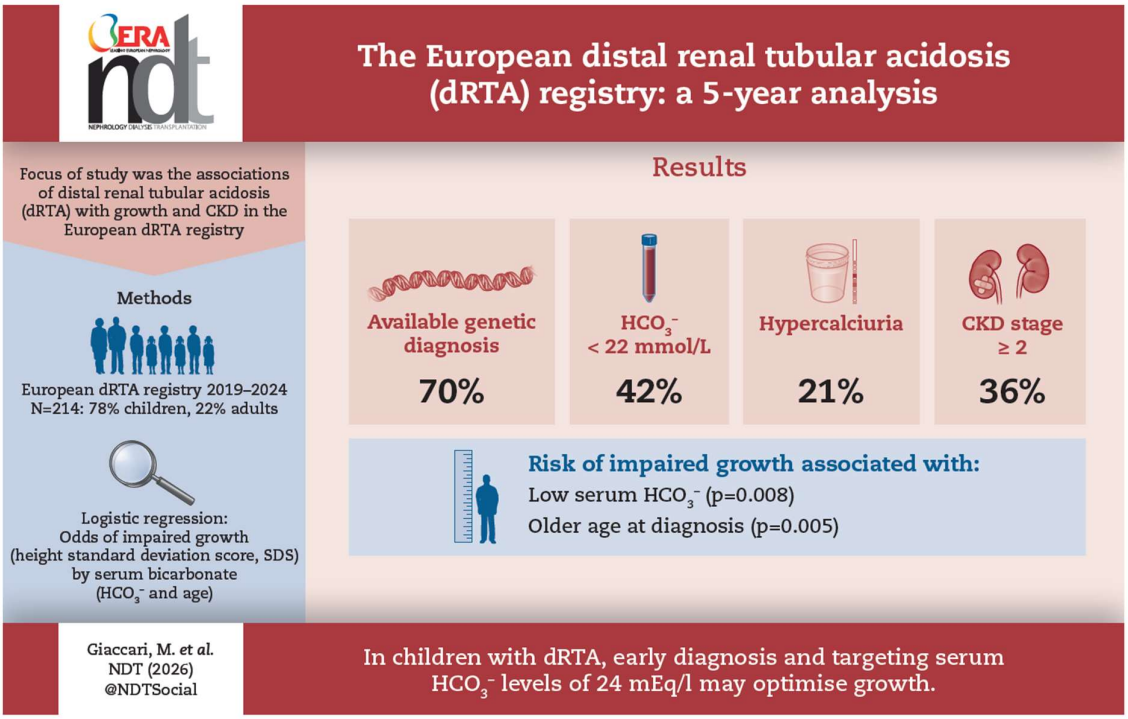
E-mail: detlef.bockenhauer@uzleuven.be

*have equally contributed and share last authorship

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

GRAPHICAL ABSTRACT



ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

ABSTRACT

Background.

Distal renal tubular acidosis (dRTA) is characterized by metabolic acidosis, growth failure nephrocalcinosis, nephrolithiasis and chronic kidney disease (CKD). Previous retrospective data suggested improved outcome with adequate metabolic control, but confirmation from prospective data is lacking. Since 2019, the European dRTA registry has collected prospective data on patients with dRTA. Herein we present results of the first data analysis.

Methods.

The registry is hosted as a subregistry of the European Rare Kidney Disease Network (www.ERKnet.org). In addition to the standard items of growth and plasma creatinine, additional data on plasma and urine biochemistries, genetics, treatment and clinical manifestations were collected from February 2019 through May 2024. Logistic regression analysis was used to identify predictors of CKD and impairedgrowth.

Results.

Of the 214 patients enrolled in the registry, only 22% were >18 years at the last visit. A genetic cause was documented in 69% of patients.

On average, low blood bicarbonate levels (<22 mmol/L) and hypercalciuria were observed in 42% and 25% of patients, respectively, independently from age. Multivariable analysis showed that height standard deviation score (SDS) was positively associated with serum bicarbonate levels (p=0.008) and with early diagnosis (p=0.005). Further modelling based on odds ratios indicated that height SDS increased progressively with serum bicarbonate levels until they

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

reached 22-24 mmol/L. Patients aged >30 years had significantly lower eGFR (p<0.001) and the overall prevalence of CKD ≥stage 2 was 36%. Patients with *SLC4A1* variants were at higher risk of CKD>1 (p=0.013).

Conclusion.

Our results in this primarily paediatric cohort highlight the importance of metabolic control and support increasing the blood bicarbonate level for therapy to 24 mmol/L to improve growth. Compared to the overall population, patients with dRTA are at higher risk of CKD from childhood, particularly if they have underlying *SLC4A1* variants.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

Key learning points

What was known:

Distal renal tubular acidosis (dRTA) is a condition characterized by metabolic acidosis, growth failure, nephrocalcinosis, nephrolithiasis and chronic kidney disease (CKD). No clear threshold for target bicarbonate levels has been established. Pathogenic variants in genes encoding for subunits of the H^+-ATPase pump tend to cause more severe phenotypes.

This study adds:

In patients with dRTA, linear growth is associated with metabolic control. Serum bicarbonate levels ≥22 mmol/l reduces the risk of growth failure. Unfortunately, this is achieved only by a minority of patients. CKD>1 is common in dRTA and was more frequent in this cohort in patients carrying heterozygous *SLC4A1* variants.

Potential impact:

Our study highlights the importance of adequate alkali treatment in reducing the risk of growth failure in patients with dRTA. Treatment should aim at a blood bicarbonate concentration of 24 mmol/L.

