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ORIGINAL ARTICLE

Serum bicarbonate is associated with kidney outcomes in autosomal dominant polycystic kidney disease

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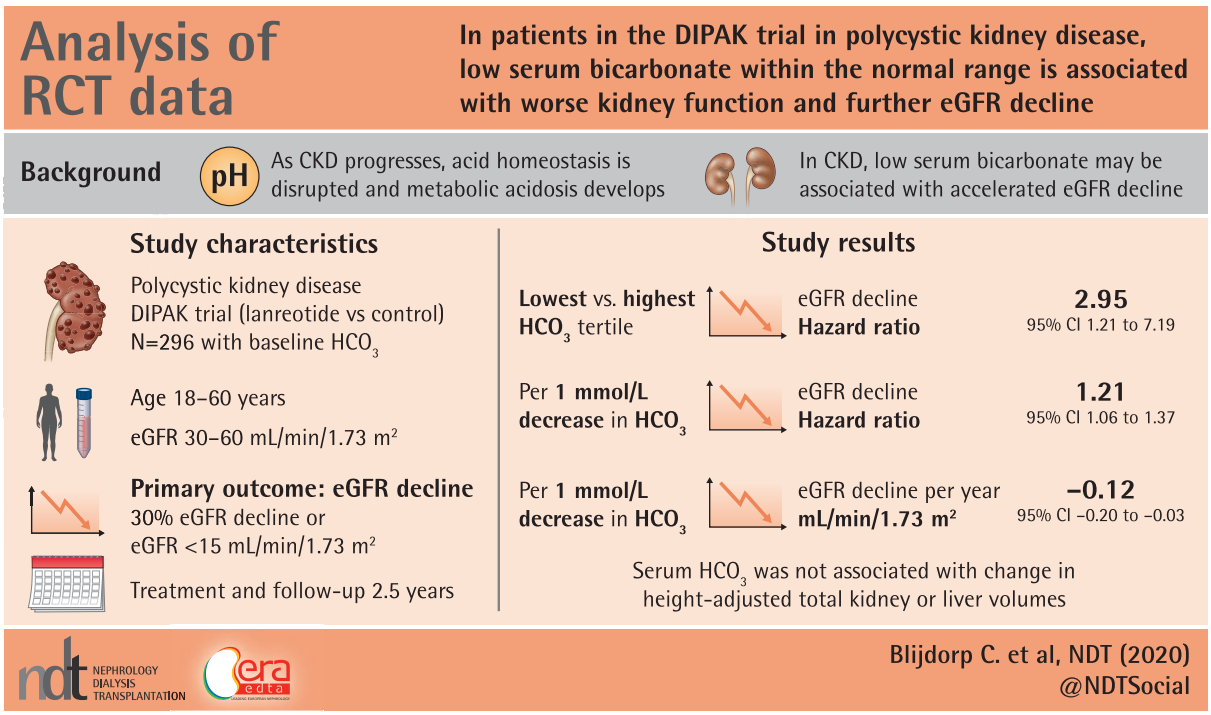
GRAPHICAL ABSTRACT



ABSTRACT

Background. Metabolic acidosis accelerates progression of chronic kidney disease, but whether this is also true for autosomal dominant polycystic kidney disease (ADPKD) is unknown.

Methods. Patients with ADPKD from the DIPAK (Developing Interventions to halt Progression of ADPKD) trial were included [$n = 296$, estimated glomerular filtration rate (eGFR) 50 ± 11 mL/min/1.73 m^2, 2.5 years follow-up]. Outcomes were worsening kidney function (30% decrease in eGFR or kidney failure), annual eGFR change and height-adjusted total kidney and liver volumes (htTKV and htTLV). Cox and linear regressions were adjusted for prognostic markers for ADPKD [Mayo image class and predicting renal

KEY LEARNING POINTS

What is already known about this subject?

- in patients with chronic kidney disease (CKD), metabolic acidosis accelerates loss of kidney function; and
- experimental data suggest that acidosis also promotes disease progression in autosomal dominant polycystic kidney disease (ADPKD), but clinical data are lacking.

What this study adds?

