Chapter 10
Effects of Metabolic Acidosis on Skeletal Muscle

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Case: P.M. is a 56-year-old woman with stage 3 chronic kidney disease (CKD) due to longstanding type 2 diabetes mellitus and hypertension. She takes an angiotensin-receptor blocker and a beta-blocker, and her diabetes is managed with a dipeptidyl peptidase-4 inhibitor and oral agents including a thiazolidinedione. On exam, her blood pressure is 109/68 mmHg and she has no edema. Over the past year her kidney function has remained stable, with an estimated glomerular filtration rate of 30 mL/min/1.73 m^2. Her serum bicarbonate is 20 mEq/L and serum potassium is 4.5 mEq/L. She requires 24 s to complete 10 repetitions of a sit-to-stand-to-sit test, which is slower than the predicted time range for women of her age group. Would treatment with alkali therapy improve muscle strength and physical performance? How should this patient be managed?

(a) Begin oral sodium bicarbonate after confirming metabolic acidosis with a venous blood gas.
(b) Measure the serum bicarbonate again in 3 months; if unchanged, recommend increased intake of fruits and vegetables.

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(c) Measure the serum bicarbonate again in 3 months; if unchanged, prescribe oral sodium bicarbonate.
(d) Prescribe oral sodium bicarbonate 0.3 mEq/kg body weight/day in two divided doses.
(e) Prescribe oral sodium bicarbonate 1 mEq/kg body weight/day in two divided doses.

Introduction

Metabolic acidosis is highly prevalent in persons with advanced CKD. This is mainly due to reduced renal mass leading to impaired ammoniagenesis and inability to excrete the daily acid load. As bone is the most important buffer of a chronic acid load, bone resorption in response to chronic acidosis is not surprising. Less well recognized by clinicians are changes in muscle metabolism in response to chronic metabolic acidosis.

The catabolic effects of chronic acidosis can be subtle and thus easily overlooked by clinicians. This has important implications, as skeletal muscle wasting is associated with increased morbidity and mortality [1]. Furthermore, the effects of acidosis are not only relevant to the population with kidney disease. A low-level acidosis, related to older age and high net endogenous acid production due to the Western diet, may be of importance in individuals without CKD. Older persons may be at greatest risk of adverse sequelae due to the age-related decline in kidney function and lesser ability than young individuals to excrete an acid load [2–4]. This may have important consequences as alkali supplementation in postmenopausal women without overt acidosis has been shown to improve nitrogen balance and skeletal metabolism [5].

Changes in Muscle Physiology Due to Metabolic Acidosis

In otherwise healthy humans, there is a continuous cycle of muscle protein synthesis and degradation. This turnover is tightly regulated because even a minimal decrease in synthesis or increase in degradation can result in a net loss in muscle mass over time [6, 7]. Chronic metabolic acidosis disturbs this homeostasis, primarily by stimulating skeletal muscle protein breakdown. Acidosis also promotes amino acid oxidation and may impair muscle protein synthesis as well [8–11].

Three main systems have been described in muscle protein degradation: lysosomal proteases (cathepsin system), the calcium-dependent calpain system, and the ATP-dependent ubiquitin-proteasome system (UPS) [12, 13]. Inhibition of the first two systems does not substantially suppress proteolysis in animal models of catabolic conditions [14, 15]. Therefore, quantitatively the UPS is the major pathway responsible for muscle protein degradation [16]. However, the UPS cannot degrade the complex structure of actomyosin. Caspase-3 initiates the process of protein degradation by catalyzing the disassembly of myofibrils into a characteristic 14-kDa

actin fragment and other substrates that are then degraded by the UPS [17]. After activation by a ubiquitin activating enzyme, E1, ubiquitin moieties are transferred to an E2 carrier protein and then conjugated to the protein substrate complex by an E3 ubiquitin-protein ligase. This process of ubiquitination targets the protein for degradation by the proteasome. The E3 ligases are specific in their actions because they only recognize a limited range of target proteins. The muscle-specific E3 ligases, atrogin-1/muscle atrophy F-box (MAFbx) and muscle ring finger 1 (MuRF1), have been linked with muscle atrophy in CKD and other catabolic states [18–21].

