Metabolic Acidosis is Associated with Failure to Thrive and Fractures/Falls in Patients with Chronic Kidney Disease

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BACKGROUND

Chronic metabolic acidosis causes muscle wasting[1] and bone loss[2] in experimental models of chronic kidney disease (CKD). However, its association with similar clinical outcomes in epidemiological studies is unknown.

OBJECTIVE

To investigate the association of chronic metabolic acidosis and adverse muscle and bone outcomes in individuals with non-dialysis CKD Stages 3-5.

METHODS

- From electronic medical records data (Optum® EMR) spanning the years 2007 to 2017, we identified non-dialysis-dependent CKD patients (N= 51,558) with ≥ 2 serum bicarbonate tests 28–365 days apart, ≥ 3 eGFR values < 60 mL/min/1.73 m^2 and who either had ≥ 2 years of follow-up data or died during this interval.
  - The Optum® EMR Database contained HIPAA-compliant, de-identified data from a cumulative population of 81 million patients in the United States, including those with all insurance types and those who were uninsured.
- Cohorts were established of patients with two serum bicarbonate values 28–365 days apart in the same range: metabolic acidosis cohort (12 to < 22 mEq/L) and normal serum bicarbonate cohort (22 to 29 mEq/L). The index date was established as the date of the first serum bicarbonate test meeting the inclusion criteria. Serum bicarbonate and eGFR values from hospital inpatient or emergency care involving acute kidney injury weren't used. Patients without a qualifying pair of serum bicarbonate tests were excluded. Patients with metabolic acidosis were over-sampled by preferential selection to ensure adequate sample size.
- Patients were followed for 2 years for adverse outcomes using ICD codes: failure to thrive (muscle/functional outcome), and a composite of falls and hip, spine, or pathological fractures (bone outcome).
- We compared bone and muscle/functional outcomes in patients with non-dialysis CKD with and without metabolic acidosis.
- The effect of serum bicarbonate on bone and muscle outcomes was examined by logistic regression over the 2-year period of required data and by Cox proportional hazards models utilizing all available follow-up data (mean 4 years, max 10 years). Potential confounders included age, sex, race, eGFR, diabetes, hypertension, heart failure, coronary artery disease, peripheral vascular disease, hemoglobin and serum albumin.

RESULTS

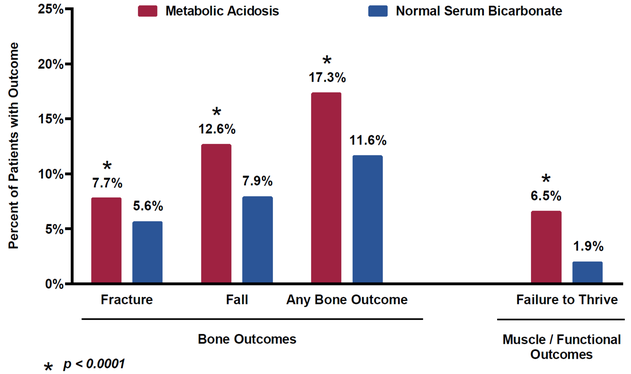
- 51,558 patients qualified for this longitudinal observational study. Patients with metabolic acidosis at baseline were younger and had more advanced kidney disease and a higher comorbidity burden (**Table 1**).

Table 1. Demographic and Baseline Characteristics

	Total Study Population (N = 51,558)	Metabolic Acidosis Cohort (N = 17,350)	Normal Serum Bicarbonate Cohort (N = 34,208)	*P* Value
Age (y), mean (SD)	72.9 (11.5)	70.3 (13.3)	74.3 (10.3)	<0.0001
Sex (F) (%)	53	52	53	0.0468
Race (%)				
African American	10	15	7	<0.0001
Asian	2	2	2	<0.0001
Caucasian	82	74	85	<0.0001
Other / Unknown	7	9	5	<0.0001
Comorbidities / Conditions (%)				
Hypertension	62	74	55	<0.0001
Diabetes	31	43	26	<0.0001
Coronary Artery Disease	28	36	24	<0.0001
Edema	25	40	18	<0.0001
Peripheral Vascular Disease	19	29	15	<0.0001
Heart Failure	19	30	14	<0.0001
Charlson Comorbidity Index (CCI) Weighted, mean (SD)	2.3 (2.7)	3.5 (3.1)	1.7 (2.3)	<0.0001
ACE Inhibitors and ARBs Prescription (%)	23	29	20	<0.0001
Alkali Treatment (%)	2	3	1	<0.0001
Serum Bicarbonate (mEq/L), mean (SD)	24.0 (3.6)	19.7 (1.1)	26.1 (2.0)	<0.0001
eGFR (mL/min/1.73 m^2), mean (SD)	41.2 (12.1)	37.2 (13.3)	43.2 (10.9)	<0.0001
Hemoglobin (g/dL), mean (SD)	12.2 (2)	11.3 (2.1)	12.6 (1.8)	<0.0001
Serum Albumin (g/dL), mean (SD)	3.7 (0.6)	3.5 (0.7)	3.9 (0.5)	<0.0001
Urinary ACR (mg/g), mean (SD)	190 (554)	277 (692)	127 (414)	<0.0001

