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

DIPAK Consortium; Blijdorp, Charles J; Severs, David; Musterd-Bhaggoe, Usha M; Gansevoort, Ronald T; Zietse, Robert; Hoorn, Ewout J

Published in:
Nephrology, Dialysis, Transplantation

DOI:
10.1093/ndt/gfaa283

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
DIPAK Consortium, Blijdorp, C. J., Severs, D., Musterd-Bhaggoe, U. M., Gansevoort, R. T., Zietse, R., & Hoorn, E. J. (2021). Serum bicarbonate is associated with kidney outcomes in autosomal dominant polycystic kidney disease. Nephrology, Dialysis, Transplantation, 36(12), 2248–2255. Advance online publication. https://doi.org/10.1093/ndt/gfaa283

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Serum bicarbonate is associated with kidney outcomes in autosomal dominant polycystic kidney disease

Charles J. Blijdorp\textsuperscript{1}, David Severs\textsuperscript{1}, Usha M. Musterd-Bhaggoe\textsuperscript{1}, Ronald T. Gansevoort\textsuperscript{2}, Robert Zietse\textsuperscript{1} and Ewout J. Hoorn \textsuperscript{1,1}; on behalf of the DIPAK Consortium\textsuperscript{†}

\textsuperscript{1}Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus Medical Center, Rotterdam, The Netherlands and 
\textsuperscript{2}Department of Nephrology, University Medical Center Groningen, Groningen, The Netherlands

\textsuperscript{†}The collaborators of the DIPAK Consortium are listed in the Acknowledgements section.
Correspondence to: Ewout J. Hoorn; E-mail: e.j.hoorn@erasmusmc.nl

**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 \([n = 296, \text{ estimated glomerular filtration rate (eGFR)} 50 \pm 11 \text{ mL/min/1.73 m}^2, \text{ 2.5 years follow-up}]. \) 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

\textcopyright The Author(s) 2020. Published by Oxford University Press on behalf of ERA-EDTA.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
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.

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 m² to 39% in patients with eGFR <20 mL/min/1.73 m² [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 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 m² 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: $6.25 \times \text{[urine urea nitrogen in g/day]} + \text{[weight in kg]} \times 0.031$ [22]. Net endogenous acid production (NEAP) was estimated by: $10.2 + (54.5 \times \text{protein intake in g/day})/\text{urine potassium in mEq/day}$ [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 $< 15 \text{ mL/min/1.73 m}^2$ [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 $> 2000 \text{ mL}$ [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 of 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 $26.1 \pm 2.8 \text{ mmol/L}$ (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...
bicarbonate (Supplementary data, Table S2). In these analyses, the covariates Mayo image class, PROPKD, CKD stage and protein intake, Mayo image class and PROPKD score. Furthermore, 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].

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/m² | 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 m² | 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         | <0.001  |
| Serum potassium, mmol/L | 4.2 ± 0.4     | 4.4 ± 0.4          | 4.2 ± 0.4          | 4.1 ± 0.5          |         |
| 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

| Variable       | B (95% CI) | St. β | P-value |
|----------------|------------|-------|---------|
| 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 m²/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) 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 m², 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 (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).

**Table 2. Variables independently associated with serum bicarbonate**

| Variable | B (95% CI) | St. β | P-value |
|----------|------------|-------|---------|
| Male sex | −0.72 (−1.33 to −0.09) | −0.13 | 0.02   |
| Body mass index, kg/m² | −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 | −0.07 (−1.36 to 0.20) | −0.11 | 0.06   |
| eGFR, mL/min/1.73 m² | 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  |

*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.

**Table 3. Variables independently associated with serum bicarbonate**

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).
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 studies in patients with CKD have shown that serum bicarbonate tertiles and serum bicarbonate 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 concentration was higher in our ADPKD cohort than in the CKD cohorts (35% versus 50%). 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 of the body's sodium and water content, leading to increased bicarbonate excretion. This produces an acid-base balance that can result in a serum bicarbonate level higher than expected in patients with ADPKD.

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

| Outcomes | Unadjusted | Model 1 | Model 2 | Model 3 |
|----------|------------|---------|---------|---------|
| eGFR, mL/min/1.73 m²/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 |
| hydrated TKV, 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 |
| hydrated TLV, 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 |
| 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 |

*Model 1: age, sex, baseline eGFR, baseline hydrated TKV, 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).
Serum bicarbonate and kidney outcomes in ADPKD

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.

