Research Article

Oral Sodium Bicarbonate Supplementation Does Not Affect Serum Calcification Propensity in Patients with Chronic Kidney Disease and Chronic Metabolic Acidosis

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Keywords

Cardiovascular disease · T₅₀ · Metabolic acidosis · Chronic kidney disease · Bicarbonate

Abstract

Background: Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD) and metabolic acidosis might accelerate vascular calcification. The T₅₀ calcification inhibition test (T₅₀-test) is a global functional test analyzing the overall propensity of calcification in serum, and low T₅₀-time is associated with progressive aortic stiffening and with all-cause mortality in non-dialysis CKD, dialysis, and transplant patients. Low serum bicarbonate is associated with a short T₅₀-time and alkali supplementation could be a simple modifier of calcification propensity. The aim of this study was to investigate the short-term effect of oral sodium bicarbonate supplementation on T₅₀-time in CKD patients. **Material and Methods:** The SoBic-study is an ongoing randomized-controlled trial in CKD-G3 and G4 patients with chronic metabolic acidosis (serum HCO₃⁻ ≤21 mmol/L), in which patients are randomized to either achieve serum HCO₃⁻ levels of 24 ± 1 mmol/L (intervention group) or 20 ± 1 mmol/L (rescue group). The effect of bicarbonate treatment on T₅₀-time was assessed. **Results:** The study cohort consisted of 35 (14 female) patients aged 57 (±15) years, and 18 were randomized to the intervention group. The mean T₅₀-time was 275 (± 64) min. After 4 weeks,

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the mean change of T₅₀-time was 4 (±69) min in the intervention group and 18 min (±56) in the rescue group ($\beta = -25$; 95% CI: -71 to 22; $p = 0.298$). Moreover, change of serum bicarbonate in individual patients was not associated with change in T₅₀-time, analyzed by regression analysis. Change of serum phosphate had a significant impact on change of T₅₀-time ($\beta = -145$; 95% CI: -237 to -52). **Conclusion:** Oral sodium bicarbonate supplementation showed no effect on T₅₀-time in acidotic CKD patients.

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Introduction

Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD) [1] and metabolic acidosis is thought to accelerate progression of both, cardiovascular disease and CKD [2–10]. Derangements of calcium and phosphorus homeostasis, parathyroid hormone and metabolic bone disease are summarized as the “chronic-kidney-disease – mineral and bone disorder – CKD-MBD,” a syndrome associated with severe vascular calcification [11]. Vascular calcification is strongly related with morbidity and mortality in CKD patients [12, 13]. Numerous promoters (phosphate, calcium, metabolic acidosis) and inhibitors (Fetuin-A, pyrophosphate, magnesium, bicarbonate) of calcification have been identified (reviewed in Shroff et al. [14]), many of which cannot be measured in clinical routine (i.e., Fetuin A, pyrophosphate). The T₅₀ calcification inhibition test (T₅₀-test) is a global functional test analyzing the overall propensity for calcification of patient serum. The in vitro diagnostic test measures the conversion (or “maturation”) of primary to secondary calciprotein particles (CPP) in serum. The half-maximum time for this conversion is called “T₅₀” and is given in minutes (min) [15]. Low T₅₀-time (i.e., low resistance towards calcification) is associated with progressive aortic stiffening and with all-cause mortality in non-dialysis CKD [16], dialysis [17], and transplant patients [18, 19].

Interventions to modify vascular calcification and to subsequently reduce mortality in CKD patients are of great importance. Aside from other potential strategies, intervening on serum bicarbonate (HCO₃⁻), which is a strong inhibitor of calciprotein particle formation in vitro, appears to be a reasonable and economically feasible intervention to improve the T₅₀-time in CKD patients (Pasch A et al., FR-PO401; Buchkremer F et al., Fr-PO 437, ASN 2016). In CKD patients, correction of acid-base disturbance with oral sodium bicarbonate supplementation is part of routine clinical care. However, the evidence on patient-level outcomes to support this practice is scarce [20–24], and its impact on reducing morbidity and mortality in CKD is unknown.

