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**

ACID-BASE BALANCE

Input

Acid load from diet and protein metabolism

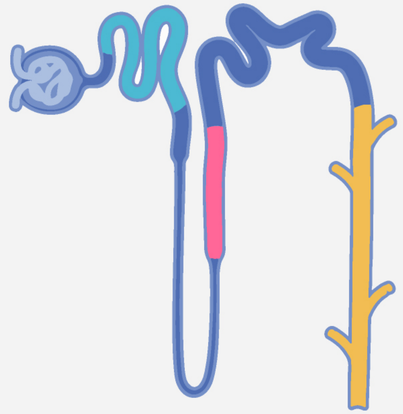
Output

Lungs (CO_2)

Kidneys (NH_4^+ and titratable acids)

MECHANISM

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



Proximal Tubule

~80% of filtered bicarbonate reabsorbed

Glutamine metabolism yields NH_4^+ and HCO_3^-

NH_4^+ enters urinary space by NHE3 (sodium-hydrogen exchanger 3) or H^+/ATPase (proton pump)

Along the Nephron

HPO_4^{2-} 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

NH_4^+ enters cells by NKCC2 (Na-K-Cl cotransporter 2)

NH_4^+ enters interstitium by NHE4 (sodium-hydrogen exchanger 4) and generates interstitial NH_4^+ concentration gradient

Collecting Duct

NH_3 and H^+ recombine to form NH_4^+ which is secreted into urine

AMMONIUM (NH_4^+)

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

TITRATABLE ACIDS

Urinary buffers derived from the systemic circulation

The principal titratable buffer is HPO_4^{2-} (90% of titratable acid excretion as $H_2PO_4^-$)

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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 Undertreated

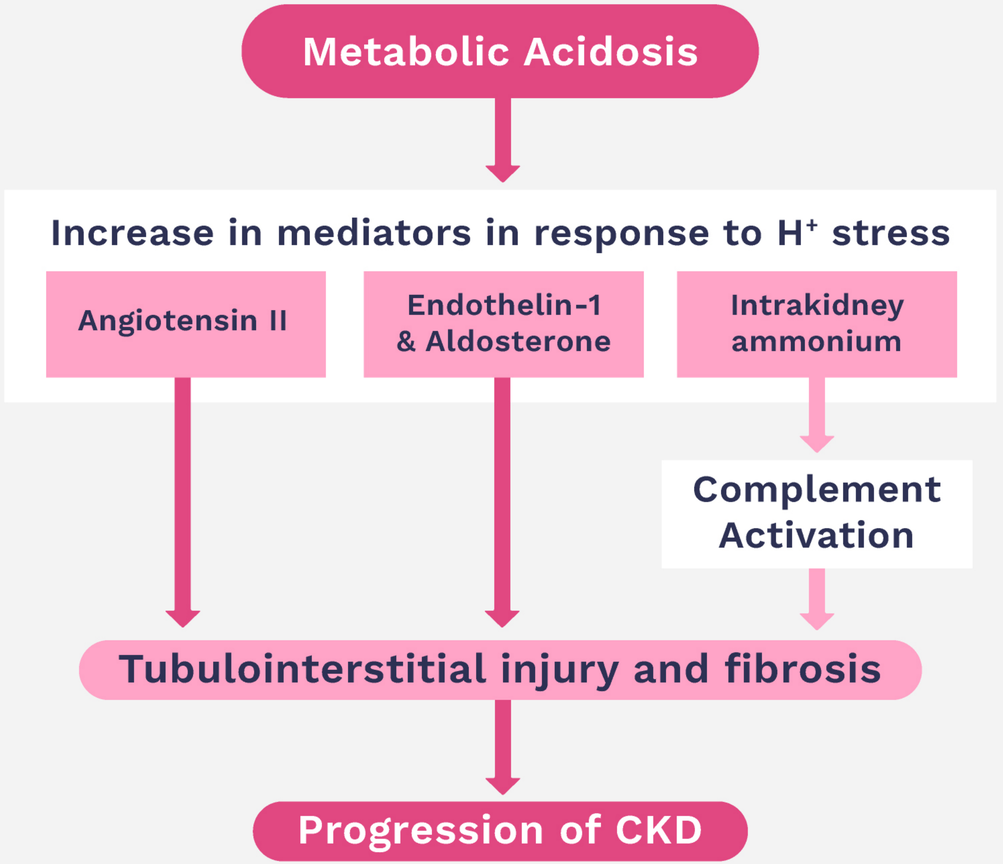
Only 2.7% of patients with CKD and serum bicarbonate ≤22 mEq/L receive oral alkali