P-values are for the comparison of the metabolic acidosis cohort with the normal serum bicarbonate cohort

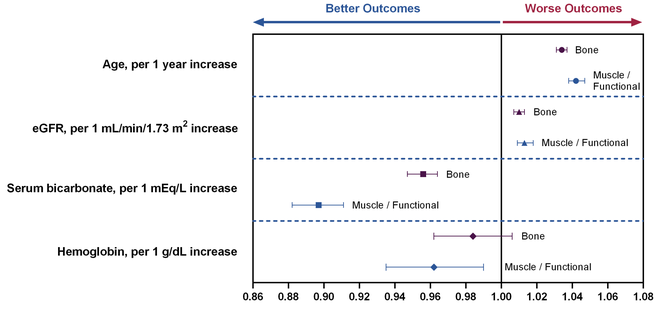
Figure 1. Incidence of Adverse Bone Outcomes and Muscle/Functional Outcomes at 2 Years, Metabolic Acidosis vs. Normal Serum Bicarbonate (Unadjusted)



* *p < 0.0001*

- The incidence of fractures or falls was significantly higher in patients with metabolic acidosis during the 2-year follow-up compared to patients with normal serum bicarbonate: bone fractures 7.7% vs. 5.6%, p<0.0001; falls 12.6% vs. 7.9%, p<0.0001 (**Figure 1**).
- The incidence of failure to thrive was significantly higher in patients with metabolic acidosis during the 2-year follow-up compared to patients with normal serum bicarbonate: muscle outcomes: 6.5% vs. 1.9%, p<0.0001 (**Figure 1**).

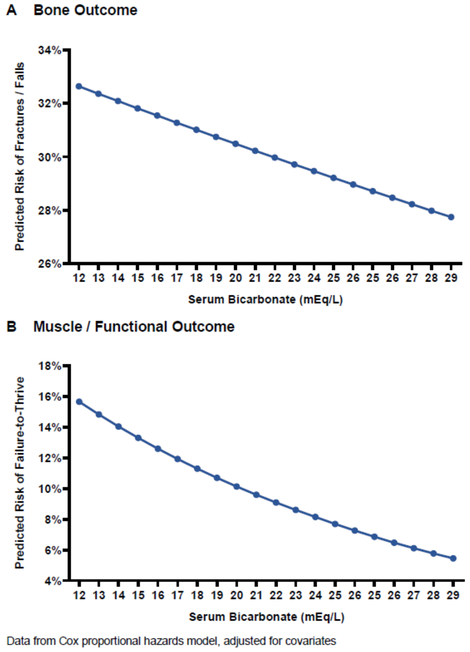
Figure 2. Adjusted Odds Ratios for 2-year Incidence of Adverse Bone and Muscle/Functional Outcomes



Hemoglobin was adjusted for interactions with race and sex to improve bone model fit. Results are shown for Caucasian females.
Continuous Variable Not Shown: Serum Albumin, per 1 g/dL Increase, Odds Ratio (95% CI):
Bone = 0.824 (0.780, 0.871), Muscle/Functional = 0.573 (0.524, 0.625)

- Serum bicarbonate was a significant predictor of both types of outcomes. Each 1 mEq/L increase in serum bicarbonate was associated with a 5% decrease in bone fractures/falls risk (odds ratio: 0.948; CI: 0.939-0.956), and a 12% decrease in failure to thrive over a 2-year period (odds ratio: 0.883, CI: 0.869-0.898), independent of age, sex, race, eGFR, diabetes, hypertension, heart failure, coronary artery disease, peripheral vascular disease, hemoglobin and serum albumin (**Figure 2**).

Figure 3. Predicted Frequency of Adverse Bone and Muscle Outcomes by Serum Bicarbonate Level in Cox Proportional Hazard Models - up to 10 Years



Data from Cox proportional hazards model, adjusted for covariates

- Within the serum bicarbonate range of 12 to 29 mEq/L, there was a linear relationship of serum bicarbonate with predicted absolute risk of diagnoses of bone fractures or falls and of failure to thrive. (Figures 3A and 3B).
- Hazard ratios per 1 mEq/L increase in serum bicarbonate were 0.991 (95% CI: 0.986, 0.997) for bone fractures/falls (**Figure 3A**) and 0.946 (95% CI: 0.935, 0.956) for failure to thrive (**Figure 3B**), both p<0.0001, in time-to-event analyses with up to 10 years (mean 4 years) of follow-up.

CONCLUSION

In this analysis of > 51,000 non-dialysis CKD patients followed for up to 10 years, chronic metabolic acidosis was independently associated with increased incidence of failure to thrive and the composite endpoint of fractures (hip, spine, or pathological) and falls.

References

1. May RC, Kelly RA, Mitch, WE. *J Clin Invest.* 79:1099–1103, 1987.
2. Bushinsky DA, Wolbach W, et al. *J Bone Miner Res.* 8:93-102, 1993.

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