The aim of this study was to investigate the short-term effect of oral sodium bicarbonate supplementation in patients with CKD stage 3 and 4 with chronic metabolic acidosis (serum bicarbonate ≤21 mmol/L) on the calcification propensity in serum, measured by the T₅₀-test. We hypothesized that patients in the interventional group will have a significant prolongation of their T₅₀-time (i.e., increase in resistance to calcification) from baseline to week 4 and will have a significantly longer T₅₀-time at week 4 compared to the rescue group.

Material and Methods

The SoBic-study (EUDRACT: 2012-001824-36, 7/12/2012) [25] is an ongoing randomized-controlled trial in CKD-G3 and G4 patients with chronic metabolic acidosis (serum HCO₃⁻ ≤21 mmol/L) at the Renal Outpatient Clinic at the Medical University of Vienna.

Fig. 1. Trial profile. * Two consecutive measurements at least 1 day apart.

The aim of the parent study is to evaluate the effect of normalizing serum bicarbonate (HCO₃⁻) levels to 24 ± 1 mmol/L (intervention group) compared to serum bicarbonate (HCO₃⁻) levels of 20 ± 1 mmol/L (rescue group) on renal function (MDRD-eGFR) over 2 years. Inclusion criteria were age >18 years, estimated glomerular filtration rate (eGFR) of 60 to 15 mL/min per 1.73 m², venous serum HCO₃⁻ of ≤21 mmol/L on two consecutive measurements (at least 1 day apart), and stable clinical condition. Exclusion criteria were malignant disease or within 5 years of successful treatment of such, morbid obesity (body mass index >40 kg/m²), chronic inflammation (C reactive protein >10 mg/dL, reference: <0.5 g/dL), current immunosuppressive medication, poorly controlled blood pressure (>150/90 mm Hg despite the use of four agents), overt congestive heart failure, or known peanut or soy allergy (both ingredients of study medication). Dependent on randomization, patients were treated with Nephrotrans[®] 840 mg tablets (sodium bicarbonate; MEDICE Pharma Pütter GmbH & Co. KG, Iserlohn, Germany) according to a treatment algorithm [25]. For patients receiving sodium bicarbonate supplementation the dose was constant for the 4 weeks of follow-up in this study.

The primary outcome of the current study was the change of T₅₀-time (min) between baseline and week 4 within patients and the difference between the T₅₀-time between subjects in the intervention group and rescue group (Fig. 1). All patients gave written informed consent, the study is in line with the Declaration of Helsinki, and the Ethics Committee of the Medical University of Vienna approved the current study.

Study Cohort and Time Line

This analysis included all 38 patients enrolled in the SoBic-study as of September 2017. We obtained demographic and medical information as well as a laboratory analysis at randomization as detailed elsewhere (visit 1 and 2 of the SoBic-study) [25]. After 4 weeks all patients underwent visit 3 (week 4) for a subsequent laboratory investigation, assessment of vital signs, body weight, and adverse events (Fig. 1).

We determined the T₅₀-time in serum specimens drawn at baseline and week 4 out of biobank samples immediately stored at -80 °C [25]. Potential relevant covariates like eGFR, serum phosphate, serum calcium, serum magnesium, comorbidities, co-medication, and demographic data has already been obtained during regular SoBic-study visits [25].

Laboratory Measures

T₅₀-time was determined by Calciscon AG, Bern, Switzerland as described previously [15]. In brief, the calcification propensity test is an in vitro nano-particle assay, which measures the time of conversion of primary to secondary CPPs. Serum samples were supersaturated with calcium and phosphate to increase their final concentrations by 10 and 6 mM, respectively. Secondary CPP formation time (T₅₀-time) was measured by a nephelostar nephelometer (BMG Labtech, Ortenberg, Germany). Other parameters were measured as detailed in Gaggl et al. [25].

