Acid-Base Balance and Physical Function

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Physical disability is common among people with CKD and is a major cause of morbidity. Reduced cardiorespiratory fitness, impaired physical performance, and severely diminished physical activity have been well documented in the ESRD population and in earlier stages of CKD as well (1,2). Multiple factors have been proposed to account for the increased risk of functional deterioration, including the high burden of comorbid disease, microvascular dysfunction, and inflammation (1,2). Ultimately, to cause disability, these would need to cause some systemic impairment—for example, in neurologic function, the cardiopulmonary system, or skeletal muscle.

Skeletal muscle turnover occurs continuously in a tightly regulated cycle of synthesis and degradation. Over time, even a mild perturbation of this balance in favor of degradation can cause a net loss of muscle mass (3). Thus, muscle wasting is seen in catabolic states. The major pathway responsible for muscle protein degradation in catabolic conditions is the ATP-dependent ubiquitin-proteasome system (UPS). The UPS may be upregulated in skeletal muscle by a number of factors, including inflammation, uremia, alterations in the insulin/IGF-1 signaling pathway, and metabolic acidosis (4).

Animal models and human physiologic studies have clearly linked acidosis with skeletal muscle protein metabolism. Acidemia in rodent models induces an insulin/IGF-1-signaling defect in skeletal muscle, stimulating proteolysis by upregulation of caspase-3, which degrades actomyosin, and the UPS (4). Other mechanisms, including increased activity of branched-chain ketoacid dehydrogenase and increased amino acid oxidation, have also been implicated (5). Several studies in patients with ESRD and advanced predialysis CKD have found that correcting acidosis reduces protein breakdown (6–9). Even a mild decrease in extracellular pH is sufficient to activate proteolysis. Administration of ammonium chloride to healthy individuals without kidney disease lowered the pH from 7.42 to 7.35 and stimulated muscle protein degradation (10). Similarly, in a study of eight patients on peritoneal dialysis, achieving a pH of 7.44 was associated with more positive nitrogen balance than a pH of 7.37 (11).

These short-term effects of acid-base balance on protein metabolism seem to translate to long-term effects on skeletal muscle mass. Among 200 patients on peritoneal dialysis randomized to high-versus low-alkali dialysate, the high-alkali group experienced greater weight gain, increased muscle mass, and fewer hospitalizations after 1 year, despite a modest difference in acid-base status: the mean pH and serum bicarbonate values in the two groups were 7.44 and 27.2 mEq/L and 7.40 and 23.0 mEq/L, respectively, at the end of the study (12). In another year-long trial of 60 patients on peritoneal dialysis, the group randomized to oral sodium bicarbonate had greater lean mass, higher Subjective Global Assessment scores (a nutritional assessment that includes muscle mass), and fewer days of hospitalization at the end of the study compared with placebo (13). Treatment with oral sodium bicarbonate for 2 years also improved mid-arm circumference and increased serum albumin in patients with stage 4 CKD (14). Thus, correction of acidosis seems to preserve muscle mass in patients with kidney disease.

Given this link with skeletal muscle, it seems natural to ask whether chronic metabolic acidosis affects muscle function and whether this contributes to impaired physical function in people with CKD. Indeed, alkali administration curbs exercise-induced acidosis (15) and enhances short-term endurance performance and lactate threshold (16). Epidemiologic data also support a role. Among older adults in the general United States population, lower serum bicarbonate levels were associated with slower gait speed and lower quadriceps strength (17). In addition, individuals with serum bicarbonate <23 mEq/L were nearly two times as likely to manifest self-reported disability compared with those who had serum bicarbonate ≥23 mEq/L. Lower bicarbonate levels were also associated with poorer cardiorespiratory fitness in younger adults, possibly mediated by differences in lean body mass, supporting the hypothesis that metabolic acidosis causes functional impairment through effects on skeletal muscle (18). At this time, only small intervention studies have further tested this hypothesis. In healthy persons 50 years of age and older, 3 months of oral bicarbonate (sodium or potassium) improved muscle strength in women but not men (19). In 20 patients with stage 3 or 4 CKD, oral sodium bicarbonate supplementation was associated with improved lower extremity muscle function after 6 weeks (20). Thus, the evidence to date suggests that chronic metabolic acidosis could adversely affect physical function.