- in patients with ADPKD, a lower serum bicarbonate within the normal range is associated with worse kidney outcomes; and
- this association is independent of established prognostic factors for ADPKD and independent of urine ammonium excretion.

What impact this may have on practice or policy?

- serum bicarbonate may add to prognostic models of ADPKD; and
- because alkali treatment reduces kidney function decline in patients with CKD, serum bicarbonate should also be explored as treatment target in patients with ADPKD.

outcomes in ADPKD (PROPKD) scores] and acid–base parameters (urinary ammonium excretion).

Results. Patients in the lowest tertile of baseline serum bicarbonate (23.1 ± 1.6 mmol/L) had a significantly greater risk of worsening kidney function [hazard ratio = 2.95, 95% confidence interval (CI) 1.21–7.19] compared with patients in the highest tertile (serum bicarbonate 29.0 ± 1.3 mmol/L). Each mmol/L decrease in serum bicarbonate increased the risk of worsening kidney function by 21% in the fully adjusted model (hazard ratio = 1.21, 95% CI 1.06–1.37). Each mmol/L decrease of serum bicarbonate was also associated with further eGFR decline (−0.12 mL/min/1.73 m^2/year, 95% CI −0.20 to −0.03). Serum bicarbonate was not associated with changes in htTKV or htTLV growth.

Conclusions. In patients with ADPKD, a lower serum bicarbonate within the normal range predicts worse kidney outcomes independent of established prognostic factors for ADPKD and independent of urine ammonium excretion. Serum bicarbonate may add to prognostic models and should be explored as a treatment target in ADPKD.

Keywords: ammonium, end-stage kidney disease, glomerular filtration rate, total kidney volume

INTRODUCTION

The combination of a typical Western diet and endogenous metabolism generates a non-volatile acid load of 70 mEq/day, which is excreted by the kidney primarily as ammonium, but also as free hydrogen ions, and titratable acid [1]. As chronic kidney disease (CKD) progresses, per-nephron ammonium excretion eventually fails to excrete the daily acid load and metabolic acidosis ensues [2]. The prevalence of metabolic acidosis (defined as serum bicarbonate <22 mmol/L) increases from 2% in patients with estimated glomerular filtration rate (eGFR) of 60–90 mL/min/1.73 m^2 to 39% in patients with eGFR <20 mL/min/1.73 m^2 [3]. In CKD patient cohorts, several studies have identified an association between a lower serum bicarbonate and accelerated eGFR decline [4–9]. Potential mechanisms include increased synthesis of angiotensin II, aldosterone and endothelin-1, which are produced to facilitate acid excretion, but also promote inflammation and fibrosis [10]. Of note, the association between serum bicarbonate and accelerated eGFR decline was not found in patients with diabetic kidney disease, suggesting differences between kidney disease aetiologies [11]. Several clinical trials found that bicarbonate supplementation reduces or stabilizes eGFR decline [12, 13], although this has not been a universal finding [14].

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and represents ∼3% of the CKD aetiology [15]. Torres *et al.* showed that patients with ADPKD and normal GFR excrete less ammonium than healthy controls after an acid load [16]. This reduction in urinary ammonium excretion was not explained by lower production of ammonia or impaired proton secretion. Instead, they attributed the lower urinary ammonium excretion to structural changes associated with ADPKD [16]. In a rat model of PKD, acid loading with ammonium chloride caused acidosis, ammoniagenesis, GFR loss and increased kidney weight, cystic dilatation and interstitial inflammation [17]. Another study showed that in these rats potassium citrate completely prevented the decline in GFR and reduced cyst size and interstitial damage [18]. Although these preclinical data suggest that acidosis also promotes disease progression in ADPKD, clinical data are lacking.

Therefore, here, our hypothesis was that serum bicarbonate is associated with kidney outcomes in patients with ADPKD. To address this hypothesis, we used data from the DIPAK (Developing Interventions to halt Progression of ADPKD) intervention trial to analyse whether a lower serum bicarbonate at baseline predicts eGFR decline, and an increase in total kidney or liver volume [19]. We show that serum bicarbonate predicts kidney outcomes independent of established ADPKD prognostic factors and independent of urinary ammonium excretion.