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



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 accelerates 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)

of Metabolic Acidosis in Chronic Kidney Disease

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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

Muscle 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

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

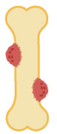
↓ **pH of interstitial fluid of bone**

↓ **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)

of Metabolic Acidosis in Chronic Kidney Disease

INTRODUCTION

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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-kinases) activity in muscle

Decreased Insulin Sensitivity

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

Insulin-like Growth Factor-1 (IGF-1)

Lower levels in metabolic acidosis

Blunted response to **administration of pharmacologic doses of growth hormone (GH)**

Correction of metabolic acidosis **improved IGF-1** responsiveness to GH administration

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

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DIETARY MODIFICATIONS

in Metabolic Acidosis and Chronic Kidney Disease

INTRODUCTION

Current Guidelines

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

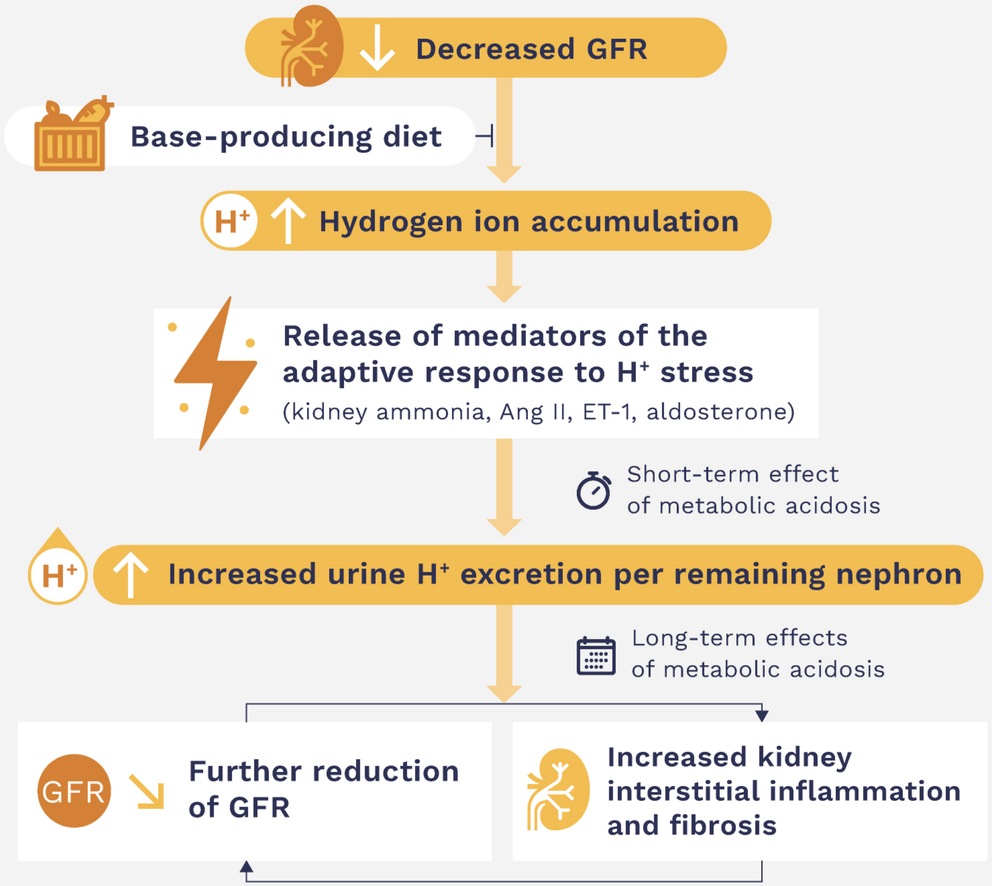
How Can We Achieve This?