The main outcome, change of T₅₀-time (min, Δ T₅₀-time), was calculated as T₅₀-time at week 4 minus baseline T₅₀-time. Similarly, we calculated change of HCO₃⁻ (mmol/L, Δ HCO₃⁻), change of eGFR (mL/min per 1.73 m², Δ eGFR), change of serum albumin (g/L, Δ serum albumin) change of serum calcium (mmol/L, Δ serum calcium), change of serum magnesium (mmol/L, Δ serum magnesium), and change of serum phosphate (mmol/L, Δ serum phosphate).

Statistical Analysis

We presented descriptive statistics as mean and standard deviation (±SD) and median and interquartile range (IQR), respectively, as appropriate. Firstly, imbalances between the investigational and rescue group were examined visually and by Student's *t* test and Wilcoxon-Mann-Whitney test, respectively, depending on test assumptions. To test changes of parameters in individuals during the 4 weeks we performed paired Student's *t* test or a Wilcoxon signed-rank test as appropriate. To analyze correlation between serum bicarbonate and other laboratory parameters we performed Spearman correlations (*r*_{ho}) and visualized the relation by means of scatterplots.

Secondly, for the intention to treat analysis we calculated two different regression models using treatment group (reference = rescue group) as the predictor: To assess the differences between groups after 4 weeks we predicted T₅₀-time (outcome), and to account for within-subject change we predicted Δ T₅₀-time (outcome). Although randomization creates equal covariate distribution in both study groups by expectation, we adjusted for variables with observed minor differences at baseline and for strong predictors of the outcome (i.e., eGFR, age, and baseline serum bicarbonate).

Thirdly, we analyzed changes of serum parameters to explore the effect on the change of T₅₀-time from baseline to week 4 (Δ T₅₀-time) by regression analysis, ignoring group randomization of study subjects.

All results are presented as point estimates and corresponding 95% confidence intervals (95% CI), and all results with a *p* value lower than 0.05 were considered statistically significant. All statistical analysis was performed with R (R Core Team (2016). "R: A language and environment for statistical computing"; R Foundation for Statistical Computing, Vienna, Austria; <https://www.R-project.org/>).

Results

As of September 2017, 38 patients were enrolled in the SoBic-study, of which 3 were excluded from this analysis, because of missing T₅₀-time. Of the 35 remaining patients, 14 were female (40%) and the mean age was 57 (±15) years. Further basic demographic information is given in Table 1 for the 18 subjects randomized to the intervention group, and for the 17 subjects of the rescue group.

The median baseline serum bicarbonate was similar in the intervention group and in the rescue group (19.20 mmol/L [IQR: 17.90–19.85] vs. 19.80 mmol/L [IQR: 17.70–20.5, *p* = 0.34]) and so was the median eGFR (23.30 mL/min per 1.72 m² [IQR: 19.22–25.87] vs. 24.40