Keywords: alkali therapy, chronic kidney disease, growth, metabolic acidosis, nephrocalcinosis

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

INTRODUCTION

Distal renal tubular acidosis (dRTA) is characterized by an impaired ability of the intercalated cells in the distal tubule to acidify urine, resulting in metabolic acidosis with abnormally alkaline urine. The retained acid is primarily buffered by the bone and patients may present with nephrocalcinosis and/or nephrolithiasis, hypokalemia, osteomalacia and/or rickets, dehydration, vomiting and in some cases, with proximal tubular dysfunction that resolves rapidly after correction of the metabolic acidosis[1, 2].

DRTA can be primary or acquired, with an analysis of the UK Clinical Practice Research Datalink database suggesting that almost 80% of cases are acquired[3]. Primary dRTA is associated with pathogenic variants in several genes, with the majority of patients having variants in *ATP6V0A4* or *ATP6V1B1,* encoding two of the sub-units of the apical proton pump, or in *SLC4A1* that encodes the type 1 anion exchanger[4]. Variants involving the proton pump are nearly always transmitted in an autosomal recessive (AR) pattern, whereas the majority of variants involving the *SLC4A1* are transmitted in an autosomal dominant (AD) pattern[4] and cause milder acidosis that usually becomes symptomatic later in life[2]. Only two variants in *ATP6V1B1*, namely the c.1181G>A; p.(Arg394Gln) and c.1180C>G; p.(Arg394Gly) variants, have been associated with autosomal dominant inheritance[5]. Variants in *WDR72* have been mainly reported in Asian patients and *FOXI1* appears to be an ultrarare cause of inherited dRTA[6-8]. Depending on the gene involved, primary dRTA can also cause sensorineural hearing loss (SNHL) or amelogenesis imperfecta[2].

Tubulopathies are frequently associated with chronic kidney disease >stage 1 (CKD). In a large cross-sectional study, 13% of adult patients with a confirmed diagnosis of inherited tubulopathies had some degree of CKD[9]. Inherited dRTA accounted for more than one-third of all diagnoses[9].

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

Retrospective cohorts of patients with dRTA from Europe and India have demonstrated a high prevalence of growth failure and CKD[10-12]. Genotypes have been shown to predict certain disease characteristics, such as age at diagnosis, degree of hypokalemia, or SNHL[10-12]. In contrast, long-term clinical outcomes, namely failure to thrive and CKD were associated with metabolic control[11]. However, current studies are limited by their retrospective nature, which precludes a reliable assessment of treatment effects on clinical outcomes.

For this reason, a prospective cohort of patients has been established in Europe within the dRTA registry under the umbrella of the European Rare Kidney Disease Registry (ERKReg) within the framework of the European Reference Network for Rare Kidney Diseases (ERKNet). Herein, we present the first interim analysis of data obtained over five years.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

MATERIALS AND METHODS

The dRTA registry has been collecting data since 2019 (https://www.erknet.org/subregistries/drta-registry-1). Only patients with a clinical diagnosis of complete dRTA were eligible for the study. Although genetic diagnosis was available for the majority of patients, the absence of a genetic diagnosis did not represent an exclusion criteria. For the current analysis, all prospective data until May 2024 where included. Each patient was included after informed consent, and has a unique pseudonymized identifier. The registry collects basic information, including genetic data if available, clinical data, and laboratory parameters at 1-year follow-up visits. For bicarbonate levels, the method of determination was not captured in the registry, but likely included measurement of total CO_2 in plasma or serum or calculation from blood gas parameters. For this study, we have considered these methods as equivalent and will refer simply to the results as "blood bicarbonate levels".

Statistical analysis was performed with IBM SPSS Statistics 21.0.0.2 software. All tests are 2-sided and considered statistically significant for p values <0.05. Categorical data are reported as counts and percentages. Continuous normal data are expressed as mean ± standard deviation (SD). Continuous data that did not follow a normal distribution are expressed as median value and interquartile range. The normality of data was tested with the Kolmogorov-Smirnov test. If a patient had more than one value for a specific variable, the average was used in the analysis. Missing data are indicated for each variable in tables.

ANOVA, Kruskal-Wallis, and chi-squared tests were used to compare subgroups as indicated. We designated the estimated glomerular filtration rate (eGFR) and height expressed as standard deviation score (SDS) at the last available follow-up visit as the two primary outcome measures. Data collected within six months of diagnosis were excluded from the analysis to ensure that patients were included only after their treatment had been fully established.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

Alkaline therapy was reviewed and expressed as mEq/kg/day of alkaline equivalents. Urine calcium-creatinine ratios were expressed as fold change relative to the upper limit of normal for age using the Lambda-Mu-Sigma (LMS)-based pediatric reference data reported by Pott et al. (Supplementary Figure 1)[13]. CKD was defined according to the KDIGO guidelines[14].

A general linear model (GLM) was used to analyze variables associated with height SDS and eGFR at the last follow-up. A type III sum of squares was used, and models were visually controlled by analyzing residual plots. Expected interactions between calciuria and bicarbonates and between the age of diagnosis and the underlying gene defect were included in the model.

Logistic regression analysis was used to analyze the relationship between serum bicarbonate levels and growth. To this end, the dRTA population was compared to a theoretical population of 2000 individuals of the same age and sex with an average SDS of 0 and a SD of 1. Modeling was performed by calculating the odds ratio (OR) of overlapping blocks of 50 patients by steps of 10 patients ranked based on mean serum bicarbonate levels. ORs were then plotted against the median bicarbonate levels of each block and fitted with a logistic curve using OriginPro 10.0 software. “Impaired growth” was defined as an average linear growth that was significantly lower than the one of the general population. To this end, we calculated the OR of having a height < 0 SDS, which corresponds to the median value of the general population. This analysis however, does not allow adjusting for the effects of variants affecting different genes and for the age at the last available follow-up. For this purpose, we conducted an additional logistic regression analysis comparing four subgroups of patients within the study cohort, ranked according to their mean serum bicarbonate levels. In this latter analysis, we

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

tested the risk of growth impairment for different height SDS thresholds. Results are cited in the result section and provided as supplementary table and figure.