A number of factors stimulate muscle breakdown through the UPS [19, 22]. In addition to acidosis, these include catabolic states such as uremia, and factors including inflammation, angiotensin II, and disturbances in insulin and insulin-like growth factor-1 (IGF-1) function. Binding of insulin and IGF-1 to their respective receptors results in tyrosine phosphorylation of insulin receptor substrate (IRS) proteins. The phosphorylated IRS protein then serves as a recruitment site for phosphatidylinositol 3-kinase (PI3-K), which signals the downstream effector Akt. Downstream effects of PI3-K/Akt signaling simultaneously suppress catabolic pathways and promote muscle protein synthesis, thereby preventing muscle atrophy [18].

Metabolic acidosis suppresses the effects of this IRS/PI3-K/Akt pathway (Fig. 10.1) [23]. In a rat model of uremia, basal signaling through the PI3-K/Akt pathway in skeletal muscle was suppressed when compared to control animals. Normalization of the extracellular pH with a sodium bicarbonate-supplemented diet partially restored basal IRS-1 associated PI3-K activity and partially reversed the increase in muscle protein degradation [24]. Acidosis also augments the transcription of genes that code for the UPS [25]. Thus acidosis increases skeletal muscle proteolysis by suppressing IRS-1/PI3-K/Akt signaling, leading to activation of caspase-3 and the UPS. This clearly implicates metabolic acidosis as an important contributor to muscle proteolysis in CKD.

Alterations in Lean Mass and Muscle Function Due to Metabolic Acidosis

A number of studies in humans suggest that the treatment of acidosis ameliorates the insulin signaling defect in skeletal muscle and decreases muscle breakdown (Tables 10.1, 10.2, and 10.3). DeFronzo and Beckles induced insulin resistance in normal subjects by acidification with ammonium chloride, a model of chronic acidosis [26]. The defect was most likely due to an effect on skeletal muscle insulin sensitivity. Mak treated eight young subjects (mean age 18 years) receiving maintenance hemodialysis with oral sodium bicarbonate for 2 weeks and found an improvement in insulin sensitivity [27]. Reaich et al. treated eight patients with advanced CKD (mean serum creatinine 7.4 mg/dL) with oral sodium bicarbonate for 4 weeks and found improvements in insulin sensitivity and reduced whole-body protein breakdown [28]. Several studies in patients receiving peritoneal dialysis (PD) and maintenance hemodialysis have shown that correcting acidosis in end-stage renal disease patients reduces protein breakdown [29, 30]. Pickering et al. found a reduction in