In this issue of CJASN, Yenchek et al. (21) provide longitudinal data examining the association of acid-base status with physical function over time. Yenchek et al. (21)
used data from the Healthy Aging and Body Composition Study, a longitudinal cohort study of adults 70–79 years old who had no functional limitation at baseline. For this analysis, a subgroup of patients in the cohort who had arterialized venous blood gases drawn during year 3 of the study was examined. Lower blood bicarbonate at baseline was associated with a greater risk of incident self-reported functional limitation and lower gait speed during follow-up. These results are strengthened by the use of persistent disability over 6 months as an outcome as opposed to a single report of functional limitation, which might be more subject to the effects of acute illness and other transient circumstances. Furthermore, the effect was graded—having a blood bicarbonate <23 mEq/L was associated with greater risk than having a blood bicarbonate=23–25 mEq/L, which was still associated with greater risk than having a bicarbonate level ≥26 mEq/L. Higher bicarbonate was monotonically associated with lower risk of functional limitation, although levels at the extreme high and low ends of the spectrum were not specifically examined. The association of bicarbonate level with functional limitation did not differ between participants with and without CKD, and it did not explain the greater likelihood of disability associated with CKD. In this respect, the small fraction of the cohort with an eGFR<60 ml/min per 1.73 m²—13.8% or 213 people—is an important limitation, which Yenchek et al. (21) acknowledged. The small sample of participants with CKD precludes any definitive conclusions.

This study by Yenchek et al. (21) has the particular strength of measures of acid–base status beyond bicarbonate. This enabled Yenchek et al. (21) to address a limitation of earlier research—that lower bicarbonate levels could represent respiratory alkalosis and simply be a marker for overt or subclinical cardiopulmonary disease. After excluding those with respiratory alkalosis (defined as pH>7.42 and pCO₂<38 mmHg), the results were unchanged. The associations found with lower bicarbonate levels did reflect associations with metabolic acidosis, even if it was subclinical in many individuals.

Surprisingly, pH was associated less strongly than bicarbonate with functional limitation. If lower blood bicarbonate represents a greater degree of metabolic acidosis, one would expect lower pH to be associated as well. This unexpected finding may be related to the much narrower distribution of pH relative to other acid-base parameters—the coefficient of variation was an order of magnitude smaller than that for bicarbonate or pCO₂ in this cohort. Because changes in pH caused by metabolic perturbations will be limited by respiratory compensation, serum bicarbonate could actually be a better marker of long-term risk than the pH.

It is also worth considering that blood acid-base parameters may simply be insufficient for determining a person’s risk of chronic complications related to metabolic acidosis. Acid retention seems to occur in people with CKD even before changes in acid-base parameters manifest (22), which may increase tissue interstitial acidity (23,24). The reduction in interstitial pH could be sufficient to activate proteolytic mechanisms in skeletal muscle. In healthy postmenopausal women without overt acidosis, oral potassium bicarbonate in doses sufficient to reduce net acid excretion to near zero reduced urinary nitrogen excretion, suggesting an improvement in muscle protein breakdown (25). Therefore, the serum bicarbonate level may not be a sufficiently sensitive measure of the acid load—mostly caused by diet but modulated by age and kidney function—to which a person is exposed.

An understanding of the mechanisms underlying the findings by Yenchek et al. (21) would also be useful. If explained by a causal pathway between acid-base status and skeletal muscle, was it because of better preserved muscle mass in the highest bicarbonate category or better muscle contractile function? Could the effects relate to endurance and fatigability and not muscle strength? If so, might alkali ingestion have a synergistic effect with exercise interventions in the elderly and patients with CKD? Did people with higher bicarbonate levels have greater protein intake (14) with accompanying anabolic effects? Although the dietary acid load was lowest in the highest bicarbonate category, both protein and potassium intake could have been high and still resulted in a lower protein-to-potassium ratio than in the lower bicarbonate categories.

Finally, there is now quite a bit of data suggesting that higher bicarbonate is better, for kidney disease progression and for preservation of muscle mass and physical function. We should keep in mind, however, that nearly all of these data comes from observational studies and small interventional studies. Although treating chronic acidosis with oral alkali seems generally safe and well tolerated, it is not without risk (26). Those at the greatest risk for possible complications have been excluded from the published interventions, possibly resulting in an exaggerated sense of reassurance regarding tolerability. We should also recall the numerous occasions on which conventional wisdom backed by biologic plausibility was not borne out by large randomized clinical trials. Fortunately, several randomized trials of oral alkali are currently underway and should provide us with important new data in the coming years. We might do well to be cautious about extrapolating these findings to clinical practice just yet.

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References

6. Graham KA, Reaich D, Channon SM, Downie S, Gilmour E, Passlick-Deetjen J, Goodship TH: Correction of acidosis in CAPD


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