MATERIALS AND METHODS

Setting and subjects

We included subjects from the DIPAK intervention trial, an open-label randomized clinical trial to examine the effect of lanreotide on disease progression in later-stage ADPKD ($n = 309$) [19]. The study protocol and outcomes of the DIPAK intervention trial have been published previously [19, 20]. Briefly, patients with ADPKD aged between 18 and 60 years and with an eGFR 30–60 mL/min/1.73 m^2 were randomized to standard

care or lanreotide in a 1:1 ratio. They were followed-up every 12 weeks for 2.5 years. Main exclusion criteria were bradycardia, a history of gall stones or pancreatitis, and diseases or medication that could confound outcome assessment (such as diabetes mellitus, and use of non-steroidal anti-inflammatory drugs, lithium or tolvaptan). The DIPAK intervention trial was performed in adherence to the Declaration of Helsinki, and all patients provided written informed consent.

Measurements

At each visit, blood pressure and body weight were measured, and blood and 24-h urine were stored for analysis. At baseline, end of treatment and end of study (12 weeks after end of treatment), an magnetic resonance imaging scan without contrast was performed to obtain total kidney volume (TKV) and total liver volume (TLV). TKV and TLV were measured on T2-weighted coronal images by manual tracing, and adjusted for height. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation [21]. eGFR slope was determined using 14 eGFR values per patient. Serum bicarbonate was measured at baseline as a pre-specified measurement of the DIPAK trial [20]. Serum bicarbonate was measured by the clinical laboratories of the separate treatment study sites by means of a phosphoenolpyruvate reaction. The serum bicarbonate levels were measured using Cobas 8000 (Roche) at the Erasmus Medical Centre in Rotterdam and Leiden University Medical Centre, ABL720 (Radiometer) at the University Medical Centre Groningen or RAPIDPoint 500 (Siemens) at the Radboudumc in Nijmegen. Baseline urinary ammonium excretion was measured using the phenol–hypochlorite reaction in 24-h urine. Daily dietary protein intake (g/day) was calculated using the equation: $6.25 \times$ (urine urea nitrogen in g/day + weight in kg) $\times 0.031$ [22]. Net endogenous acid production (NEAP) was estimated by: $10.2 + (54.5 \times$ protein intake in g/day)/urine potassium in mEq/day [23].

Outcomes

The primary outcome of this study was worsening kidney function, which was pre-defined in the original DIPAK trial as 30% decrease in baseline eGFR or the development of kidney failure, defined as eGFR <15 mL/min/1.73 m^2 [20, 24–26]. Secondary outcomes were annualized eGFR slope (mL/min/1.73 m^2/year), change in height-adjusted TKV (htTKV), change in height-adjusted TLV (htTLV) and change in htTLV in patients with polycystic liver disease (PLD), defined previously for this patient study as liver size >2000 mL [20]. For our analysis, we used the htTKV and htTLV values obtained at the end of study.

