Epidemiology + Pathogenesis
of Metabolic Acidosis in Chronic Kidney Disease

Introduction

Prevalence
Affects ~15% of all CKD patients with prevalence increasing in later stages of CKD.

Definition
A condition in which the body has an acid content that is too high to support good health, defined as a serum bicarbonate <22 mEq/L in a patient.

Mechanism

Kidney acid excretion is decreased in chronic kidney disease due to reduced nephron mass.

Along the Nephron
HPO₄²⁻ binds to secreted H⁺. When urine pH ≤5.5, virtually all phosphate is protonated and buffers like uric acid and creatinine contribute to titratable acid excretion.

Thick Ascending Limb
15% of filtered bicarbonate reabsorbed.
NH₄⁺ enters cells by NKCC2 (Na⁺-K⁺-Cl⁻ cotransporter 2).
NH₄⁺ enters interstitium by NHE4 (sodium-hydrogen exchanger 4) and generates interstitial NH₄⁺ concentration gradient.

Proximal Tubule
~80% of filtered bicarbonate reabsorbed.
Glutamine metabolism yields NH₄⁺ and HCO₃⁻.
NH₄⁺ enters urinary space by NHE3 (sodium-hydrogen exchanger 3) or H⁺/ATPase (proton pump).

Collecting Duct
NH₃ and H⁺ recombine to form NH₄⁺, which is secreted into urine.

Ammonium (NH₄⁺)

Produced mainly in proximal tubule from glutamine metabolism.

Glutamine is mainly from diet and muscle protein degradation.

Excreted in urine as major adaptive kidney response to acid load.

Titratble Acids

Urinary buffers derived from the systemic circulation.

The principal titratable buffer is HPO₄²⁻ (90% of titratable acid excretion as H₂PO₄⁻).

REFERENCES

Developed with support from Tricida
Content compiled by Dr Michelle Lim @whatsthefr
CONSEQUENCES (1)

of Metabolic Acidosis in Chronic Kidney Disease

**INTRODUCTION**

Prevalence
Affects ~15% of all CKD patients with prevalence increasing in later stages of CKD

Currently Under-treated
Only 2.7% of patients with CKD and serum bicarbonate ≤22 mEq/L receive oral alkali

Why Should We Treat?
Metabolic acidosis is associated with faster progression of CKD and increased mortality.
Multiple studies have shown that treatment can slow the decline in kidney function.

**PROGRESSION OF CKD**

Metabolic Acidosis

Increase in mediators in response to H+ stress

- Angiotensin II
- Endothelin-1 & Aldosterone
- Intrakidney ammonium

Complement Activation

Tubulointerstitial injury and fibrosis

Progression of CKD

**REFERENCES**


**Angiotensin II**

Can trigger interstitial inflammation, fibrosis, tubular atrophy, and proteinuria that progressively reduces kidney function

Enhances ammoniagenesis and kidney production of endothelin-1 and aldosterone, therefore possibly accelerating progression of kidney dysfunction

This can be reduced by alkali supplementation and consumption of base-producing foods, which can then slow the rate of eGFR decline in patients with CKD

**Endothelin-1 (ET-1) and Aldosterone**

Sustained elevated ET-1 levels are associated with increased tubulointerstitial damage, inflammation and fibrosis, leading to increased glomerular permeability and overall GFR decline

Aldosterone generation (in response to stimulation of intrakidney renin-angiotensin-aldosterone system) increases distal nephron acidification and causes hemodynamic and profibrotic effects that promote kidney damage

Alkali supplementation was shown to ameliorate kidney injury due to ET-1 and reduced kidney cortical aldosterone production (in a rat remnant kidney model)

**Ammoniagenesis**

Ammonia reacts with complement C3 to form a convertase that activates the alternative complement pathway, increases inflammation and tubulointerstitial damage

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CONSEQUENCES (2)
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PROTEIN CATABOLISM

Metabolic Acidosis

- Pro-inflammatory cytokines
- Muscle pH
- Glucocorticoids

Activation of ubiquitin-proteasome pathway

Caspase-3 proteolysis

Insulin/IGF-1 signalling

Muscle Protein Degradation + Wasting

Characterized by increased muscle turnover rate and atrophy of type II muscle fibers
Associated with increased muscle protein degradation without a change in muscle protein synthesis