**ACKNOWLEDGEMENTS**

The Collaborators of DIPAK Consortium are Joost P.H. Drenth, MD, PhD, Department of Gastroenterology and Hepatology, Radboudumc Nijmegen, The Netherlands; Johannes W. de Fijter, MD, PhD, Department of Nephrology, Leiden University Medical Centre, Leiden, The Netherlands; Esther Meijer, MD, PhD, Department of Nephrology, University Medical Centre Groningen, Netherlands; Esther Meijer, MD, PhD, Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands; Monique Losekoot, MD, PhD, Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands; Esther Meijer, MD, PhD, Department of Nephrology, University Medical Centre Groningen,
REFERENCES

No conflicts of interest are declared by the authors.

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.

REFERENCES

1. Hamm LL, Nakhoul N, Hering-Smith KS. Acid-base homeostasis. Clin J Am Soc Nephrol 2015; 10: 2232–2242
2. Raphael KL. Metabolic acidosis in CKD: core curriculum 2019. Am J Kidney Dis 2019; 74: 263–275
3. Moranne O, Froissart M, Rossert J. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in stage 3 and stage 4 chronic kidney disease. Nephrol Dial Transplant 2009; 24: 1232–1237
4. Shah SN, Abramowitz M, Hostetter TH et al. Serum bicarbonate levels and the progression of kidney disease: a cohort study. Am J Kidney Dis 2009; 54: 270–277
5. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant 2008; 24: 1232–1237
6. Menon V, Tighiouart H, Vaughn NS et al. Serum bicarbonate and long-term outcomes in CKD. Am J Kidney Dis 2010; 56: 907–914
7. Navaneethan SD, Schold JD, Arrigain S et al. Serum bicarbonate and mortality in stage 3 and stage 4 chronic kidney disease. Clin J Am Soc Nephrol 2011; 6: 2395–2402
8. Dohre M, Yang W, Chen J et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study. Am J Kidney Dis 2013; 62: 670–678
9. Raphael KL, Wei G, Baird BC et al. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. Kidney Int 2011; 79: 356–362
10. Wesson DE, Buysse JM, Bushinsky DA. Mechanisms of metabolic acidosis-induced kidney injury in chronic kidney disease. J Am Soc Nephrol 2020; 31: 469–482
11. Schutte E, Lambers Heerspink HJ, Lutgers HL et al. Serum bicarbonate and kidney disease progression and cardiovascular outcome in patients with diabetic nephropathy: a post hoc analysis of the RENAIIL (Reduction of End Points in Non-Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan) study and IDNT (Irbesartan Diabetic Nephropathy Trial). Am J Kidney Dis 2015; 66: 450–458
12. de Brito-Ashurst L, Varagunam M, Rafferty MJ et al. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol 2009; 20: 2073–2084
13. Mahajan A, Simoni J, Sheather SJ et al. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int 2010; 78: 303–309
14. Bi C. Clinical and cost-effectiveness of oral sodium bicarbonate therapy for older patients with chronic kidney disease and low-grade acidosis (BiCARB): a pragmatic randomised, double-blind, placebo-controlled trial. BMC Med 2020; 18: 91
15. Groopman EE, Marasa M, Cameron-Christie S et al. Diagnostic utility of exome sequencing for kidney disease. N Engl J Med 2019; 380: 142–151
16. Torres VE, Keith DS, Offord KP et al. Renal ammonia in autosomal dominant polycystic kidney disease. Kidney Int 1994; 45: 1745–1753
17. Torres VE, Mujwidi DK, Wilson DM et al. Renal cystic disease and ammoniagenesis in Han: SPRD rats. J Am Soc Nephrol 1994; 5: 1193–1200
18. Tanner GA. Potassium citrate/citric acid intake improves renal function in rats with polycystic kidney disease. J Am Soc Nephrol 1998; 9: 1242–1248
19. Meijer E, Visser FW, van Aerts RMM et al. Effect of lanreotide on kidney function in patients with autosomal dominant polycystic kidney disease: the DIPAK 1 randomized clinical trial. JAMA 2018; 320: 2010–2019
20. Meijer E, Drenth JP, d’Agnolo H et al. Rationale and design of the DIPAK 1 study: a randomized controlled clinical trial assessing the efficacy of lanreotide to Hald disease progression in autosomal dominant polycystic kidney disease. Am J Kidney Dis 2014; 63: 446–455
21. Levey AS, Stevens LA, Schmid CH et al.; for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–612
22. Maroni BJ, Steinman TI, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. Kidney Int 1985; 27: 58–65
23. Frassetto LA, Todd KM, Morris RC Jr et al. Estimation of net endogenous noncarboxylic acid production in humans from diet potassium and protein contents. Am J Clin Nutr 1998; 68: 576–583
24. Levey AS, Inker LA, Matsushita K et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis 2014; 64: 821–835
25. Chang WX, Asakawa S, Toyoki D et al. Predictors and the subsequent risk of end-stage renal disease - usefulness of 30% decline in estimated GFR over 2 years. PLoS One 2015; 10: e0132927
26. Corens J, Turin TC, Matsuhashi K et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA 2014; 311: 2518–2531
27. Irazabal MV, Rangel LJ, Berghstrahl EJ et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. J Am Soc Nephrol 2015; 26: 160–172
28. Cornec-Le Gall E, Audrezet MP, Rousseau A et al. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2016; 27: 942–951
29. Vallet M, Metzger M, Haymann JP et al. Urinary ammonia and long-term outcomes in chronic kidney disease. Kidney Int 2015; 88: 137–145
30. Raphael KL, Carroll DJ, Murray J et al. Urine ammonium predicts clinical outcomes in hypertensive kidney disease. J Am Soc Nephrol 2017; 28: 2483–2490
31. Navaneethan SD, Shao J, Buysse J et al. Effects of treatment of metabolic acidosis in CKD: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2019; 14: 1011–1020
32. Banerjee T, Crews DC, Wesson DE et al. High dietary acid load predicts ERSD among adults with CKD. J Am Soc Nephrol 2015; 26: 1693–1700
33. Zittema D, Boerthien WE, van Beek AP et al. Vasopressin, copeptin, and renal concentrating capacity in patients with autosomal dominant polycystic kidney disease.