Statistical analysis

Serum bicarbonate was studied both in tertiles and as a continuous variable. Multivariable linear regression was used to analyse which baseline variables were associated with serum bicarbonate. We used Cox regression to determine the effect of serum bicarbonate on the primary outcome. Censoring was applied at end of study (after 132 weeks) or in case of loss to follow-up. The unadjusted effect of serum bicarbonate was assessed before correcting for 15 covariates in the three additive models. Model 1 was adjusted for age, sex, eGFR, htTKV, treatment group and study site, because these are the main factors associated with ADPKD progression [27]. Model 2 was additionally adjusted for onset of hypertension before the age 35 years, onset of urological events before the age of 35 years and *PKD* mutation (*PKD1* truncating, *PKD1* non-truncating or *PKD2*), because those have previously also been defined as prognostic predictors of ADPKD [28]. In Model 3, we included urinary excretion of ammonium, serum potassium, renin–angiotensin inhibitor use, diuretic use, estimated dietary protein intake and body mass index, all of the variables we considered relevant for acid–base homoeostasis [29, 30]. We also analysed serum bicarbonate in regression models in which only Mayo image class, predicting renal outcomes in ADPKD (PROPKD) score, CKD stage or study site was added. Serum bicarbonate (tertiles) met the assumptions of the Cox proportional hazard model based on the partial residuals. We used linear regression to evaluate the association between serum bicarbonate and secondary outcomes. Homoscedasticity of the multivariable analysis was checked by a fitted versus residual plot, and normality using a Q–Q-plot. The statistical analyses were performed using SPSS version 25.0.0.1 (IBM). A $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Of the 309 DIPAK participants that were randomized, serum bicarbonate was available in 296 patients. The average serum bicarbonate was 26.1 ± 2.8 mmol/L (Table 1). Patients in the highest tertile of serum bicarbonate had lower body mass index, lower serum potassium and lower urine ammonium excretion (Table 1). Most patients were of primarily European descent; five patients were of Asian descent and ethnicity was not reported in five patients. The distributions for Mayo image class, PROPKD scores, CKD stage and study sites are shown in Supplementary data, Table S1. No patients used alkali supplementation at baseline, while four patients used it during follow-up (three in the lowest tertile and one in the highest tertile). Serum bicarbonate showed a positive association with diuretic use and eGFR, and a negative association with male sex, body mass index, study sites 2 and 3, serum potassium and Mayo image class (Table 2).

Lower serum bicarbonate increases the risk of worsening kidney function

Patients with lower serum bicarbonate had a greater risk of worsening kidney function (Figure 1; log-rank $P = 0.004$). When compared with the third serum bicarbonate tertile, patients in the first tertile had a significantly greater risk of worsening kidney function in the fully adjusted model [hazard ratio = 2.95, 95% confidence interval (CI) 1.21–7.19; Figure 2]. The same trend was observed for patients in the second tertile, although this was not statistically significant. In the continuous analysis, each mmol/L decrease in serum bicarbonate increased

Table 1. Baseline characteristics according to serum bicarbonate tertiles

Variable	Total ($n = 296$)	Tertile 1 ($n = 99$)	Tertile 2 ($n = 99$)	Tertile 3 ($n = 98$)	P-value
General characteristics					
Age, years	48 ± 7	48 ± 7	48 ± 7	49 ± 8	0.3
Men, *n* (%)	137 (46)	45 (45)	47 (47)	45 (46)	0.9
Body mass index, kg/m^2	27 ± 5	28 ± 6	27 ± 4	26 ± 4	**0.002**
Systolic blood pressure, mmHg	133 ± 13	132 ± 13	134 ± 14	134 ± 13	0.4
RAS-blocking agents, *n* (%)	223 (75)	74 (75)	74 (75)	75 (77)	0.8
Diuretics, *n* (%)	103 (35)	29 (29)	35 (35)	39 (40)	0.1
Laboratory values					
eGFR, mL/min/1.73 m^2	50 ± 11	49 ± 11	49 ± 12	52 ± 11	0.07
Creatinine clearance, mL/min	73 ± 27	71 ± 25	71 ± 25	78 ± 30	0.2
Serum bicarbonate, mmol/L	26.1 ± 2.8	23.1 ± 1.6	26.2 ± 0.8	29.0 ± 1.3	–
Serum potassium, mmol/L	4.2 ± 0.4	4.4 ± 0.4	4.2 ± 0.4	4.1 ± 0.5	**<0.001**
Urine sodium, mmol/day	161 ± 65	168 ± 65	160 ± 66	156 ± 65	0.4
Urine ammonium, mmol/kg/day	0.21 ± 0.09	0.20 ± 0.09	0.20 ± 0.08	0.22 ± 0.09	**0.03**
Dietary protein, g/day	87 ± 25	90 ± 26	86 ± 26	84 ± 23	0.1
ADPKD characteristics					
htTKV, mL/m	1083 (728–1679)	1209 (864–1797)	1037 (677–1688)	987 (668–1554)	0.07
htTLV, mL/m	1188 (998–1526)	1210 (1007–1512)	1127 (970–1507)	1210 (1041–1660)	0.7
TLV >2000 mL, *n* (%)	170 (57)	56 (57)	54 (55)	60 (61)	0.5
Truncating *PKD1*, *n* (%)	133 (45)	48 (48)	44 (44)	41 (42)	0.3
Non-truncating *PKD1*, *n* (%)	69 (23)	18 (18)	25 (25)	26 (27)	0.2
Other mutation, *n* (%)	94 (32)	33 (33)	30 (30)	31 (32)	0.8
Hypertension <35 years, *n* (%)	116 (39)	41 (41)	41 (41)	34 (35)	0.3
Urologic events <35 years, *n* (%)	68 (23)	16 (16)	25 (25)	27 (28)	0.06

