New aspects of acid-base disorders

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My guiding thoughts, courtesy of HL Mencken

Life is a struggle,

Not against sin,
Not against the money power,
But against hydrogen ions.
Acidosis is a constant risk

- Lipids and carbohydrates metabolism produces CO$_2$
  - $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}^+ + \text{HCO}_3^-$
  - 10 mmol per min
    - Hold your breath for 1 min, pCO$_2$ increases ~10 mm Hg
- Protein metabolism
  - Phosphoric and sulfuric acid production
    - 0.8 mmol/kg/day
    - 56 mmol/d for 70 kg individual
    - 1 pint of pH 1 HCl every day!
Why and how do the kidneys “struggle” against $\text{H}^+$?

- Kidneys excrete acidic urine
  - pH 4.4, $[\text{H}^+] = 40 \mu\text{mol} \text{ L}^{-1}$

- Volume to excrete daily acid production
  - $V = \text{Amnt} \div \text{Concentration}$
  - $V = 56 \text{ mmol H}^+ / \text{d} \div 40 \mu\text{mol/L}$
  - $= 1.4$
  - $= 1400 \text{ L (!)}$
  - 1440 minutes in a day
Why and how do the kidneys “struggle” against H⁺?

- Net acid excretion =
  - Titratable acids
  - Ammonia

- Titratable acid
  - Luminal buffers accept H⁺
  - Secreted H⁺ + filtered HPO₄⁻ → H₂PO₄⁻
  - H⁺ binding sites saturated at pH ≤ 6

- Ammonia
  - Glutamine → 2 NH₄⁺ + 2 HCO₃⁻

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### Net Acid Excretion - Basal and Acid Stimulated (~125 mmol d⁻¹)

<table>
<thead>
<tr>
<th></th>
<th>Excretion (mmol d⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>32</td>
</tr>
<tr>
<td>Acidosis, Day 1</td>
<td>50</td>
</tr>
<tr>
<td>Acidosis, Day 3</td>
<td>53</td>
</tr>
<tr>
<td>Acidosis, Day 5</td>
<td>48</td>
</tr>
</tbody>
</table>

What is NH₃?

• Gas molecule
  ➢ Boiling point -33°C

• Traditional view
  ➢ Uncharged
  ➢ Freely diffusible across lipid membranes

• Actually ...
  ➢ Polar molecule
  ➢ High water solubility
  ➢ Limited lipid solubility

Space-filling, electrostatic models generated using Avogadro, ver 1.0.1, software and molecular coordinates from NCBI Pubchem project, CID 222 (NH₃) and CID962 (H₂O)
What is NH₃?

- Rhesus glycoproteins
  - Related to Rhesus antigens on RBC
  - Specific NH₃ transporters
  - Critical role in renal ammonia and H⁺ excretion

Space-filling, electrostatic models generated using Avogadro, ver 1.0.1, software and molecular coordinates from NCBI Pubchem project, CID 222 (NH₃) and CID962 (H₂O)
How do I feel talking about clinical aspects of acid-base disorders?
Why care about chronic metabolic acidosis?
Metabolic acidosis is common in patients with CKD

Prevalence of metabolic acidosis by eGFR (ml/min/1.73m²)

- 60-89 eGFR: 3%
- 50-59 eGFR: 4%
- 40-49 eGFR: 5%
- 30-39 eGFR: 11%
- 20-29 eGFR: 21%
- <20 eGFR: 40%

What are the risks of treating chronic metabolic acidosis in people with CKD?

- **NaHCO₃ and/or Na-citrate**
  - Na⁺ load
    - Worsening of BP control?
    - Worsening of CHF?
    - Worsening of proteinuria?
    - Worsening progression of CKD?

- **K-citrate**
  - Worsening of hyperkalemia?
  - Risk of Al⁺³ overload
    - Major barrier to intestinal Al⁺³ uptake is charge
    - Citrate complexes with Al⁺³ in the gastrointestinal tract
    - Increases Al⁺³ absorption ~100x
Should we treat metabolic acidosis in CKD patients?

• Patients studied
  ➢ Stage IV CKD
  ➢ Plasma HCO$_3^-$
    • > 16 and < 20
  ➢ Stable medical condition

• Excluded
  ➢ Malignancy
  ➢ Morbid obesity
  ➢ Poorly controlled hypertension (> 150/90 despite ≥ 4 meds)
  ➢ Overt CHF

• Treatment
  ➢ Oral NaHCO$_3$, dosed to serum HCO$_3^-$ ≥ 23
Sodium bicarbonate improved metabolic acidosis

![Graph showing the improvement in plasma bicarbonate levels with sodium bicarbonate therapy compared to control. The graph indicates a statistically significant decrease in metabolic acidosis with sodium bicarbonate therapy, as indicated by the marked decrease in plasma bicarbonate levels over the duration of therapy (months). The graph also highlights the statistically significant reduction in metabolic acidosis with sodium bicarbonate therapy at 6, 12, 18, and 24 months, as indicated by the asterisks and P-values.]
Sodium bicarbonate did not worsen BP
Sodium bicarbonate did not worsen proteinuria
Sodium bicarbonate slowed progression of CKD

