Metabolic Acidosis in the Renal Replacement Therapy Patient: Should We Treat More Aggressively?

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A Confusion of Terms

Acidosis vs Acidemia

Alkalosis vs Alkalemia

Acidosis: A process promoting the accumulation of acid in the body (or in blood)

Alkalosis: A process promoting the loss of acid from the body (or blood)

Acidemia: The presence of excessive amounts of acid in the blood (or body)

Alkalemia: The presence of abnormally low amounts of acid in the blood orbody

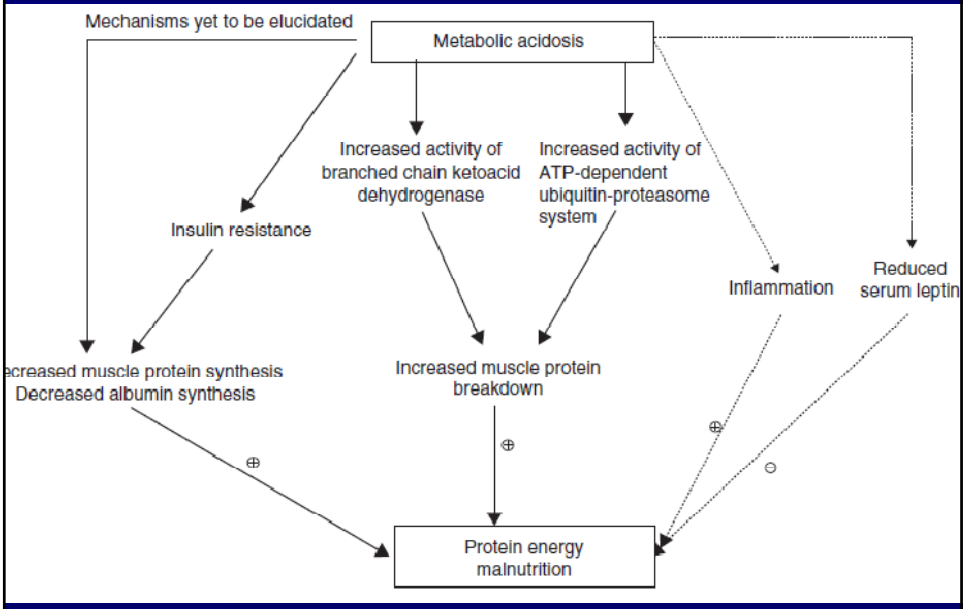
Adverse Systemic Effects of Metabolic Acidemia - Summary

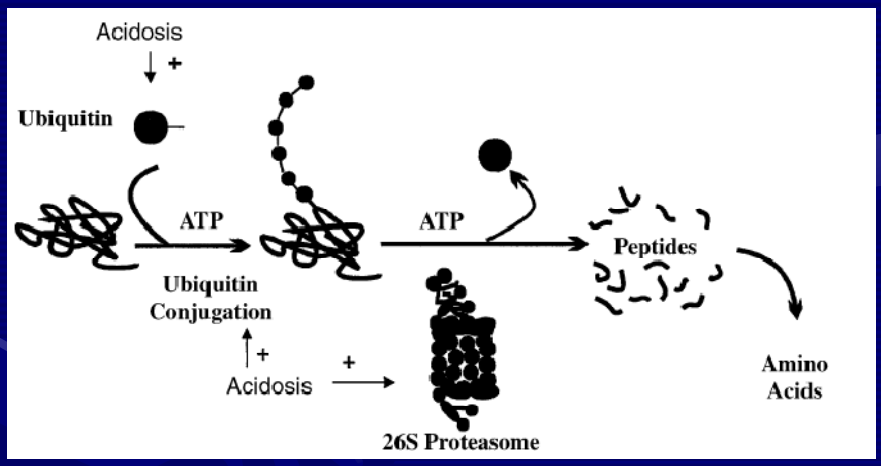
1. Nutritional disorders – reduced protein mass
2. Bone loss
3. More rapid progression of kidney failure
4. Multiple endocrine disorders
5. Systemic inflammation
6. Increased cytokine levels
6. Increased β2-Microglobulin
7. Hypertriglyceridemia
8. Hypotension
9. Malaise

Adverse Systemic Effects of Metabolic Acidemia (1)

1. Nutritional Effects
   - i. Increased protein catabolism
   - ii. Decreased protein synthesis
   - iii. Insulin resistance
   - iv. Systemic inflammation
   - v. Decreased serum leptin concentrations