Bold font indicates statistically significant results ($P < 0.05$).
Data are presented as mean ± SD or median (interquartile range), unless otherwise indicated.

Table 2. Variables independently associated with serum bicarbonate

Variable[a]	B (95% CI)	St. β	P-value
Male sex	−0.72 (−1.33 to −0.09)	−0.13	0.02
Body mass index, kg/m^2	−0.08 (−0.14 to −0.02)	−0.13	0.02
Diuretic use	0.89 (0.24 to 1.54)	0.15	0.01
Study site 2	−2.34 (−3.09 to −1.59)	−0.36	<0.0001
Study site 3	−0.67 (−1.36 to 0.20)	−0.11	0.06
eGFR, mL/min/1.73 m^2	0.03 (0.02 to 0.06)	0.11	0.04
Serum potassium, mmol/L	−1.07 (−1.83 to −0.31)	−0.17	0.01
Mayo image class	−0.55 (−0.91 to −0.19)	−0.17	0.003

[a]Covariates related to acid–base homeostasis or ADPKD progression were included in the model, including age, sex, body mass index, systolic blood pressure, renin–angiotensin inhibitor use, diuretic use, study site, eGFR, creatinine clearance, serum potassium, 24-h urinary sodium excretion, 24-h urinary ammonium excretion, NEAP, dietary protein intake, Mayo image class and PROPKD score.

the risk of worsening kidney function by 21% in the fully adjusted model (hazard ratio = 1.21, 95% CI 1.06–1.37; Figure 2). The covariates Mayo image class, PROPKD, CKD stage and study site were also added individually in a model with serum bicarbonate (Supplementary data, Table S2). In these analyses, serum bicarbonate was also independently associated with the primary outcome. We also analysed if NEAP or dietary protein intake (as measures of dietary acid load), and urinary ammonium (as measure of kidney acidifying capacity) were associated with the primary or secondary outcomes, which was not the case (data not shown).

Serum bicarbonate independently predicts changes in eGFR but not TKV and TLV

A lower serum bicarbonate was associated with greater annual eGFR decline (P for trend <0.001; Figure 3A). Each mmol/L decrease in serum bicarbonate increased the annual decline in eGFR by 0.12 mL/min/1.73 m^2/year (95% CI −0.20 to −0.03) in the fully adjusted model (Table 2). A lower serum bicarbonate was not associated with a change in htTKV (0.1 percentage point, 95% CI −0.2 to 0.4; Figure 3B and Table 3). Serum bicarbonate was also not associated with TLV growth in all participants (−0.1 percentage point, 95% CI −0.5 to 0.2) or in the subset of participants with PLD (−0.2 percentage point, 95% CI −0.8 to 0.3).

DISCUSSION

In this study, we show that in patients with ADPKD and eGFR 30–60 mL/min/1.73 m^2, serum bicarbonate is independently associated with kidney outcomes. A lower serum bicarbonate was associated with a greater risk of 30% eGFR decline or kidney failure (the composite primary outcome) and a more rapid annual eGFR decline (secondary outcome). A lower serum bicarbonate was not associated with a greater increase in htTKV and htTLV. Of interest, the association between serum bicarbonate and kidney outcomes was independent of variables that are included in two established prognostic models for ADPKD, the Mayo image class and PROPKD score [27, 28]. Furthermore, the association was also independent of urinary ammonium excretion, a measure of urinary acidification capacity. Our data suggest that serum bicarbonate adds to the current prognostic

Table 3. Linear regression analysis for associations between serum bicarbonate and secondary outcomes