Table 1. Patients' demographic information and laboratory parameters

	Intervention group	Rescue group	<i>p</i> value ¹	All
Age, years	59.94±12.46	53.12±17.74	0.20	56.63±15.42
Female, yes	6 (33.3%)	8 (47.1%)	0.50	14 (40%)
BMI ² , kg/m ²	27.16±4.45	26.31±3.76	0.55	26.73±4.10
Medical history				
Arterial hypertension	18 (100%)	16 (94.1%)	0.49	34 (97%)
Hyperlipidemia	3 (16.7%)	4 (23.5%)	0.69	7 (20%)
Diabetes mellitus	7 (38.9%)	3 (17.6%)	0.26	10 (28.6%)
Cardiovascular disease	3 (16.7%)	1 (5.9%)	0.60	4 (11.4%)
Congestive heart failure	1 (5.6%)	2 (11.8%)	0.60	3 (8.6%)
Peripheral arterial disease	3 (16.7%)	3 (17.6%)	1.0	6 (17.1%)
COPD	0	1 (5.9%)	0.49	1 (2.9%)
<i>Baseline</i>				
Serum bicarbonate, mmol/L	18.78±1.59	19.28±1.55	0.35	19.02±1.57
T ₅₀ -time, min	269±63	281±67	0.60	275±64
eGFR, mL/min per 1.73 m ²	23.64±5.87	27.45±10.05	0.19	25.49±8.28
Serum sodium, mmol/L	140±3.03	139±2.6	0.31	139±2.8
Serum chloride, mmol/L	106±3.23	105±3.13	0.36	106±3.2
Serum potassium, mmol/L	4.83±0.47	4.94±0.61	0.54	4.88±0.54
Serum calcium, mmol/L	2.26±0.15	2.29±0.13	0.55	2.27±0.14
Serum phosphate, mmol/L	1.11±0.22	1.19±0.26	0.35	1.15±0.24
Serum magnesium, mmol/L	0.78±0.12	0.81±0.10	0.52	0.80±0.11
Serum albumin, g/L	41±3.7	41±4.7	0.63	41±4.2
Urine sodium ³ , mmol/24 h	188±92	167±69	0.48	179±82
Urine pH	5.36±0.59	5.35±0.63	0.97	5.36±0.6
<i>Week 4</i>				
Serum bicarbonate, mmol/L	21.61**±1.4	20.95**±1.66	0.21	21.29±1.55
T ₅₀ -time, min	273±85	298±48	0.29	286±70
eGFR, mL/min per 1.73 m ²	22.94±5.77	28.76±12.14	0.09	25.77±9.37
Serum sodium, mmol/L	140±3.13	140*±2.4	0.95	140±2.7
Serum chloride, mmol/L	104*±3.96	104±3.3	0.93	104±3.6
Serum potassium, mmol/L	4.70±0.44	4.85±0.48	0.37	4.77±0.46
Serum calcium, mmol/L	2.29±0.19	2.29±0.14	1.00	2.29±0.16
Serum phosphate, mmol/L	1.11±0.28	1.12±0.21	0.91	1.11±0.25
Serum magnesium, mmol/L	0.78±0.10	0.80±0.10	0.47	0.79±0.10
Serum albumin, mmol/L	41±3.5	41±4.9	0.84	41±4.2
Urine sodium ⁴ , mmol/24 h	212±81	174±82	0.19	194±82
Urine pH	6.39**±0.95	6.0*±0.97	0.24	6.20±1.0

Values present mean ± standard deviation and count (percent), respectively. BMI, body mass index; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease. ¹ Independent sample Student's *t* test for continuous variables and χ^2 test for categorical variables, respectively; ² 1 missing; ³ 4 missing; ⁴ 3 missing. * *p* < 0.05 and ** *p* < 0.001, respectively, for paired *t* test.

mL/min per 1.72 m² [IQR: 21.20–34.30, *p* = 0.43]). The mean serum phosphate was 1.11 (±0.22) mmol/L in the intervention group and 1.19 (±0.26) in the rescue group (*p* = 0.35).

Other baseline parameters were approximately similar between both groups. According to the pre-specified treatment algorithm all patients in the intervention group received oral sodium bicarbonate, but only 9 patients in the rescue group (Fig. 2). However, one patient from the intervention group stopped taking sodium bicarbonate 8 days before the study visit because of problems with the study medication supply. At week 4, patients randomized to the

Fig. 2. Relation between change of T₅₀-time and change of serum bicarbonate in the intervention group (grey dots) and the rescue group (black dots). The daily oral sodium bicarbonate dose is depicted by dot size.

Fig. 3. Relation between change of T₅₀-time and change of serum phosphate in the intervention group (grey dots) and the rescue group (black dots). The daily oral sodium bicarbonate dose is depicted by dot size.

intervention group received a median dose of oral sodium bicarbonate of 4,200 (IQR: 2,520–5,040) mg per day (mean [±SD] = 45 [±20] mg per kilogram bodyweight/day), whereas the rescue group received a median dose of 1,680 (IQR: 1,680–2,520) mg per day (mean [±SD] = 15 [±14] mg per kilogram bodyweight/day).