Mechanisms by which Metabolic Acidemia can Engender Protein Wasting





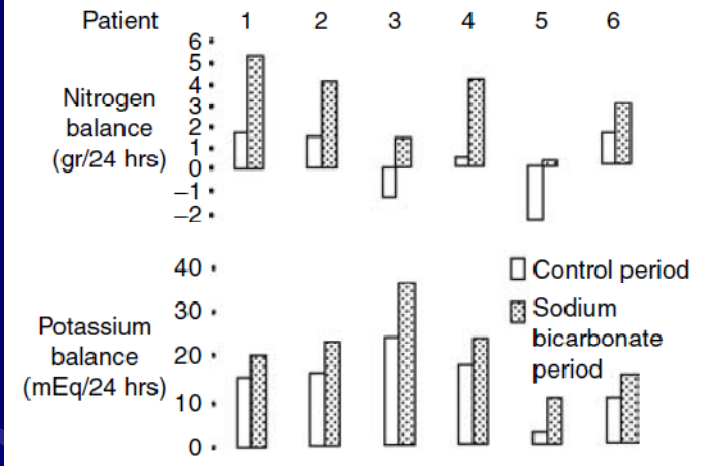


Fig. 1. Nitrogen and potassium balance in 6 nondialyzed uremic patients pre- and postsupplementation with sodium bicarbonate. (From [4]).

Papadoyanakis et al. AJCN 1984;40:623-627

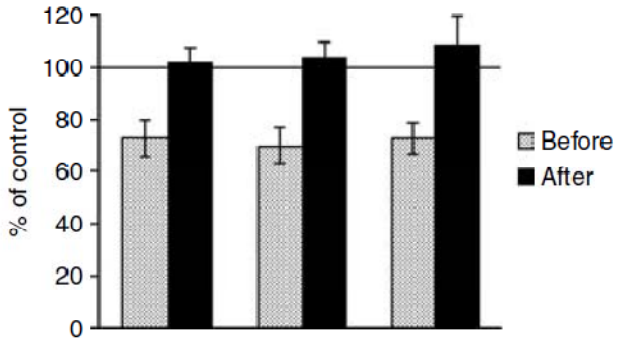


Fig. 2. Branched chain amino acid levels measured in 9 hemodialysis patients before and after 6 months of bicarbonate treatment. A significant increase in the concentration of valine, leucine, and isoleucine was seen on correction of the metabolic acidosis. (From [4]).

Papadoyanakis et al. AJCN 1984;40:623-627

Table III. Albumin Synthesis Rates

	FSR	
	Control	Acidosis
Low dose group		
1	10.1	9.3
2	8.7	7.9
3	11.0	7.9
4	9.8	8.5
Mean±SD	9.9±1.0	8.4±0.7
High dose group		
5	9.4	7.5
6	7.0	5.8
7	9.4	6.9
8	7.4	5.1
Mean±SD	8.3±1.3	6.3±1.1*
Total	9.1±1.4	7.4±1.4‡

Albumin synthesis of the subjects in the control period and during metabolic acidosis, expressed as FSR in percent per day (%/d). * $P < 0.01$; ‡ $P < 0.001$ versus control period.

Ballmer et al. J Clin Invest 1995;95:39-45

Table IV. Hormone Plasma Concentrations

	Control				Acidosis			
	IGF-I	fT_4	T_3	TSH	IGF-I	fT_4	T_3	TSH
Mean±SD	42.5±15.4	17.6±1.6	2.3±0.5	2.2±1.0	31.6±14.7*	15.9±1.7*	2.0±0.5*	2.1±1.1

Plasma concentrations of insulin-like growth factor-I (IGF-I in nmol/liter), free thyroxine (fT_4 in pmol/liter), tri-jodthyronine (T_3 in nmol/liter), and thyroid-stimulating hormone (TSH in mU/liter) in the control period and during metabolic acidosis. * $P < 0.05$ versus control period.