Except for genetic results, data were complete for nearly all patients. Missing data were not handled.

The layout of the manuscript follows the STROBE recommendations for observational studies. The study has been approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg (reference number S-902/2021).

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

RESULTS

Overall, 214 patients were included in the analysis, with equal sex distribution (Table 1). Patients were recruited in 39 centers from 13 European countries. The median age at diagnosis was 0.7 [0.2-4.1] years. The median age at the last visit was 12.8 [7.3-17.4] years. The majority of patients were of pediatric age. Only 22% were older than 18 years at their last visit. In 73% of patients, more than one record was available (mostly 2-4 records). Genetic information was available in 69% of cases. Of these, 79% had causative variants in *ATP6V0A4* or *ATP6V1B1* and 20% in *SLC4A1*, the latter mostly with dominant inheritance. One patient had recessive pathogenic variants in *FOXI1* and one in *WDR72*. All patients in which kidney ultrasound data was available (N=166) had nephrocalcinosis. The second most frequent symptom was hearing loss, reported in 35% of patients. Rickets was reported in 27 cases (13%) and nephrolithiasis was documented in 7 patients (3%). At the last visit, the mean height SDS was -0.85 ± 1.5 and mean eGFR was 102 ± 32 ml/min/1.73 m^2.

Table 2 shows the distribution of variables per gene. Patients with pathogenic variants in *ATP6V0A4* were on average diagnosed earlier than the rest of the cohort ($p<0.001$), while patients with dominant *SLC4A1* variants were on average diagnosed later ($p<0.001$). At the last follow-up, patients with *SLC4A1* dominant variants also had significantly lower eGFR compared to the rest of the cohort ($p=0.021$), despite having a similar median age. SNHL was reported in 71% of patients with *ATP6V1B1* variants, in 32% of patients without genetic diagnosis and in 19% of patients with *ATP6V0A4* variants. Also, the patient in the cohort affected with the *FOXI1* variant showed SNHL.

Inadequate control of metabolic acidosis, defined as a mean bicarbonate level <22 mEq/L, was observed in 42% of the cohort, independently of age (Figure 1 A). The prescribed dose of alkali supplements per kg of body weight decreased progressively with age. Median daily dose was

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

approximately 3 mEq/kg/day in preschool children and 1 mEq/kg/day in adults (Figure 1 B). Hypercalciuria was observed in 25% of the cohort and did not correlate with age once data were normalized (Figure 1 C). Calciuria and serum bicarbonate tended to be negatively associated; the correlation however did not reach statistical significance (p=0.050; Supplementary figure 2).

Seventy-six patients (36%) had CKD at their last follow-up. This included 33% of children aged <12 years. Patients with CKD at the last follow-up had a median age at diagnosis significantly higher than the rest of the cohort (1.5 years [0.33-5.5] vs. 0.5 [0.2-3.3]; p = 0.013) and were more likely to harbor dominant variants in the *SLC4A1* (p=0.013). Mean eGFR (at the last follow-up) remained stable until early adulthood and decreased significantly in adults aged >30 years (p=0.001, compared to the rest of the cohort) (Figure 1D). No patient had reached kidney failure.

While most patients were of normal height, their linear growth was significantly stunted at all ages in both sexes compared to the general population (Figure 2).

A general linear model (GLM) was used to identify variables associated with low eGFR or poor linear growth. eGFR at the last follow-up was only negatively associated with dominant variants in *SLC4A1* (p = 0.013) (Table 3). Height SDS at the last follow-up visit was positively associated with blood bicarbonate levels (p = 0.008) and negatively associated with the age at diagnosis (p = 0.005) (Table 4). The association between height and bicarbonate levels was analyzed further by modelling the odds ratios (ORs) of a logistic regression comparing patients with dRTA to the normal population, showing substantial odds of impaired growth with low blood bicarbonate levels (Figure 2 D). The OR values were no longer significant when mean bicarbonate levels increased above 23.5 mEq/L, indicating that in this cohort, patients with mean serum bicarbonate levels above this threshold had heights that were no longer

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

significantly different from those of the general population. A logistic analysis was also performed analyzing the study cohort divided in four subgroups according to their bicarbonate levels. Data were adjusted for the mutated gene, sex, and the age at the last follow-up. Results of this latter analysis confirm the benefits of higher bicarbonate levels on linear growth. An average of 24 mmol/L serum bicarbonate concentration reduced the risk of impaired growth across all height SDS strata (Supplementary Table 1 and Supplementary Figure 3).

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

DISCUSSION

The present study describes the largest prospective cohort of patients with dRTA assembled to date and our analysis has yielded some important results.

Growth and metabolic control

Arguably, our most relevant finding is the significant association of metabolic control with growth. Growth improved when patients were treated early and well with alkali supplements. As patients with more severe acidosis tend to present earlier, the fact that an earlier age at diagnosis was still associated with improved height further highlights the importance of early diagnosis and treatment. Considering that growth velocity is fastest in the first years of life and that alkali is needed for bone formation, the importance of adequate treatment in that time is arguably not surprising. While our analysis was restricted to the height at the last follow-up and not final adult height due to the low number of adult patients in the registry, our results fit well with the findings from our previous retrospective study which showed a significant association between metabolic control and final height[10].