Outcomes	Unadjusted			Model 1[a]			Model 2			Model 3		
	β (95% CI)	P-value	R^2	β (95% CI)	P-value	R^2	β (95% CI)	P-value	R^2	β (95% CI)	P-value	R^2
eGFR, mL/min/1.73 m^2/year	−0.15 (−0.23 to −0.07)	**<0.001**	0.05	−0.13 (−0.22 to −0.05)	**0.001**	0.18	−0.13 (−0.21 to −0.05)	**0.003**	0.20	−0.12 (−0.20 to −0.03)	**0.008**	0.20
htTKV, pp/year	0.1 (−0.2 to 0.4)	0.5	0.00	0.1 (−0.2 to 0.4)	0.5	0.17	0.1 (−0.2 to 0.4)	0.4	0.20	0.1 (−0.2 to 0.4)	0.5	0.23
htTLV, pp/year	−0.1 (−0.4 to 0.1)	0.3	0.00	−0.1 (−0.4 to 0.2)	0.4	0.05	−0.1 (−0.4 to 0.2)	0.5	0.06	−0.1 (−0.5 to 0.2)	0.3	0.07
htTLV in PLD, pp/year	−0.2 (−0.4 to 0.2)	0.4	0.01	−0.2 (−0.7 to 0.3)	0.5	0.06	−0.2 (−0.7 to 0.3)	0.5	0.08	−0.2 (−0.8 to 0.3)	0.4	0.10

[a]Model 1: age, sex, baseline eGFR, baseline htTKV, treatment group (lanreotide or not) and study site; Model 2: Model 1 and hypertension before the age of 35 years, urologic events before the age of 35 years and *PKD* mutation; Model 3: Model 2 and urinary ammonium excretion, baseline serum potassium, renin–angiotensin inhibitor use, diuretic use, dietary protein and body mass index. pp, percentage point.
Bold font indicates statistically significant results ($P < 0.05$).

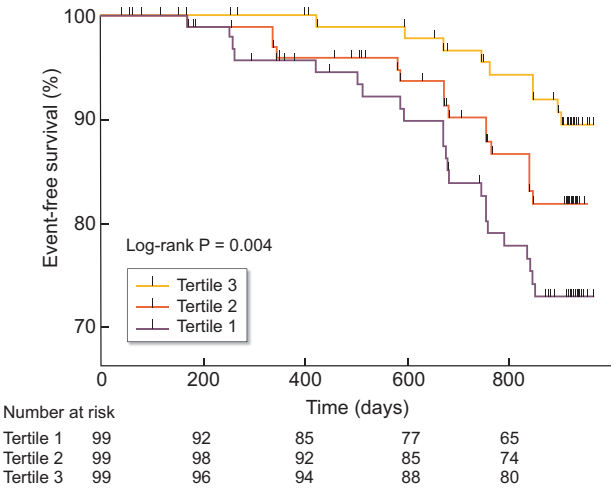


FIGURE 1: Survival analysis for worsening kidney function by baseline serum bicarbonate tertiles. Worsening kidney function (primary outcome) was defined as >30% eGFR loss or kidney failure. Censoring was applied at end of study (after 132 weeks) or in case of loss to follow-up.