Ballmer et al. J Clin Invest 1995;95:39-45

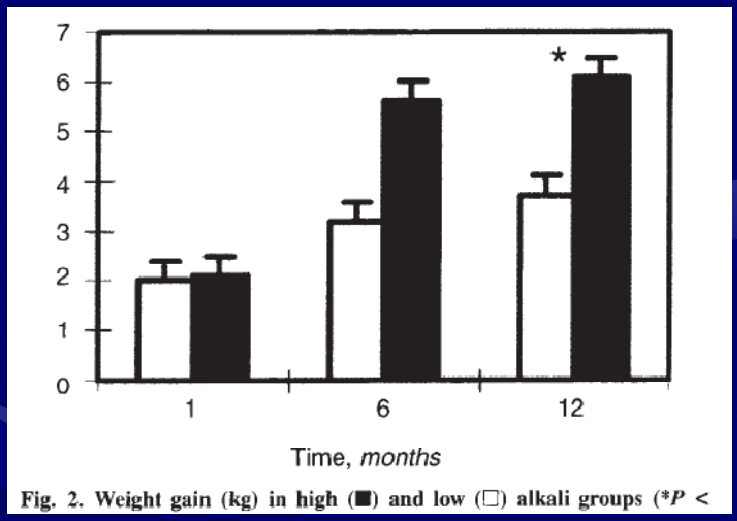


Fig. 2. Weight gain (kg) in high (■) and low (□) alkali groups (*P <

Stein et al. Kidney Int 1997;52:1089

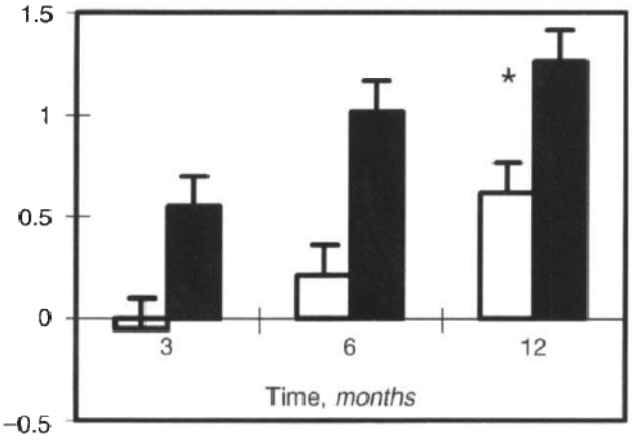


Fig. 3. Midarm circumference gain (cm) in high (■) and low (□) alkali groups (*P < 0.05).

Stein et al. Kidney Int 1997;52:1089

Adverse Systemic Effects of Metabolic Acidemia (2)

2.Bone Disease

i.Direct Effects

- -Physicochemical dissolution of bone
- -Decreased osteoblast function
- -Increased osteoclast function

ii.Indirect Effects

- -Increased release of PTH
- -Increased number of PTH receptors
- -Increased binding of PTH to its receptor
- -Reduced activity of 1-α hydroxylase

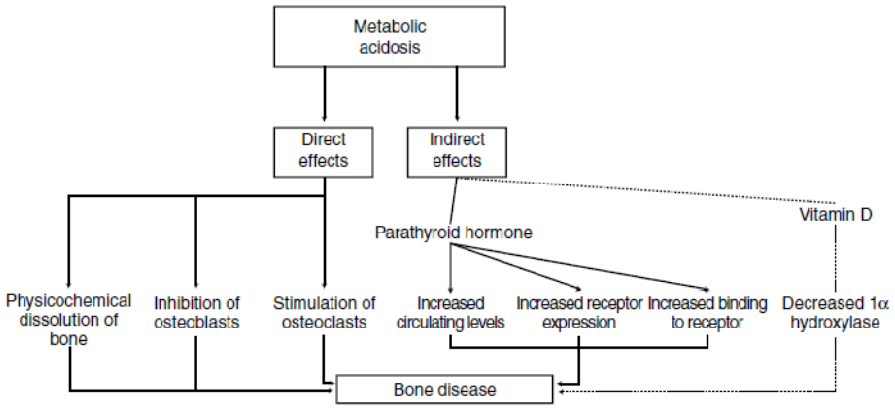


Fig. 4. The various mechanisms by which metabolic acidosis may contribute to bone disease. (From [3]).

Adverse Systemic Effects of Metabolic Acidemia (3)

3. More Rapid Progression of CKD

Adverse Systemic Effects of Metabolic Acidemia (4)

3. Increased Generation and Release of β2-Microglobulin
4. Hypertriglyceridemia
5. Resistance to Catecholamines
6. Hypotension
7. Malaise

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NKF or KDIGO Guidelines on Nutrition and on Bone Mineral Disease

I n CKD patients, the serum bicarbonate should be maintained at or above 22 mEq/L

What is the Optimal pH for Maintaining Healthy Nutritional Status?