The overall T₅₀-time was 275 (±15) min at baseline, 269 (±63) min and 281 (±67) min for the intervention and rescue group, respectively. Overall, baseline T₅₀-time was not correlated with age and body mass index, and did not differ with regard to gender. With respect to baseline laboratory measurements T₅₀-time was not correlated with serum bicarbonate

($r_{ho} = 0.29$, $p = 0.10$), eGFR ($r_{ho} = 0.22$, $p = 0.10$), serum calcium ($r_{ho} = 0.21$, $p = 0.22$), serum albumin ($r_{ho} = -0.07$, $p = 0.750$), or serum magnesium ($r_{ho} = 0.10$, $p = 0.60$). In contrast, baseline serum phosphate was strongly correlated with baseline T₅₀-time ($r_{ho} = -0.61$, $p < 0.001$). Correlation patterns were identical at week 4, but the correlation between serum phosphate and T₅₀-time was weakened ($r_{ho} = -0.49$, $p = 0.003$).

After 4 weeks, the overall mean change of T₅₀-time was 11 (± 62) min, 4 (± 69) min in the intervention group and 18 min (± 56) in the rescue group. Subjects randomized to the intervention group did not have a different T₅₀-time after 4 weeks compared to those from the rescue group ($\beta_{crude} = -25$; 95% CI: -71 to 22; $p = 0.30$). Adjustment for baseline renal function, baseline serum bicarbonate and age did not change the null-effect ($\beta_{adj} = -15$; 95% CI: -64 to 34; $p = 0.60$).

When individual changes of T₅₀-time were taken into account (Δ T₅₀-time), there was still no difference observed between intervention and rescue group in the crude ($\beta_{crude} = -14$, 95% CI: -55 to 28; $p = 0.53$) and adjusted model ($\beta_{adj} = -10$; 95% CI: -51 to 32; $p = 0.65$; Fig. 2).

Furthermore, we explored the effect of the change in known promoters and inhibitors on Δ T₅₀-time: Interestingly, from modulators of the T₅₀-time suggested by in vitro experiments [26], only Δ serum phosphate (mean change -0.004 (± 0.2) mmol/L) had a significant impact on Δ T₅₀-time (Fig. 3). For subjects with a 1 mmol/L increase of serum phosphate from baseline to week 4 the model adjusted for Δ serum bicarbonate suggested a decrease of 141 (95% CI: -226 to -56) min of T₅₀-time from baseline to week 4 (model 5). When age and Δ eGFR were added into the model (model 7), the magnitude of the effect slightly increased ($\beta_{adj} = -145$; 95% CI: -237 to -52).

Discussion

In this randomized trial in patients with CKD stage 3 to 4 and overt metabolic acidosis we tested the effect of sodium bicarbonate treatment on vascular calcification propensity (T₅₀-time). Our study showed that a high dose of oral sodium bicarbonate (median 4.2 g/day vs. 1.7 g/day) did not increase T₅₀-time at week 4 (high resistance towards calcification) relative to baseline T₅₀-time. Although there was neither at baseline nor at week 4 a correlation between serum bicarbonate and T₅₀-time, our finding might be partly caused by the small mean treatment contrast of 0.75 mmol/L serum bicarbonate between study groups at week 4. Since the mean increase in plasma bicarbonate in the overall cohort was 2.8 mmol/L (range: 0.1–8.1) we subsequently explored the effect of Δ serum bicarbonate on Δ T₅₀-time. Our data does not support positive associations observed in in vitro [15] and observational studies [17, 18] between serum bicarbonate and T₅₀-time (Table 2, adjusted model 7). Ignoring statistical significance, the magnitude of the here observed effect is probably of little clinical relevance, because of the relatively narrow range of serum bicarbonate encountered in clinical practice. In a previous study, all-cause mortality in CKD patients with a mean T₅₀-time of 227 ± 44 was 2.2 to 4.7 (depending on adjustment set) times the mortality in CKD patients with a T₅₀-time of 434 ± 58 min. [16] Given our point estimate of 2 min change of T₅₀-time per mmol/L change of serum bicarbonate, we theoretically would have to increase the serum bicarbonate concentration by 100 mmol/L to reduce all-cause mortality, when extrapolating our results to findings reported by Smith et al. [16].