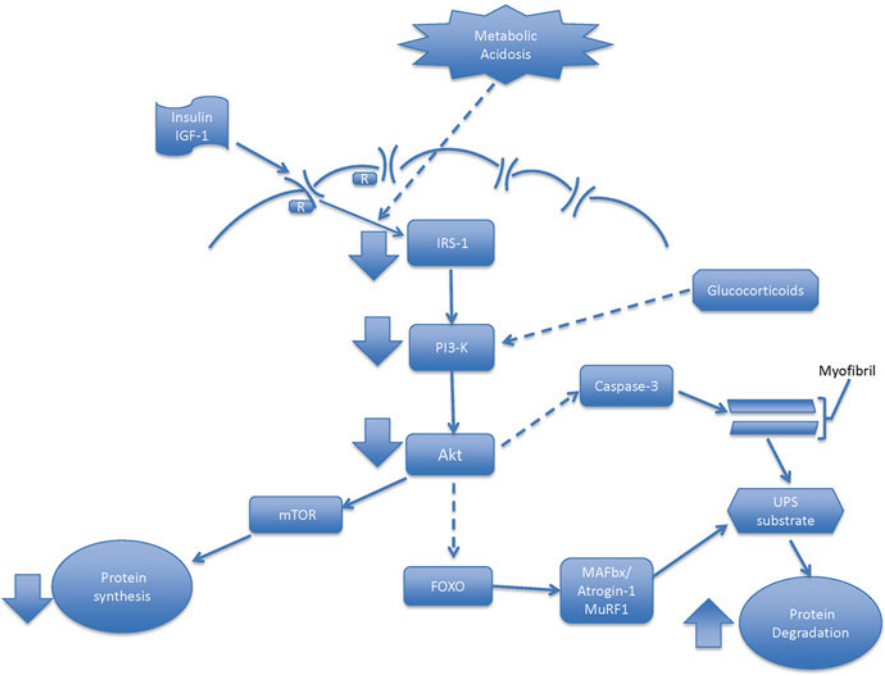

Fig. 10.1 Mechanism of metabolic acidosis-induced muscle protein breakdown. Acidosis (*bold arrows*) impairs signaling downstream of insulin and insulin-like growth factor-1 via the insulin receptor substrate/phosphatidylinositol 3-kinase/Akt pathway. This activates proteolytic pathways including caspase-3, which degrades actomyosin, producing substrates that are then degraded by the ubiquitin-proteasome system. Upregulation of FOXO stimulates expression of the E3 ubiquitin ligases MAFbx and MuRF1. Glucocorticoids appear to have a permissive effect on acidosis-induced proteolysis. Decreased activation of Akt may also impair protein synthesis by reducing mTOR activity. *Abbreviations*: *IGF-1* insulin-like growth factor-1, *IRS* insulin receptor substrate, *PI3-K* phosphatidylinositol 3-kinase, *UPS* ubiquitin-proteasome system, *MAFbx* muscle atrophy F-box, *MuRF1* muscle ring finger 1, *mTOR* mammalian target of rapamycin. "R" denotes insulin and IGF-1 receptors

skeletal muscle ubiquitin mRNA after correction of acidosis in eight PD patients, indicating that UPS-mediated proteolysis is ameliorated by alkali therapy [31]. Even a mild decrease in extracellular pH is sufficient to activate proteolysis. Ammonium chloride-induced acidosis in normal participants lowered pH from 7.42 to 7.35 and stimulated muscle protein degradation [32]. Furthermore, in healthy postmenopausal women without overt acidosis or CKD, oral potassium bicarbonate reduced urinary nitrogen excretion, suggesting an improvement in muscle protein breakdown [33].

Studies in patients with CKD with reduced GFR suggest that correction of acidosis also preserves muscle mass (Tables 10.1, 10.2, and 10.3). In a year-long single-blinded randomized trial of high versus low-alkali dialysate in 200 patients receiving PD, the high-alkali intervention led to weight gain, increased muscle mass (measured anthropometrically by mid-arm circumference), and fewer hospitalizations [34]. Of note, the difference in acid–base status between the two groups was relatively modest: at the end of the study, the mean pH and serum bicarbonate were

7.44 and 27.2 mEq/L in the high-alkali group and 7.40 and 23.0 mEq/L in the low-alkali group, respectively. Similarly, a double-blinded randomized trial of oral sodium bicarbonate in 60 PD patients found greater lean mass, higher Subjective Global Assessment scores (a nutritional assessment that includes muscle mass), and fewer days of hospitalization after 1 year [35]. Treatment with oral sodium bicar-

Table 10.1 Studies examining effects of metabolic acidosis on skeletal muscle in persons without kidney disease

Physiological studies/body composition	Outcome
Nitrogen balance before and after treatment of acidosis	$KHCO_3$ improved nitrogen balance [33, 48].
Protein breakdown and nitrogen balance before and after inducing acidosis	NH_4Cl increases protein breakdown [32] and induces negative nitrogen balance [10].
Amino acid oxidation before and after acidosis	NH_4Cl increases amino acid oxidation [32].
Albumin synthesis before and after inducing acidosis	Chronic NH_4Cl decreases albumin synthesis [10]. Acute NH_4Cl does not decrease albumin synthesis [49].
Muscle protein synthesis before and after inducing acidosis	Acute NH_4Cl decreases muscle protein synthesis [49].
Muscle strength and function	
Muscle performance before and after treatment with bicarbonate	Bicarbonate improved muscle performance in women but not in men [43].
Interval training before and after bicarbonate ingestion	$NaHCO_3$ improves endurance performance [38].
High intensity work before and after treatment of acidosis	$NaHCO_3$ improved performance in high intensity work [50].

Table 10.2 Studies examining effects of metabolic acidosis on skeletal muscle in persons with pre-dialysis chronic kidney disease

Physiological studies/body composition	Outcome
Skeletal muscle ubiquitin gene expression before and after sodium bicarbonate treatment	No difference in expression of ubiquitin mRNA with $NaHCO_3$ treatment [51].
Protein degradation and nitrogen balance before and after acidosis treatment	$NaHCO_3$ decreases protein degradation [9] and protein catabolic rate [52] and improves nitrogen balance [53].
Amino acid oxidation before and after treatment	$NaHCO_3$ decreases amino acid oxidation [9].
Serum albumin before and after acidosis treatment	Correction of acidosis improves serum albumin [36, 52].
Dietary protein intake and mid-arm muscle circumference before and after acidosis treatment	$NaHCO_3$ supplementation improves dietary protein intake and mid-arm muscle circumference and slows CKD progression [36].
Muscle strength and function	
Lower extremity muscle strength before and after acidosis treatment	$NaHCO_3$ treatment improved lower extremity muscle strength [42].