Goal Arterial pH

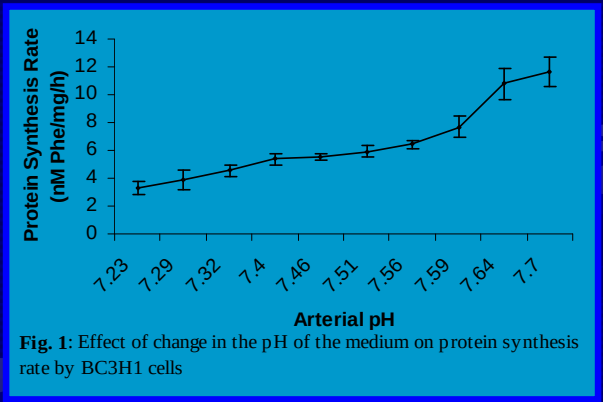


Fig. 1: Effect of change in the pH of the medium on protein synthesis rate by BC3H1 cells

Ding, JASN (abstr) '98

Similar results reported by England et al, Am J Physiol '91

Does Increasing Arterial pH Improve Nutritional Status In ESRD?

Criticism, by skeptics of previous studies:

- Improvement in nutritional status, as assessed by change in body weight and anthropometry, may be confounded by increased total body water (with sodium bicarbonate treatment).

Most studies have used serum total CO_2 binding as a measure of acidosis.

The entire range of arterial pH from 7.37 through 7.44 has been assumed to be both normal and healthy.

What Is The Optimal Arterial pH For Protein Balance in Automated Peritoneal Dialysis Patients?

Hypothesis:

In maintenance dialysis pts. undergoing automated peritoneal dialysis, an arterial pH of 7.43-7.45 is associated with a significantly greater net positive protein balance than an arterial pH of 7.36-7.38

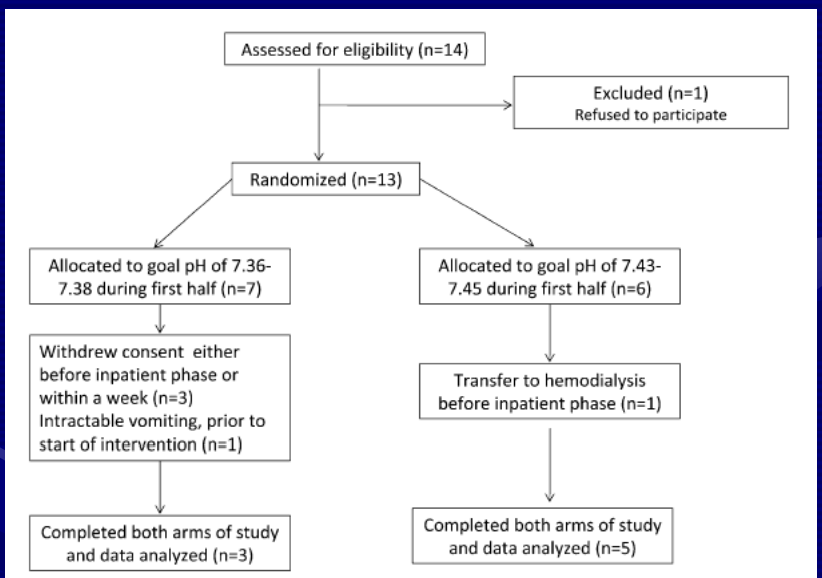


FIGURE 2. Chart summarizing the flow of patients throughout the clinical trial.

Demographic, clinical, and peritoneal dialysis therapy characteristics of the 8 study subjects

Characteristic	Value
Age (y)	43.1 ± 15.3[1]
Sex (M/F)	5/3
Race-ethnicity (*n*)	
Latino	6
Asian	1
Black	1
History of diabetes mellitus (*n*)[2]	3
Peritoneal dialysis vintage (mo)	19.0 (58.4)[3]

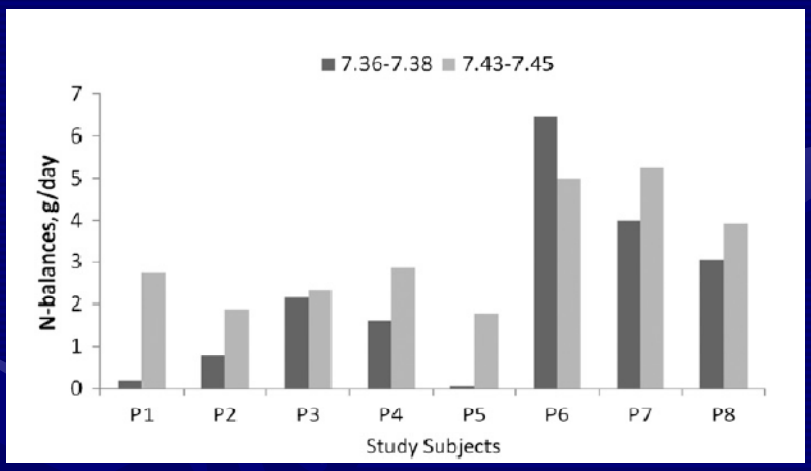
Summary of nitrogen balances for the 8 study subjects