Downloaded from https://academic.oup.com/ndt/article/36/12/2248/6055244 by University of Groningen user on 09 February 2022
kidney disease without renal impairment. *Clin J Am Soc Nephrol* 2012; 7: 906–913

34. Olteanu D, Liu X, Liu W et al. Increased Na+/H+ exchanger activity on the apical surface of a cilium-deficient cortical collecting duct principal cell model of polycystic kidney disease. *Am J Physiol Cell Physiol* 2012; 302: C1436–C1451

35. Wesson DE, Simoni J. Acid retention during kidney failure induces endothelin and aldosterone production which lead to progressive GFR decline, a situation ameliorated by alkali diet. *Kidney Int* 2010; 78: 1128–1135

36. Loghman-Adham M, Soto CE, Inagami T et al. The intrarenal renin-angiotensin system in autosomal dominant polycystic kidney disease. *Am J Physiol Renal Physiol* 2004; 287: F775–F788

37. Saigusa T, Dang Y, Mullick AE et al. Suppressing angiotensinogen synthesis attenuates kidney cyst formation in a Pkd1 mouse model. *FASEB J* 2016; 30: 370–379

38. Salih M, Bovee DM, Roksnoer LCW et al. Urinary renin-angiotensin markers in polycystic kidney disease. *Am J Physiol Renal Physiol* 2017; 313: F874–F881

39. Nath KA, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. *J Clin Invest* 1985; 76: 667–675

40. Su Z, Wang X, Gao X et al. Excessive activation of the alternative complement pathway in autosomal dominant polycystic kidney disease. *J Intern Med* 2014; 276: 470–485

41. Salih M, Demmers JA, Bezstarosti K et al. Proteomics of urinary vesicles links plakins and complement to polycystic kidney disease. *J Am Soc Nephrol* 2016; 27: 3079–3092

42. Torres JA, Rezaei M, Broderick C et al. Crystal deposition triggers tubule dilation that accelerates cystogenesis in polycystic kidney disease. *J Clin Invest* 2019; 129: 4506–4522

43. Brenner RJ, Spring DB, Sebastian A et al. Incidence of radiographically evident bone disease, nephrocalcinosis, and nephrolithiasis in various types of renal tubular acidoses. *N Engl J Med* 1982; 307: 217–221

44. Nishiura JL, Neves RF, Eloi SR et al. Evaluation of nephrolithiasis in autosomal dominant polycystic kidney disease patients. *Clin J Am Soc Nephrol* 2009; 4: 838–844

45. Allardet-Servent J, Lebsir M, Dubroca C et al. Point-of-care versus central laboratory measurements of hemoglobin, hematocrit, glucose, bicarbonate and electrolytes: a prospective observational study in critically ill patients. *PLoS One* 2017; 12: e0169593

Received: 8.6.2020; Editorial decision: 7.9.2020