Our results are in line with a randomized cross-over study in acidotic (serum HCO₃⁻ <22 mmol/L) CKD 3b and 4 patients receiving sodium bicarbonate over 6 weeks to target a serum HCO₃⁻ of ≥ 23 mmol/L by Kendrick et al. [27]. T₅₀-time, which was a secondary outcome, was unaffected by the intervention, even though the difference between serum HCO₃⁻ in the intervention and control group was more distinct compared to our study (mean difference 2.7 mEq/L, 95% CI: 0.9, 4.6). However, they also observed a significant increase in serum phos-

Table 2. Change of T₅₀-time with respect to various laboratory parameters

	Beta	95% CI	p value
<i>Crude model</i>			
Δ serum bicarbonate	6.32	–3.51 to 16.16	0.22
<i>Adjusted model 1</i>			
Δ serum bicarbonate	5.95	–4.04 to 15.94	0.25
Δ eGFR	1.22	–2.53 to 4.96	0.53
<i>Adjusted model 2</i>			
Δ serum bicarbonate	7.12	–1.96 to 16.20	0.13
Age	–1.67	–2.91 to –0.42	0.01
<i>Adjusted model 3</i>			
Δ serum bicarbonate	5.56	–4.36 to 15.47	0.28
Δ serum magnesium	–155.35	–442.72 to 132.02	0.30
<i>Adjusted model 4</i>			
Δ serum bicarbonate	8.10	–3.30 to 19.49	0.17
Δ serum calcium	–84.14	–349.82 to 181.54	0.54
<i>Adjusted model 5</i>			
Δ serum bicarbonate	1.34	–7.83 to 10.52	0.78
Δ serum phosphate	–140.59	–225.70 to –55.49	0.003
<i>Adjusted model 6</i>			
Δ serum bicarbonate	6.23	–3.72 to 16.19	0.23
Δ serum albumin	–2.80	–13.54 to 7.94	0.61
<i>Adjusted model 7</i>			
Δ serum bicarbonate	2.22	–6.37 to 10.80	0.62
Δ eGFR	–1.11	–4.67 to 2.46	0.55
Age	–1.41	–2.55 to –0.28	0.02
Δ serum phosphate	–144.68	–237.33 to –52.03	0.01

95% CI, 95% confidence interval; Δ, change between baseline and week 4; eGFR, estimated glomerular filtration rate (mL/min per 1.73 m²); Δ serum bicarbonate (mmol/L); age (years); Δ serum magnesium (mmol/L); Δ serum calcium (mmol/L); Δ serum phosphate (mmol/L); Δ serum albumin (g/L).

phate, which is in contrast to ours and a study by Chen et al. [28]. They speculated based on animal experiments that acidosis might induce a tubular phosphate leak. Neither group allocation (Fig. 3) nor Δ serum HCO₃[–] had a significant effect on Δ serum phosphate (adjusted for Δ eGFR) in our study (data not shown).

In vitro experiments suggested that other serum electrolytes than serum bicarbonate influence the T₅₀-time: recently, Bressendorff et al. demonstrated that magnesium supplementation compared to placebo in 36 patients with CKD 3 and 4 over 8 weeks changed the T₅₀-time on average by 40 min [29]. Although the clinical relevance of the observed effect is still unclear, it is worth mentioning that the result reached statistical significance with a similar sample size and standard deviation of T₅₀-time to the here presented study. Based on that we can argue that our study was not underpowered to avoid a type II error.