	Low-normal pH	High-normal pH	*P* value[1]
Final arterial pH	7.37 ± 0.01[2]	7.44 ± 0.02	<0.001
Intake (g N/d)			
Diet	12.57 ± 1.88	12.54 ± 1.79	0.73
Medications[3]	2.31 ± 0.41	2.32 ± 0.42	0.32
Total	14.88 ± 1.89	14.86 ± 1.80	0.82
Output (g N/d)			
Dialysate	9.21 ± 3.30	7.99 ± 2.73	0.04
Urinary[4]	0.04 (0.21)[5]	0.12 (1.00)	0.02
Fecal	3.01 ± 0.67	2.66 ± 0.87	0.26
Total	12.64 ± 3.15	11.35 ± 1.75	0.06
Adjustment in nitrogen retention for changes in serum urea nitrogen and body weight (g N/d)	0.07 (0.54)	0.11 (0.63)	0.26
Net nitrogen balance (g/d)	2.29 ± 2.18	3.22 ± 1.37	0.06

[1] Significance of difference between means tested by paired *t* test and of medians by Wilcoxon's signed-rank test.

[2] Mean ± SD (all such values).

[3] Includes ammonium chloride and/or ammonium acetate in the 4 patients who received them.



Summary of urine and serum biochemical measures at baseline and at the end of the 2 study periods[1]

	Baseline	Low-normal pH	High-normal pH	*P* value[2]
Final arterial pH	—	7.37 ± 0.01[3]	7.44 ± 0.02	<0.001
Urine volume (mL/d)[4]	—	16.9 (84.4)[5]	41.1 (335.3)	0.03
Urinary urea nitrogen (mg/d)[4]	—	15.3 (129.5)	78.2 (668.3)	0.25
Urinary urea clearance (mL/min)[4]	—	0.02 (0.14)	0.09 (1.02)	0.03
Urinary creatinine clearance (mL/min)[4]	—	0.08 (0.51)	0.16 (1.4)	0.35
Urine protein excretion (mg/d)[4]	—	47 (143)	148 (457)	0.12
Venous bicarbonate (mEq/L)	23.0 ± 2.6	18.9 ± 2.2	24.6 ± 2.6	0.002
Arterial pCO_2 (mm Hg)	37.5 ± 3.6	35.9 ± 3.0	41.8 ± 3.7	0.001
Serum urea nitrogen (mg/dL)	55.0 ± 17.1	64.4 ± 20.2	54.1 ± 13.7	0.01
Serum creatinine (mg/dL)	13.7 ± 4.6	13.6 ± 4.1	12.9 ± 3.5	0.18

Summary of [^{13}C]leucine turnover studies in the 8 study subjects[1]

	Low-normal pH	High-normal pH	*P* value[2]
	$\mu mol \cdot kg^{-1} \cdot h^{-1}$	$\mu mol \cdot kg^{-1} \cdot h^{-1}$	
Final arterial pH	7.37 ± 0.01	7.44 ± 0.02	<0.001
Fasting			
Leucine flux	77.7 ± 10.4	84.0 ± 13.8	0.02
Leucine oxidation	10.0 ± 2.6	10.8 ± 4.7	0.54
Protein synthesis	67.7 ± 9.0	73.3 ± 12.0	0.01
Protein degradation	77.7 ± 10.4	84.0 ± 13.8	0.02
Protein balance	−10.0 ± 2.6	−10.8 ± 4.7	0.54
Postprandial			
Leucine flux	90.2 ± 17.4	95.9 ± 13.7	0.17
Leucine oxidation	15.9 ± 3.5	17.2 ± 6.2	0.63
Protein synthesis	73.6 ± 16.4	78.7 ± 13.0	0.23
Protein degradation	29.0 ± 24.9	35.2 ± 15.2	0.22
Protein balance	44.6 ± 11.7	43.5 ± 7.3	0.77

[1] All values are means ± SDs.

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Take-Home Message

Acidemia has many pervasive effects that are detrimental to health.

Even very mild acidemia appears to have adverse effects.

Take-Home Questions

1. What is the optimal arterial blood pH for ESRD patients?
2. How often should we monitor acid levels in ESRD?
3. Is monitoring venous serum bicarbonate an adequate measure?
4. Is arterial blood pH the best standard for monitoring body acid levels?
5. What is the best source of alkali – what about the hazards of citrate if we need to give oral alkali?


The End