Usually, adequate metabolic control in dRTA is defined as blood bicarbonate levels in the normal range in the absence of hypercalciuria. Chronic metabolic acidosis affects bone metabolism through various mechanisms, including promoting osteoclast over osteoblast activity and dissociation of calcium from hydroxyapatite, resulting in hypercalciuria[4]. Although we observed a trend, there was no significant association between calciuria and blood bicarbonate levels or with height SDS. In our retrospective study, 43% of patients had inadequate blood bicarbonate levels compared to 15% with hypercalciuria. Overall, these data suggest, that hypercalciuria is a less sensitive marker for metabolic control than blood bicarbonate.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

Treatment

Our results can have direct clinical implications with respect to treatment. The ERKNet/ESPN recommendations on dRTA suggest treating patients with alkali solutions aiming at blood bicarbonate levels of ≥22 mmol/l[15]. Yet, as in our retrospective previous study, a substantial proportion of our patients (42%) did not reach this target[10]. Importantly, our analysis of the association between growth and blood bicarbonate shows that the probability of growing within the expected range increases progressively with serum bicarbonate levels until these reached 22-24 mmol/l. Moreover, these level was found to be protectively associated with decreased odds of impaired growth across different height SDS strata (supplemental table S1 and figure S3). These findings support increasing the target level for alkali therapy to 24 mmol/l, although this may be difficult to achieve in some patients. This target value, which is more in the middle of the normal range, would ensure that there is more reserve for acid buffering at times of increased acid stress and may allow more continuous metabolic control, thereby facilitating optimal growth.

Data on alkali doses were challenging to analyze, as these were collected from 13 different countries with different commercial and/or galenic preparations available. The variability of prescriptions, including using single or combined alkali preparations, dose adaptation during childhood, and frequent switch from one type of alkali to another, prevented a thorough comparison between different approaches. Nonetheless, we did not observe clear differences in outcome when using a specific type of alkali versus another (data not shown), as also reported by others[10]. Recently a long-acting alkali preparation combining potassium bicarbonate and potassium citrate has been developed[16, 17]. The number of patients

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

treated with this compound was however, insufficient to analyze possible differences in outcome.

In line with previous reports, alkali requirements expressed per kg of body weight decreased with age[10]. In very young children, alkali doses of 5 mEq/kg/day or more were often prescribed to normalize serum bicarbonate (Figure 1).

CKD

Our analysis confirms shows that patients with dRTA are at increased risk of CKD. Fortunately, and in line with previous reports, no patient in this study had reached kidney failure[9-11]. However, our cohort included primarily children. Patients aged >30 years had significantly lower eGFR compared to the rest of the cohort. Noticeably, the prevalence of patients with CKD2 was elevated in all age groups. López-García *et al.* had already shown that whilst the annual eGFR slope is comparable to that of the general population, in dRTA, eGFR is lower at the beginning of adulthood so the decline starts from a lower baseline[10]. Projected in the long-term, this suggests that some patients with dRTA could reach kidney failure in late adulthood.

Typically, patients with dRTA develop nephrolithiasis, in particular during adulthood[4]. Surprisingly, we observed a very low prevalence of nephrolithiasis (3%) in our cohort, presumably because the cohort was mainly pediatric although we cannot exclude underreporting.

While we did not observe a significant association between the efficacy of metabolic control and eGFR at the last follow-up, this is likely attributable to the limited time of follow-up for each patient and the low average age of the analyzed cohort. However, our results confirm that patients with dRTA have an increased risk for progressive CKD. Therefore, careful long-term monitoring is warranted.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

Genetics

Most patients in this cohort were children with genetic forms of dRTA and the distribution of underlying genes in the current cohort was in line with other European reports[10, 11]. Of note, patients with dominant *SLC4A1* variants had significantly lower eGFR at the last follow-up, as recently also reported by Betton et al[9]. This was somewhat surprising, as these patients are considered to have milder symptoms during early childhood reflected in a later age at diagnosis[10, 11]. Yet, perhaps, it is exactly this delay in diagnosis and consequent delayed initiation of therapy, which may explain the worse outcome of these patients in terms of eGFR[9]. While the risk of CKD associated with *SLC4A1* variants was not modified significantly after adjusting for the age at diagnosis, the numbers are small, limiting the powers of detection.

SNHL was more prevalent in patients with pathogenic variants in *ATP6V1B1* and, to a lesser degree, in patients with *ATP6V0A4* variants (Table 2). The overall observed SNLH prevalence was lower compared to other reports[10, 11]. Most likely, this was due to the high number of very young patients, many of whom may not have developed hearing impairment yet, particularly those with variants in *ATP6V0A4* who typically develop SNHL later during childhood[12, 18]. Of note, 2/24 patients with *SLC4A1* variants were reported to suffer from SNHL. Detailed results of hearing tests were not available. The deafness rate in this genetic sub-group is probably not different from the prevalence reported in the general pediatric population, as detailed previously[10].

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

Limitations

Our study has limitations. The limited number of adult patients and short duration of follow-up do not allow for analysis of the long-term benefits of metabolic control on kidney function, and on the incidence of nephrolithiasis. Although results of genetic tests were available for the majority of patients, this information was lacking in some patients and their diagnosis was based solely on clinical and laboratory characteristics and some of these patients may have acquired dRTA. Data in the registry are real-world data with all its limitations, including variability in the timing of blood tests with respect to alkali intake and differences in blood bicarbonate determination. Moreover, parental height was not available, nor pubertal status or potential additional diagnoses, all of which can affect individual height. Nevertheless, there is no reason to assume that any of these limitations would have systematically biased our results. The dRTA registry was only established in 2019; follow-up data of individual patient are still limited. Results of the current report are therefore based on very limited longitudinal data. Future analyses will be better placed to study long-term outcomes, including kidney function decline. They will also allow using parameters that are more sophisticated, such as time-average bicarbonate levels that may be better estimates of the efficacy of alkali therapy. Efforts are also being made to include more adult patients in the registry. For the future, a key challenge will be to ensure continuation of data collection when patient will transition from pediatric to adult centers.

