How Does Metabolic Acidosis Impair Muscle and Bone Health?
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Disclosure: Dr. Bushinsky is a consultant to Tricida, Inc.
Three Million Patients with Stage 3 to 5 CKD Affected by Metabolic Acidosis

- ~1.4 Million Patients with Metabolic Acidosis
- ~1.1 Million Patients with Metabolic Acidosis
- >600,000 Patients with Metabolic Acidosis

Stage 4 & 5

Stage 3b

Stage 3a

9%

18%

Data on file. NHANES 1999-2004 reports prevalence of CKD Stages 3 and 4 for the US adult population ages 20 and older. CKD Stage 3 and 4 prevalence was calculated using NHANES prevalence and 2016 US Census data. Stage 3a (70%) and 3b (30%) were approximated using NCCD-CDC Surveillance System. MA prevalence by Stage 3a, 3b, and 4 reported in Inker LA et al., J Am Soc Nephrol 22:2322-31, 2011.
Metabolic Acidosis as Defined by Guidelines

Serum Bicarbonate Levels Fall Below 22 mEq/L

- **Normal Range**: 22 – 29 mEq/L
- **Metabolic Acidosis**: 12 – <22 mEq/L
- **Acute/Severe Metabolic Acidosis**: <12 mEq/L

Body Adapts Prior to Decrease from Normal Serum Bicarbonate Range

Serum Bicarbonate Levels

Body Adapts Prior to Decrease from Normal Serum Bicarbonate Range

Small Increases in Muscle Degradation Will Cause a Loss of Muscle Mass

1. Continuous Skeletal Muscle Turnover
2. Small Increase in Muscle Degradation
3. Loss in Muscle Mass

References:
Putative Mechanisms that Contribute to Muscle Wasting in Patients with CKD and Metabolic Acidosis

Putative Mechanisms that Contribute to Muscle Wasting in Patients with CKD and Metabolic Acidosis

- Systemic pH
  - Pro-Inflammatory Cytokines
  - Insulin/IGF-1 Signaling
  - Activation of Ubiquitin-Proteasome Pathway
  - Caspase-3 Proteolysis

- Muscle pH
  - Muscle Protein Degradation
  - Muscle Wasting

Studies Show Association Between Metabolic Acidosis and Impaired Physical Function
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Acid Buffering by Bone with Increased Acid Retention

**Physicochemical Dissolution**

**Short-Term Acute Response**

- $\text{CO}_3^{2-}$
- $\text{PO}_4^{3-}$
- $\text{Na}^+$
- $\text{K}^+$
- $\text{Ca}^{2+}$

**Long-Term Chronic Response**
Acid Buffering by Bone with Increased Acid Retention

### Short-Term Acute Response

- Physicochemical Dissolution
- Releases
  - $\text{CO}_3^{2-}$
  - $\text{PO}_4^{3-}$
  - $\text{Na}^+$
  - $\text{K}^+$
  - $\text{Ca}^{2+}$

### Long-Term Chronic Response

- Cell Mediated Resorption
- Decreased Osteoblastic Bone Formation
- Increased Osteoclastic Bone Resorption
- Decreased Bone Quality and Mass

CKD Practice Guidelines Suggest Treatment if Serum Bicarbonate Levels are Below 22 mEq/L
The End