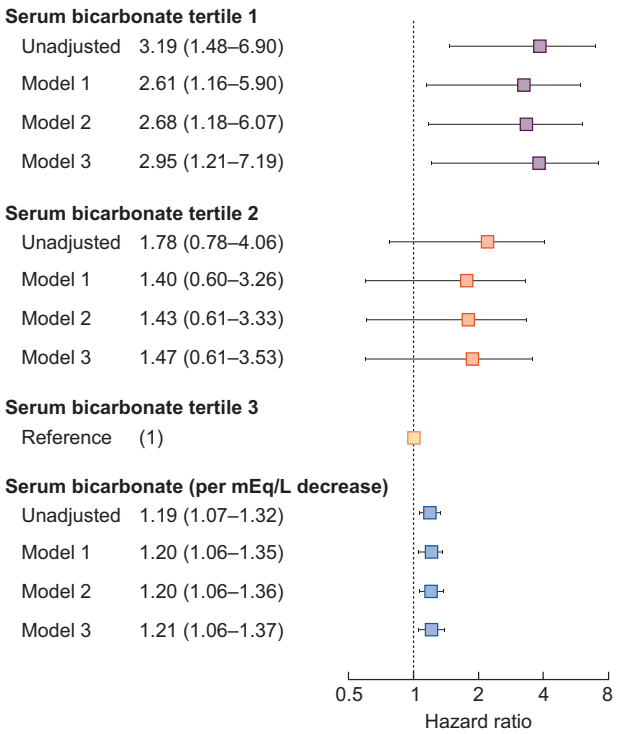


FIGURE 2: Graphical display of hazard ratios with 95% CIs for serum bicarbonate tertiles and serum bicarbonate.

models for ADPKD, and may be considered as a treatment target.

Several studies in patients with CKD have shown that serum bicarbonate is associated both with kidney outcomes and mortality [4–9]. Furthermore, there is low-to-moderate certainty evidence that alkali supplementation slows the rate of kidney function decline in patients with CKD [31]. Of interest, several of these cohorts or trials also included patients with ADPKD, although they likely represented a minority and were not analysed separately. Compared with CKD, the effect size of the association between serum bicarbonate and kidney outcomes appears to be similar or even greater for ADPKD [4–9]. However, two differences in acid–base balance between ADPKD and CKD merit emphasis. First, dietary acid load or urinary ammonium did not predict kidney outcomes in our ADPKD cohort. This was unexpected because previous studies in CKD cohorts identified dietary acid load and urinary ammonium excretion as risk factors for kidney outcomes independent of serum bicarbonate [29, 30, 32]. This suggests that in CKD, ammonium handling is affected differently than in ADPKD, as has been suggested previously [16]. Secondly, the average serum bicarbonate concentration was higher in our ADPKD cohort than in previous CKD cohorts with similar eGFR range [8, 30]. In fact, only 7.4% of the patients in our cohort had a serum bicarbonate <22 mmol/L that would classify as metabolic acidosis [2]. Although serum bicarbonate was correlated with diuretic use, fewer participants used diuretics in our cohort than in the CKD cohorts (35% versus >50%). This suggests that the target value for serum bicarbonate may depend on the underlying kidney disease. A possible explanation for higher serum bicarbonate in patients with ADPKD may be that the urinary concentrating defect causes slight volume depletion

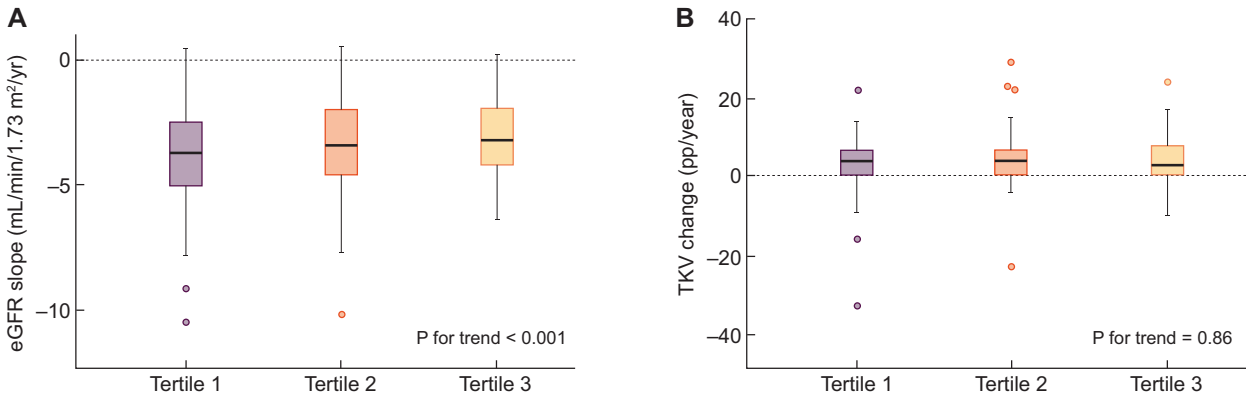


FIGURE 3: eGFR slope (**A**) and change in TKV (**B**) by serum bicarbonate tertile. pp, percentage point.