[Graph showing creatinine clearance over months for sodium bicarbonate and control groups, with statistical significance indicated.]
Sodium bicarbonate decreased development of ESRD

Sodium bicarbonate improved plasma albumin

![Bar chart showing plasma albumin levels at different months with the control and bicarbonate groups.](chart.png)
Big muscles are better than small ones ...
Sodium bicarbonate increased skeletal muscle mass

Control
Bicarbonate

P < 0.05
P < 0.0001

Mid-arm muscle circumference (cm)

Months
0
12
24

CKD and metabolic acidosis

- Common
- Easily treatable
- Safe and beneficial to treat
  - Double-check results if $\text{HCO}_3^- < 20 \text{ mmol/L}$
  - Start $\text{NaHCO}_3$, 1300 mg bid
    - Titrate, as needed, to $\text{HCO}_3^-$ of 24 mmol/L
- What determines who develops CKD-associated metabolic acidosis?
Endogenous acid production predicts serum HCO$_3$
Endogenous acid production predicts changes in GFR
Why do some with CKD develop metabolic acidosis?

- Inaccuracies in eGFR determination
- Factors other than GFR predict acid excretion
- Dietary differences in endogenous acid production
  - Animal-based proteins → $H^+$ production
  - $K^+$-containing fruits and vegetables → $HCO_3^-$ production
Endogenous acid production predicts changes in GFR

Net Endogenous Acid Production

- Quartile 1
- Quartile 2
- Quartile 3
- Quartile 4

Difference in iGFR slope compared with lowest quartile (ml/min/1.73m²)

P-trend = 0.01

Endogenous acid production predicts changes in GFR

- Net Endogenous Acid Production
  - Quartile 1
  - Quartile 2
  - Quartile 3
  - Quartile 4

- Protein
  - Quartile 1
  - Quartile 2
  - Quartile 3
  - Quartile 4

Difference in iGFR slope compared with lowest quartile (ml/min/1.73m²)

P-trend = 0.01
P-trend = 0.37
Endogenous acid production predicts changes in GFR

Net Endogenous Acid Production
- Quartile 1
- Quartile 2
- Quartile 3
- Quartile 4

Protein
- Quartile 1
- Quartile 2
- Quartile 3
- Quartile 4

Potassium
- Quartile 1
- Quartile 2
- Quartile 3
- Quartile 4

Difference in iGFR slope compared with lowest quartile (ml/min/1.73m²)

P-trend = 0.01
P-trend = 0.37
P-trend = 0.07
Modest hyperkalemia is safer than generally thought

Does renal acid excretion exactly equal acid production?

Endogenous acid production (mmol, total, over 3-8 days)

Net Acid Excretion (mmol, total, over 3-8 days)

Renal acid excretion may not equal acid production in patients with CKD

22 year old male with chronic glomerulonephritis and sickle cell anemia with BUN 58 and two year history of acidosis.

Is acid production balanced by acid excretion with normal kidneys?

Metabolic acidosis induces renal calcium losses

Effects of chronic metabolic acidosis on bones

- Alkali content in bones is 5x content in all body fluids
- Acidosis
  - Stimulates bone resorption
  - Represses bone formation
  - Calcium released during bone resorption excreted by kidneys

JA Bettice, AJP Renal 247:F326-30, 1984
Aging leads to chronic, mild metabolic acidosis

- Low bone mineral density is present in 50% of postmenopausal women.
- Could age-related acid-base changes contribute to low bone density?

Can oral alkali therapy improve bone metabolism in post-menopausal women?

- 18 post-menopausal women
- Control diet (per 60 kg) for 6 days
  - Ca$^{+2}$, 16 mmol
  - Protein, 1.6 gm/kg
  - Na$^{+}$, 119 mmol
  - K$^{+}$, 59 mmol
- Treatment
  - KHCO$_3$, 1-2 mmol/kg
  - 18 days

Alkali administration decreases urinary Ca$^{+2}$ excretion

Is there a long-term benefit to alkali therapy?

- 181 non-vegetarian, post-menopausal women
- All had low lumbar spine BMD
  - T score, <-1 and >-4
- Exclusion criteria
  - Cr > 120 µmol/L
  - Medications: glucocorticoids, thiazide or K-sparing diuretics, NSAID, Cox-2,
  - Osteoporotic therapy within last 3 years
- Randomized
  - Treatment, K-citrate (Urocit-K), 10 mmol x3 per day
  - Control, KCl, 10 mmol x3 per day

Alkali administration decreases urinary calcium excretion

Alkali administration improves bone density

Similar effects on femoral neck and hip

Alkali administration improves bone density

% Change BMD
L_2 - L_2

% Change BMD
Femoral Neck

% Change BMD
At Hip

K Citrate therapy also decreases blood pressure

Summary

- Metabolic acidosis is common in CKD
  - Treatment with NaHCO₃ improves multiple outcome parameters
- Dietary K⁺ intake in CKD patients predicts
  - Serum HCO₃⁻
  - Stability of CKD
- In post-menopausal women with low bone mineral density
  - Treatment with K-citrate
    - Improves bone density
    - Lowers blood pressure