Among all measured serum electrolytes, only Δ serum phosphate had a strong association with Δ T₅₀-time. An increase by 1 mmol/L of serum phosphate from baseline to week 4 led to a decrease of T₅₀-time by 145 (95% CI: –237 to –52) min. This result compares well

with several other lines of research, which had identified hyperphosphatemia levels as the number one driver of vascular calcification in CKD patients (reviewed in Ritter et al. [30]). In cell cultures high phosphate levels transform vascular smooth muscle cells into osteoblast-like cells [31], and cells from CKD patients lack inherent pathways to prevent calcification compared to healthy control cells [32]. Importantly, there is evidence that current treatment practice in CKD is hampering natural preventive mechanisms against vascular calcification in CKD patients. Zhang et al. [33] showed in 5/6 nephrectomized male Sprague-Dawley rats that acidic milieu prevents calcitriol-induced calcium absorption to vascular smooth muscles cells, which is in line with previously reported results by Mendoza et al. [34]. Similarly, alkalization in a high phosphorus environment induced mRNA and protein expression of L-type calcium channel β 3-subunit on rat vascular smooth muscle cells, furthermore suggesting increased calcium uptake [35]. In small studies in humans NH₄Cl-induced acidosis led to phosphaturia [36, 37] and the observed increase of serum phosphate after correction of metabolic acidosis with sodium bicarbonate by Kendrick et al. [27] adds another important fact to the discussion. These highly interesting aspects of the complex CKD syndrome suggest that the gradual development of metabolic acidosis with decreasing renal function could actually mitigate vascular calcification. Notably, in those animal models acidosis was induced by NH₄Cl enhanced water, which is known to be only partially comparable with human uremic acidosis [38]. However, results from analysis of the Chronic Renal Insufficiency Cohort (CIRC) suggest that there is no association between parameters of cardiac structure and serum bicarbonate after adjustment for demographics, traditional cardiovascular disease risk factors, medications, and kidney function [39]. Additionally, the risk of heart failure and mortality is actually increased in patients with persistent high serum bicarbonate levels (>26 mmol/L) compared to those with bicarbonate concentrations between 22 and 26 mmol/L [40]. In view of this complex interplay, it is worth mentioning that we observed a 3.5-times lower Δ T₅₀-time in the intervention group compared to the rescue group, although the change was only of small magnitude and the difference statistical insignificant. However, it might be thinkable, that the “mineralization paradox [41] – the inverse relation of bone mineralization and vascular calcification – in dialysis patients is partly driven by the therapeutic compensation of acidosis with high bicarbonate dialysate concentrations [42–44] in combination with vitamin D treatment [11] and insufficient control of hyperphosphatemia [45]. Furthermore, high serum bicarbonate levels are associated with higher mortality in dialysis [46] and non-dialysis CKD populations [47].

Several limitations are worth mentioning: Our study might have yielded more distinct results by a longer follow-up period, such as 8 or 12 weeks like presented by others [48, 49]. However, in theory increasing serum bicarbonate should have had an instantaneous effect on the T₅₀-time and after 4 weeks of high dose sodium bicarbonate treatment a change in T₅₀-time should have been apparent, given that our hypothesis was true.

We cannot exclude the possibility that due to multiple testing, we observed the association between Δ serum phosphate and Δ T₅₀-time out of chance.

In conclusion, our study showed no effect of a 4-week oral sodium bicarbonate supplementation on vascular calcification propensity (T₅₀-time) in patients with metabolic acidosis and CKD stage 3 to 4. In this cohort serum bicarbonate concentrations were neither at baseline nor after 4 weeks correlated with T₅₀-times. Furthermore, our study suggests that a change in serum phosphate is the most potent modulator of the T₅₀-time.

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Statement of Ethics

Subjects (or their parents or guardians) have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have nothing to disclose.

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Author Contributions

M.G., G.S.-P., and D.C. designed the study; C.A., C.S., M.F., M.G., and G.S.-P. conducted the study and collected the data; C.A., M.G., D.C., and G.S.-P. drafted the manuscript.

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