Muscle Wasting

Administration of alkali supplementation to patients with CKD not yet on dialysis or those on maintenance dialysis increased lean body mass, improved muscle strength and dietary protein intake, reduced protein catabolic rate, increased serum albumin levels, and improved physical functioning

BONE DISEASE

pH of interstitial fluid of bone
Systemic pH
Intracellular pH of osteoclasts and osteoblasts

Increased dissolution of bone mineral
Decreased bone formation
Increased cell-mediated bone resorption

Osteomalacia
Osteitis fibrosa cystica

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CONSEQUENCES (3)
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ENDOCRINE ABNORMALITIES

Metabolic Acidosis
Decreased binding of insulin to its cognate receptor due to acidic environment
Interference with insulin-induced intracellular signalling by suppression of PI3K (phosphoinositide 3-kinase) activity in muscle

Decreased Insulin Sensitivity
Insulin resistance correlated with severity of metabolic acidosis in patients with CKD without diabetes

Thyroid Function
Induction of metabolic acidosis in humans with normal kidney function showed signs of hypothyroidism
Patients with CKD demonstrated reduced plasma T3 and T4 levels with normal thyroid stimulating hormone and a blunted response to thyrotropin
Correction of metabolic acidosis in hemodialysis patients restored plasma T3 levels

COGNITION

A lower serum bicarbonate level is independently associated with lower performance in tests evaluating global cognitive / executive function

Proposed mechanisms of acidosis-induced neuronal dysfunction include:
Inhibition of NMDA (N-methyl-D-aspartate)-activated currents by acidosis leading to overexcitation of neural networks
Acidosis induced by a Western diet (irrespective of eGFR) promoting neural excitotoxicity and subsequent cognitive impairment

REFERENCES
**DIETARY MODIFICATIONS**

in Metabolic Acidosis and Chronic Kidney Disease

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**INTRODUCTION**

**Current Guidelines**

To aim for a normal serum bicarbonate level (22-29 mEq/L)

**How Can We Achieve This?**

Reduce endogenous acid production by promoting a **base-producing diet** and minimizing intake of animal protein

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**MECHANISM**

- Decreased GFR
- **Base-producing diet**
- **H⁺** Hydrogen ion accumulation
- Release of mediators of the adaptive response to H⁺ stress (kidney ammonia, Ang II, ET-1, aldosterone)
  - **H⁺** Increased urine H⁺ excretion per remaining nephron
  - **GFR** Further reduction of GFR
  - **Increased kidney interstitial inflammation and fibrosis**

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**EVIDENCE**

A base-producing diet increased serum bicarbonate levels, reduced urine angiotensinogen and preserved eGFR compared to usual diet

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**BASE-PRODUCING DIETS**

This includes most fruit and vegetables

- Exercise caution regarding potassium content

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**CONCLUSION**

A **base-producing diet** of mostly fruit & vegetables can be an effective option for **correcting metabolic acidosis** and preserving kidney function

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**REFERENCES**


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TREATMENT: BICARBONATE SUPPLEMENTATION
for Metabolic Acidosis in Chronic Kidney Disease

INTRODUCTION

When Should Treatment Be Started?

This depends on the severity of acidosis, blood pressure, volume status and presence of hyperkalemia. Treatment is reasonable with metabolic acidosis (HCO₃⁻ <22 mEq/L) if no reversible causes found.

What Are Our Options?

Supplements like sodium bicarbonate and sodium citrate are the only currently available options for management of metabolic acidosis.

MAIN SIDE EFFECTS

BICARBONATE

Reacts with hydrochloric acid in gastric lumen

Produces CO₂

Bloating and belching

Common to both
Poor Palatability

CITRATE

Binds readily with aluminium

Release in circulation and enhance aluminium absorption in gut

Acute aluminium encephalopathy

Does the accompanying cation matter?

This is usually sodium.

The amount of sodium can be substantial (~500 mg sodium/day from 600 mg of sodium bicarbonate three times daily).

This can lead to weight gain and hypertension from fluid retention.

High sodium intake affects the efficacy of renin-angiotensin-aldosterone system inhibition in slowing CKD progression.

Potassium salts are an option but is associated with a risk of life-threatening hyperkalemia.

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