Conclusions

This first interim analysis of the European dRTA registry shows that patients with dRTA at increased risk of growth retardation and CKD since early childhood. The risk of CKD is even higher in patients with *SLC4A1* variants. Early initiation of alkali therapy achieving serum

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

bicarbonate levels of at least 22 mmol/L is needed to ensure normal growth. Aiming at higher bicarbonate levels (~24 mEq/L) may provide further advantage.

Conflict of interest statement

OB, DB, FE, DH,JH, JO, FS, ABT, RT have received honoraria from Advicenne Pharma SA.

Funding

This project was supported by the European Society for Pediatric Nephrology (ESPN). One or more authors of this publication are member of the ESPN working group on Inherited Kidney Diseases.

The study was supported by the European Reference Network for Rare Kidney Diseases (ERKNet), which is funded by the European Union within the framework of the EU4Health Programme (101085068) 2021-2027.

One or more authors of this publication are member of the European Renal Association (ERA) Genes and Kidney / Immunonephrology Working Group

The European dRTA registry was supported by an unconditional grant from Advicenne Pharma SA.

Acknowledgements

This work is dedicated to the memory of Prof. Stephen Ben Walsh

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

Authors' contributions

DB, DH, FE, RVP, GA, FS have established the dRTA registry and are the current members of the steering committee that have reviewed annually data entries. MG, FE and DB have performed the data analysis and have written the first draft of the manuscript. All authors have contributed by including patient data and critically reviewing the manuscript. All authors have approved the final version.

Data availability statement

The underlying data are available subject to consent from the ERKNet data monitoring board.

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

REFERENCES

1. Besouw MTP, Bienias M, Walsh P *et al*. Erratum to: Clinical and molecular aspects of distal renal tubular acidosis in children. *Pediatr Nephrol* 2017;32:1095. https://doi.org/10.1007/s00467-017-3631-6
2. Giglio S, Montini G, Trepiccione F *et al*. Distal renal tubular acidosis: a systematic approach from diagnosis to treatment. *J Nephrol* 2021;34:2073–2083. https://doi.org/10.1007/s40620-021-01032-y
3. Bianic F, Guelfucci F, Robin L *et al*. Epidemiology of Distal Renal Tubular Acidosis: A Study Using Linked UK Primary Care and Hospital Data. *Nephron* 2021;145:486–495. https://doi.org/10.1159/000516876
4. Wagner CA, Unwin R, Lopez-Garcia SC *et al*. The pathophysiology of distal renal tubular acidosis. *Nat Rev Nephrol* 2023;19:384–400. https://doi.org/10.1038/s41581-023-00699-9
5. Daenen M, Hureaux M, Ashton E *et al*. A novel, dominant disease mechanism of distal renal tubular acidosis with specific variants in ATP6V1B1. *Nephrol Dial Transplant* 2025;40:1531–1537. https://doi.org/10.1093/ndt/gfaf016
6. El-Sayed W, Parry DA, Shore RC *et al*. Mutations in the beta propeller WDR72 cause autosomal-recessive hypomaturation amelogenesis imperfecta. *Am J Hum Genet* 2009;85:699–705. https://doi.org/10.1016/j.ajhg.2009.09.014
7. Enerbäck S, Nilsson D, Edwards N *et al*. Acidosis and Deafness in Patients with Recessive Mutations in FOXI1. *J Am Soc Nephrol* 2018;29:1041–1048. https://doi.org/10.1681/asn.2017080840
8. Thakare S, Lila A, Keskar V *et al*. Molecular genetics and long-term outcomes of primary distal renal tubular acidosis in Asia. *Nephrol Dial Transplant* 2025https://doi.org/10.1093/ndt/gfaf222
9. Betton M, Blanchard A, Houillier P *et al*. Prevalence of kidney failure in adults diagnosed with hereditary tubulopathies. *J Nephrol* 2024;37:1973–1983. https://doi.org/10.1007/s40620-024-02054-y
10. Lopez-Garcia SC, Emma F, Walsh SB *et al*. Treatment and long-term outcome in primary distal renal tubular acidosis. *Nephrol Dial Transplant* 2019;34:981–991. https://doi.org/10.1093/ndt/gfy409
11. Palazzo V, Provenzano A, Becherucci F *et al*. The genetic and clinical spectrum of a large cohort of patients with distal renal tubular acidosis. *Kidney Int* 2017;91:1243–1255. https://doi.org/10.1016/j.kint.2016.12.017
12. Priyadarshini S, Sinha A, Jana M *et al*. Etiology and outcomes of primary renal tubular acidosis. *Pediatr Nephrol* 2025;40:2515–2527. https://doi.org/10.1007/s00467-025-06747-9
13. Pott V, Tietze H, Kanzelmeyer N *et al*. LMS-Based Pediatric Reference Values for Parameters of Phosphate Homeostasis in the HARP Cohort. *J Clin Endocrinol Metab* 2024;109:668–679. https://doi.org/10.1210/clinem/dgad597
14. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2024;105:S117–s314. https://doi.org/10.1016/j.kint.2023.10.018
15. Trepiccione F, Walsh SB, Ariceta G *et al*. Distal renal tubular acidosis: ERKNet/ESPN clinical practice points. *Nephrol Dial Transplant* 2021;36:1585–1596. https://doi.org/10.1093/ndt/gfab171
16. Bertholet-Thomas A, Guittet C, Manso-Silván MA *et al*. Efficacy and safety of an innovative prolonged-release combination drug in patients with distal renal tubular acidosis: an open-label comparative trial versus standard of care treatments. *Pediatr Nephrol* 2021;36:83–91. https://doi.org/10.1007/s00467-020-04693-2
17. Bertholet-Thomas A, Manso-Silván MA, Navas-Serrano V *et al*. Bone mineral density and growth changes in patients with distal renal tubular acidosis after two-years