with angiotensin II-mediated bicarbonate reabsorption [33]. Of interest, a tubular form of metabolic alkalosis was recently reported in the so-called Oak Ridge polycystic kidney mouse, which exhibits increased sodium–hydrogen exchanger activity in the cortical collecting duct [34]. Therefore, an alternative explanation may be that the higher serum bicarbonate in ADPKD is caused by a change in tubular acid–base handling. It is not clear if serum bicarbonate in the high–normal range can also cause complications. Some studies identified U- or J-shaped associations between serum bicarbonate and mortality [5, 7], although this finding is not consistent [6, 8, 9]. In the Chronic Renal Insufficiency Cohort, a higher serum bicarbonate was associated with heart failure, but this study excluded patients with ADPKD [8].

Although our study cannot prove causality between a lower serum bicarbonate and faster kidney function decline, experimental models of both CKD and ADPKD do support a direct link between acid retention and kidney injury [17, 35]. Three of the explanations for why metabolic acidosis can cause kidney damage in CKD may also be relevant for ADPKD. First, the renin–angiotensin system (RAS) in the kidney has been implicated in acidosis-induced kidney injury and also in the progression of ADPKD [10, 36, 37]. Recently, we showed that patients with ADPKD have a 5- to 6-fold higher urinary excretion of renin and angiotensinogen compared with matched CKD patients [38]. Secondly, increased ammoniagenesis by dietary acid loads may activate the complement system and promote kidney fibrosis [39]. The complement system has also been implicated in the progression of PKD [17, 40]. In a recent proteomic analysis, we detected more complement in urinary extracellular vesicles of patients with ADPKD than with CKD [41]. Thirdly, metabolic acidosis causes hypocitraturia, which may promote crystal deposition in the kidney and which in turn may promote the progression of ADPKD [42, 43]. Hypocitraturia is common in ADPKD, and calculi can be found in up to 25% of patients with ADPKD [44]. Challenging PKD rat models with calcium oxalate or phosphate deposition increased cystogenesis and disease progression through a mammalian target of rapamycin-dependent pathway [42]. A higher serum bicarbonate could also reflect higher dietary intake of citrate, which will reduce crystal deposition, and was linked to slower disease progression [18, 42].

To our knowledge, this is the first study to specifically analyse the association between serum bicarbonate and kidney outcomes in patients with ADPKD. The strength of this study is that the data are based on a randomized clinical trial, with standardized procedures and prospectively defined outcomes. In the DIPAK trial, lanreotide reduced the rate of growth in TKV [19] and therefore treatment allocation was included in our models. Furthermore, we were able to correct for multiple confounders, including established risk factors for progression of ADPKD, urinary ammonium excretion (measured specifically for this study) and use of renin–angiotensin inhibitors and diuretics. However, a number of limitations should be mentioned. First, follow-up time was too short to analyse kidney failure or mortality, outcomes that have previously been associated with serum bicarbonate [4–9]. Secondly, different analysers were used to measure serum bicarbonate, although interchangeability has previously been established [45]. The average serum bicarbonate was significantly lower in one study site despite the use of the same analyser as in one of the other sites. However, neither stratification nor correction for study site changed the results.

In conclusion, in patients with ADPKD, a lower serum bicarbonate within the normal range predicts worse kidney outcomes independent of established prognostic factors for ADPKD and independent of urine ammonium excretion. Serum bicarbonate may add to prognostic models and should be explored as a treatment target in ADPKD.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

Research idea and study design was by C.J.B., D.S., R.Z. and E.J.H; data acquisition was performed by C.J.B., U.M.M.-B. and R.T.G.; data analysis/interpretation was carried out by C.J.B., D.S., R.T.G., R.Z. and E.J.H.; statistical analysis was performed by C.J.B., D.S. and E.J.H.; supervision or mentorship was provided by D.S., R.Z. and E.J.H. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions and agrees to ensure that questions pertaining to the accuracy and integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest are declared by the authors.

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