Table 10.3 Studies examining effects of metabolic acidosis on skeletal muscle in persons with chronic kidney disease requiring dialysis

Physiological studies/body composition	Outcome
Skeletal muscle levels of ubiquitin mRNA before and after treatment of acidosis	Ubiquitin mRNA decreased significantly after correcting acidosis [31].
Protein degradation before and after treatment of acidosis	Bicarbonate therapy decreased protein degradation [8, 29, 54–56].
Amino acid oxidation before and after treatment of acidosis	$NaHCO_3$ reduces amino acid oxidation [55].
Serum albumin levels before and after treatment of acidosis	Oral $NaHCO_3$ treatment failed to improve serum albumin [57, 58]. Oral $NaHCO_3$ improves serum albumin in patients without inflammation [8].
Nutritional status before and after treatment of acidosis	$NaHCO_3$ therapy improves subjective global assessment (SGA) score [35]. Sodium citrate treatment improves growth hormone sensitivity [59].
Changes in body composition before and after treatment of acidosis	Acidosis treatment increases body mass index, but no significant change in mid-arm circumference [31]. Triceps skin-fold thickness increased with bicarbonate dialysis [60]. No increase in triceps skin-fold with correction of acidosis [31, 34]. Correcting acidosis improves muscle and weight gain [31, 34].

bonate for 2 years also improved mid-arm circumference and increased serum albumin in patients with stage 4 CKD [36].

The adverse effects of metabolic acidosis on muscle physiology and muscle mass imply that correcting chronic acidosis might improve muscle strength and function (Tables 10.1 and 10.2). Indeed, alkali administration suppresses exercise-induced acidosis [37] and has produced improvements in short-term endurance performance and lactate threshold [38]. Epidemiologic data support this hypothesis. Among older adults in the general US population, metabolic acidosis was associated with slower gait speed, lower quadriceps strength, and greater likelihood of self-reported disability [39]. Lower serum bicarbonate due to metabolic acidosis was also associated with low cardiorespiratory fitness in younger adults, possibly mediated by changes in lean body mass, supporting the hypothesis that metabolic acidosis causes functional impairment via effects on skeletal muscle [40]. In a prospective observational study of older adults with and without CKD, lower serum bicarbonate was associated with a higher risk of incident functional limitation [41]. To date, two interventional studies have examined this question. Oral sodium bicarbonate administered to 20 adults with CKD and mild acidosis produced a dose-dependent increase in serum bicarbonate and improved lower extremity muscle strength after 6 weeks of therapy [42]. In healthy adults ≥50 years of age, 3 months of oral bicarbonate improved muscle strength in women but not men [43].

A reasonable approach to treating metabolic acidosis in patients with CKD is to first repeat the measurement of the serum bicarbonate. In selected patients a blood gas should be checked to rule out a respiratory acid–base disorder (in stable outpatients, a venous blood gas will suffice). While the optimal pH and serum bicarbonate are not known, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend maintaining serum bicarbonate ≥22 mEq/L [44]. For patients with only mild acidosis (e.g., serum bicarbonate ≥20 mEq/L), a dietary intervention alone is an appropriate first step [45]. This should focus on increasing fruit and vegetable intake, which will not only reduce the dietary acid load and raise the serum bicarbonate, but bestow additional important health benefits such as weight loss and improved blood pressure control [46, 47]. Because of the increased potassium intake, this intervention is only appropriate for patients at low risk of hyperkalemia. If dietary modification is not successful, and for patients with more severe acidosis, oral alkali should be prescribed. This should usually be initiated at a low dose (e.g., sodium bicarbonate 650 mg twice daily—each 650 mg tablet provides 7.74 mEq alkali) to minimize side effects. The dose can then be titrated to achieve the desired level of serum bicarbonate.

Conclusions

Chronic metabolic acidosis has a number of negative effects on skeletal muscle. While the physiologic alterations have been well-documented, only a few studies have addressed functional outcomes. In the case presented, mild metabolic acidosis is likely associated with increased muscle protein degradation relative to synthesis. Treatment of acidosis could reverse this defect and might, over time, preserve lean mass and muscle strength in this patient at risk for functional decline. Given the mild degree of acidosis and absence of hyperkalemia, a dietary intervention would be an appropriate first step after confirming that the serum bicarbonate is low (choice B). A blood gas is likely not required based on the clinical history. If treatment with oral sodium bicarbonate was subsequently required, it would be prudent to begin with a low dose.

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