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

treatment with a new alkalizing drug (ADV7103). *Nefrologia (Engl Ed)* 2023;43:458-466. https://doi.org/10.1016/j.nefroe.2022.02.012

18. Vargas-Poussou R, Houillier P, Le Pottier N *et al*. Genetic investigation of autosomal recessive distal renal tubular acidosis: evidence for early sensorineural hearing loss associated with mutations in the ATP6V0A4 gene. *J Am Soc Nephrol* 2006;17:1437-1443. https://doi.org/10.1681/asn.2005121305

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

TABLES

Table 1 *Patient characteristics*

Parameter	Units	N	Value
Patient characteristics			
Age at last visit	Years	214	12.8 [7.2-17.4]
Sex	M : F (%)	214	109:105 (51:49)
Age at diagnosis	Years	214	0.7 [0.2-4.1]
Gene , N (%)	*ATP6V0A4*	62	(29)
	ATP6V1B1	55	(26)
	SLC4A1 AD	24	(11)
	SLC4A1 AR	5	(2)
	FOXI1	1	(1)
	WDR72	1	(1)
	N/A	66	(30)
Height at last visit	SDS	181	-0.85 ±1.5
BMI	SDS	190	0.24 ±1.1
Systolic BP	SDS	190	0.13 ±0.8
Diastolic BP	SDS	180	0.33 ±0.7
*Symptoms and radiological findings**			
Rickets	Yes	209	27 (13)
Nephrocalcinosis	Yes	166	166 (100)
Nephrolithiasis	Yes	182	7 (3)
Kidney cysts	Yes	182	31 (15)
Dehydration	Yes	213	19 (9)
Vomiting	Yes	212	22 (10)
Diarrhea	Yes	181	4 (2)
Abdominal pain	Yes	221	11 (5)
Hearing loss	Yes	168	58 (35)
Biochemistry§			
eGFR at last visit	ml/min/1.73 m^2	214	102 ±32
Serum bicarbonate	mEq/L	208	22.3 ±3.1
Serum Sodium	mEq/L	214	140±2
Serum potassium	mEq/L	214	3.9±0.5
Serum chloride	mEq/L	214	106±4
Serum calcium	mmol/L	214	2.4±0.1
Serum phosphate	mg/dL	195	1.38±0.3
Parathormone	pmol/L	141	11.1 [2.4-30]
Urine Ca/Cr	Val/ULN	214	0.39 [0.25-0.68]
Urine pH		182	7.65 [7.2-8.1]

* For patients with more than one record, symptoms or radiological finding were considered positive if reported at least once

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

§ Mean bicarbonate and median calciuria values were calculated excluding data within 6 months from diagnosis

Abbreviations:SDS= standard deviation score; BP = blood pressure; N/A = not available; Urine Ca/Cr ratio = urinary calcium / creatinine ratio; ULN = upper limit of normal values (see reference 13).

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

ORIGINAL UNEDITED MANUSCRIPT

Table 2. Patient characteristics and outcomes variables according to the gene involved.

Parameter	**Units**	***ATP6V0A4***	***ATP6V1B1***	***SLC4A1 AD***	***SLC4A1 AR, FOXI1, WDR72***	**N/A**	***p***
N	(%)	62 (29)	55 (26)	24 (11)	7 (3)	66 (31)	
Sex	M:F	32:30 (52:48)	32:23 (58:42)	14:10 (58:42)	2:5 (29:71)	28:37 (43:57)	0.320
Age at diagnosis	**Years**	**0.3 [0.1-2.1]**	**1.0 [0.4-3.3]**	**4.6 [1.4-9.0]**	**3.9 [1.3-10.4]**	**0.5 [0.2-3.3]**	**<.0001**
Symptoms, radiological findings, and alkali therapy during follow-up							
Median age	Years	9.1 [4.2-15.7]	11.7 [7.0-15.4]	11.0 [6.7-16.4]	10.6 [1.7-15.5]	13.4 [7.0-17.3]	0.173
Rickets	Yes	7 (11)	6 (11)	4 (17)	3 (43)	7 (11)	0.179
Dehydration	Yes	9 (15)	5 (9)	1 (4)	1 (14)	3 (5)	0.311
Hearing loss	**Yes**	**10 (16)**	**29 (53)**	**2 (8)**	**1 (14)**	**17 (26)**	**<.0001**
Nephrolithiasis	Yes	2 (3)	5 (9)	0 (0)	1 (14)	10 (15)	0.091
Cysts	Yes	15 (24)	16 (29)	5 (21)	3 (43)	21 (332)	0.591
Nephrocalcinosis	Yes	62 (100)	55 (100)	24 (100)	7 (100)	66 (100)	N/A
Fatigue	Yes	7 (11)	13 (24)	2 (8)	2 (29)	11 (17)	0.152
Mean serum bicarbonate	mEq/L	22.5±2.9	22.0±2.4	22.9±3.5	22.8±2.2	21.9±3.7	0.662
Urine Ca/Cr	**val/ULN**	**0.7 [0.5-1.0]**	**0.5 [0.3-0.9]**	**0.5 [0.2-0.7]**	**0.6 [0.5-0.6]**	**0.8[0.4-1.3]**	**0.006**
Alkali supplements	**mEq/kg die**	**2.3 [1.1-3.5]**	**1.6 [0.9-2.6]**	**1.3 [0.8-2.6]**	**1.8 [1.2-2.1]**	**1.1 [0.5-2.4]**	**0.016**
Data at the last visit							
Age	Years	10.8 [5.3-17.2]	13.0 [7.8-17.2]	12.4 [8.6-17.4]	10.6 [3.3-17.3]	14.2 [8.4-18.3]	0.437
Height	SDS	-0.8 ± 1.1	-0.8± 1.7	-0.8±1.6	-1.1±1.2	-0.9±1.5	0.977
eGFR	**ml/min/1.73 m²**	**112 ± 33**	**104±26**	**87±33**	**106±29**	**97±33**	**0.010**