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

EVIDENCE

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

MECHANISM



BASE-PRODUCING DIETS

This includes most fruit and vegetables

Exercise caution regarding potassium content

CONCLUSION

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

REFERENCES

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TREATMENT: BICARBONATE SUPPLEMENTATION

for Metabolic Acidosis in Chronic Kidney Disease

INTRODUCTION

When Should Treatment Be Started?

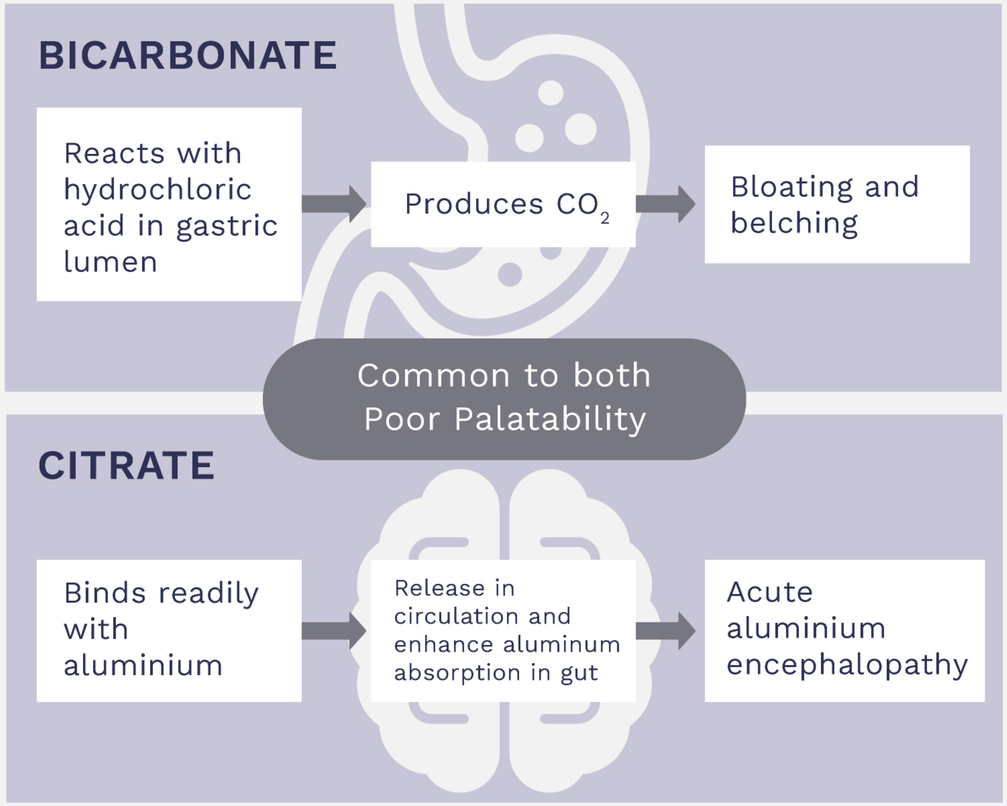
This depends on the severity of acidosis, blood pressure, volume status and presence of hyperkalemia

Treatment is reasonable with metabolic acidosis (HCO_3^- <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



CATION

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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Raphael KL. **Metabolic Acidosis in CKD: Core Curriculum 2019.** Am J Kidney Dis. 2019;74(2):263-275.

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