Abbreviations: AR = autosomal recessive, AD = autosomal dominant, N/A = not available

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

Table 3. *General linear model (GLM) testing variables associated with eGFR at the last follow-up*

	Units	Sum of squares	df	F	β	95% CI	p
Model		**23851**	**14**	**2.01**			**0.019**
Sex	M vs. F	167	1	0.20	-1.86	-10.11 - 6.40	0.658
Gene		**11176**	**4**	**3.29**			**0.012**
ATPV0A4					9.27	-2.63 - 21.18	0.126
ATPV1B1					-1.69	-14.55 - 11.16	0.795
SLC4A1 Rec					-17.68	-61.88 - 26.52	0.431
***SCC4A1* Dom**					**-26.41**	**-47.16 - -5.67**	**0.013**
Age at diagnosis	years	2469	1	2.91	-0.43	-1.42 - 0.57	0.090
Age at last visit	years	1215	1	1.43	-0.30	-0.80 - 0.20	0.233
Urine Ca/Cr	value/ULN	193	1	0.23	-3.86	-19.87 - 12.14	0.634
Serum bicarbonate	mEq/L	8	1	0.01	0.08	-1.51 - 1.68	0.921
Interactions							
Urine Ca/Cr • serum bicarbonate		34	1	0.04			0.842
Gene • age at diagnosis		7537	4	2.22			0.068

Abbreviations: ULN = upper limit of normal values (see reference 13)

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

Table 4. *General linear model (GLM) testing variables associated with the height at the last follow-up*

	Units	Sum of squares	df	F	β	95% CI			p
Model		**50.83**	**14**	**1.93**					**0.026**
Sex	M vs. F	1.81	1	0.96	0.21	-0.21	-	0.64	0.328
Gene		5.06	4	0.67					0.611
ATPV0A4					-0.30	-0.92	-	0.32	0.344
ATPV1B1					0.13	-0.55	-	0.81	0.704
SLC4A1 Rec					0.11	-1.98	-	2.20	0.917
SCC4A1 Dom					0.40	-0.65	-	1.46	0.454
Age at diagnosis	**years**	**15.55**	**1**	**8.28**	**-0.08**	**-0.17**	**-**	**0.01**	**0.005**
Age at last visit*	years	0.06	1	0.03	0.00	-0.04	-	0.05	0.858
Urine Ca/Cr	value/ULN	0.63	1	0.34	0.33	-0.78	-	1.43	0.562
Serum bicarbonate	**mEq/L**	**13.39**	**1**	**7.14**	**0.12**	**0.03**	**-**	**0.20**	**0.008**
Interactions									
Urine Ca/Cr • serum bicarbonate		0.75	1	0.40					0.527
Gene • age at diagnosis		8.10	4	1.08					0.369

Abbreviations: Rec= recessive; Dom= dominant. ULN = upper limit of normal values (see reference 13)

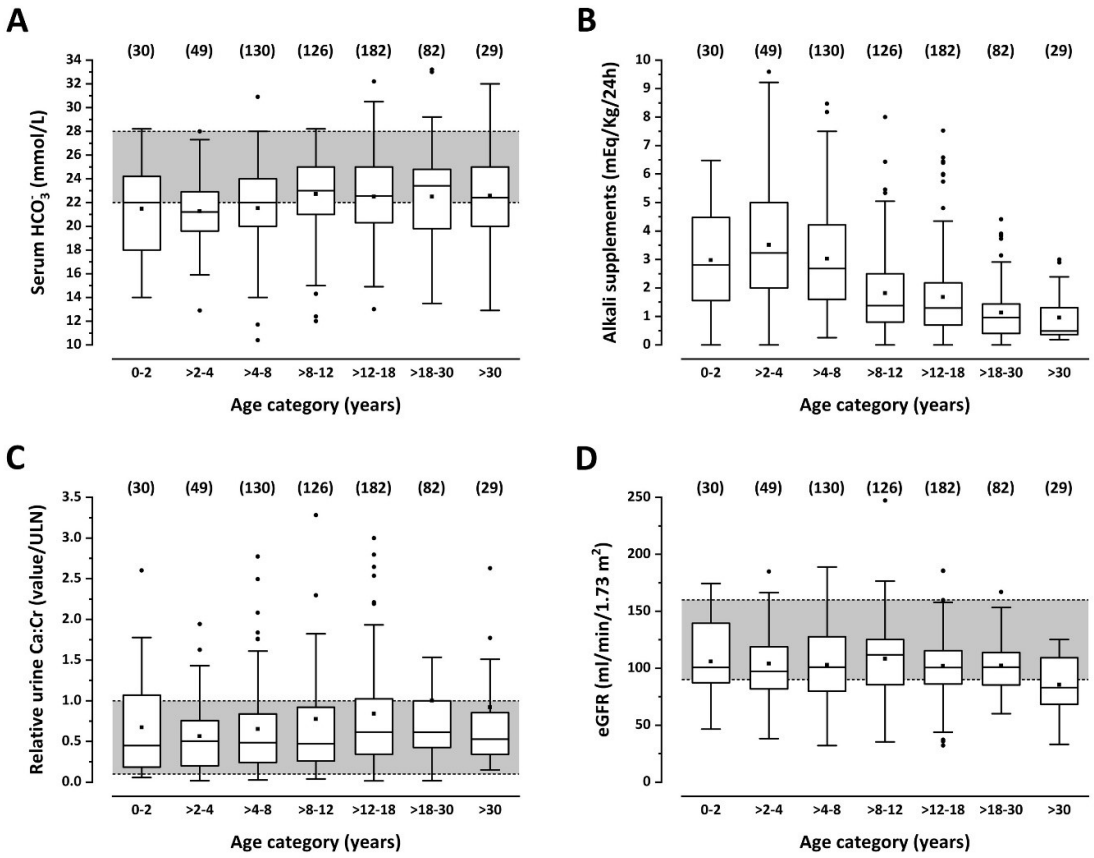
(*) The maximum age of the last visit was set at 20 years for patients older than 20, since growth is expected to be finished at 20 years METHODS

ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

FIGURES

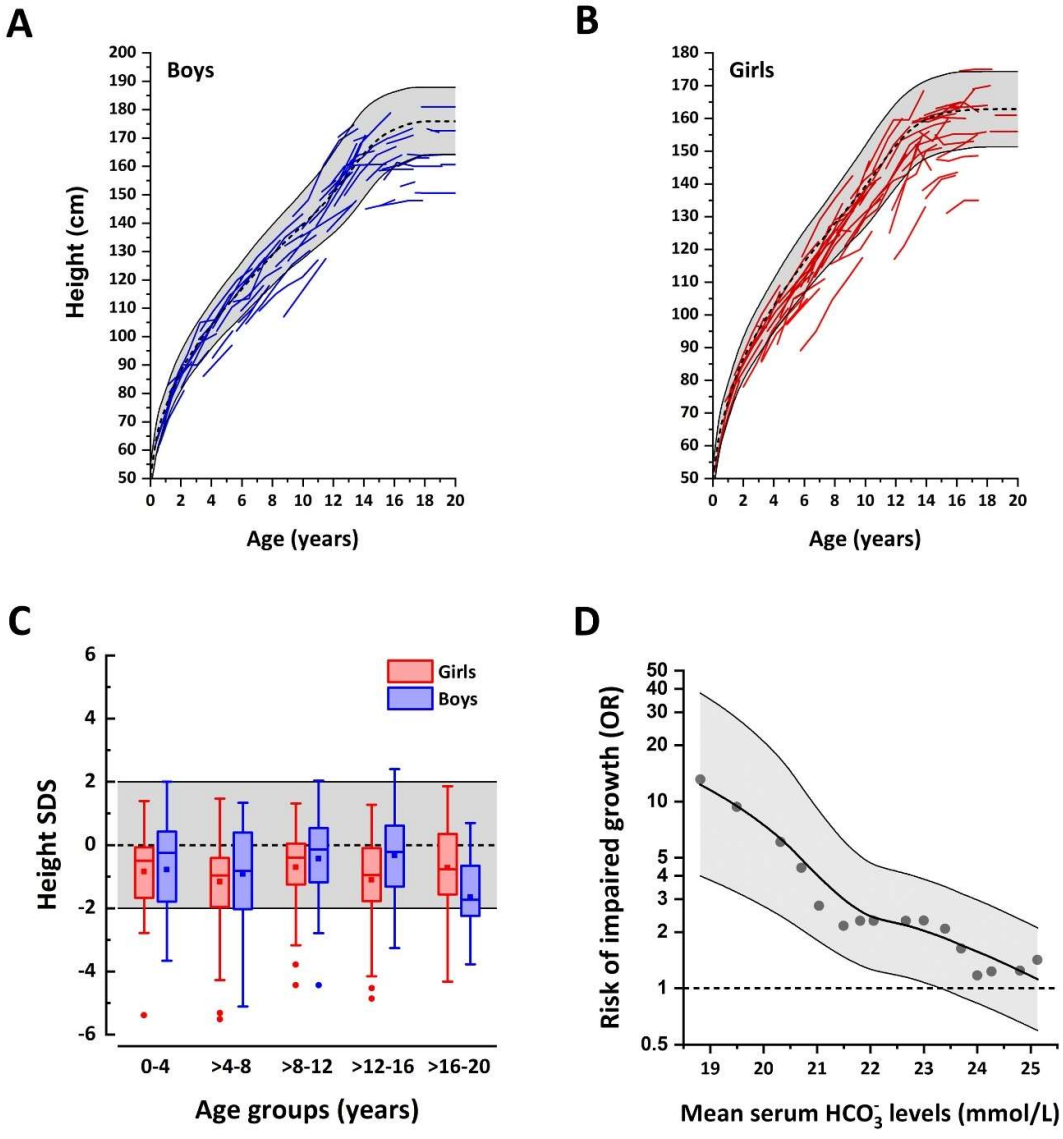
Figure 1 *Distribution of serum bicarbonate (A), alkali supplements (B), calciuria (C), and eGFR (D) per age groups*.



ORIGINAL UNEDITED MANUSCRIPT

Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026

Figure 2 *Linear growth in patients aged ≤ 20 years: according to sex (A and B), age groups (C) and mean serum bicarbonate levels (D).* The odds ratio modeling shows the odds of having a impaired growth at the last follow-up visit in comparison to the normal population, as a function of blood bicarbonate levels. For each patient, serum bicarbonate was calculated using the mean value of all records in the registry. Values were no longer significant when levels reached 23.5 mmol/l.



Downloaded from https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfag051/8509366 by INACTIVE user on 10 March 2026