Intensive Care Unit–Acquired Weakness in Patients With Acute Kidney Injury: A Contemporary Review

J. Pedro Teixeira, Kirby P. Mayer,* Benjamin R. Griffin, Naomi George, Nathaniel Jenkins, C. Anil Pal, Felipe González-Seguel, and Javier A. Neyra*

Acute kidney injury (AKI) and intensive care unit–acquired weakness (ICU-AW) are 2 frequent complications of critical illness that, until recently, have been considered unrelated processes. The adverse impact of AKI on ICU mortality is clear, but its relationship with muscle weakness—a major source of ICU morbidity—has not been fully elucidated. Furthermore, improving ICU survival rates have refocused the field of intensive care toward improving long-term functional outcomes of ICU survivors. We begin our review with the epidemiology of AKI in the ICU and of ICU-AW, highlighting emerging data suggesting that AKI and AKI treated with kidney replacement therapy (AKI-KRT) may independently contribute to the development of ICU-AW. We then delve into human and animal data exploring the pathophysiologic mechanisms linking AKI and acute KRT to muscle wasting, including altered amino acid and protein metabolism, inflammatory signaling, and deleterious removal of micronutrients by KRT. We next discuss the currently available interventions that may mitigate the risk of ICU-AW in patients with AKI and AKI-KRT. We conclude that additional studies are needed to better characterize the epidemiologic and pathophysiologic relationship between AKI, AKI-KRT, and ICU-AW and to prospectively test interventions to improve the long-term functional status and quality of life of AKI survivors.

Complete author and article information provided before references.

**J.P.T. and K.P.M. contributed equally to this work.*

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Acute kidney injury (AKI) is a common complication of critical illness, and up to 15% of patients with AKI in the intensive care unit (ICU) receive kidney replacement therapy (KRT).[1] Though further studies are needed, AKI and treatment with KRT may contribute to skeletal muscle dysfunction through multiple mechanisms. This article reviews the proposed pathophysiology of skeletal muscle loss and dysfunction in critical illness with a focus on patients with AKI treated by KRT (AKI-KRT). We describe preclinical and clinical data suggesting that AKI and AKI-KRT may independently contribute to ICU-acquired weakness (ICU-AW) (Fig 1), suggest interventions that may mitigate or prevent ICU-AW in AKI patients, and identify areas of uncertainty in need of future research. Despite the many unanswered questions, we propose that nephrologists should recognize AKI as risk factor for long-term functional impairment after critical illness and learn to routinely consider referring AKI survivors to physical rehabilitation.

AKI in the ICU: Incidence and Outcomes

In contemporary international cohorts, the incidence of AKI ranges from 20% to >50% of all ICU admissions, with 5% to 15% of critically ill patients developing AKI-KRT.[2,3] Moreover, the rates of AKI, AKI-KRT, and AKI-related mortality have increased substantially in the last 20 years.[4,5] Recently, the COVID-19 pandemic has further increased KRT use in the ICU. AKI complicates 25% to 40% of all COVID-19 admissions, and AKI-KRT develops in 20% to 45% of critically ill COVID-19 patients.[6] AKI, especially AKI-KRT, carries a high short-term mortality of ≥50% across diverse ICU populations with or without COVID-19.[1,4,6-10] Furthermore, observational studies have increasingly linked AKI to long-term impairments in functional status, including limited mobility, worsened quality of life (QoL), and muscle weakness.[11-13]

Despite chronic kidney disease (CKD) being a recognized risk factor for AKI, the relationship between AKI-on-CKD and outcomes of critical illness appears to be complex, with data suggesting mortality rates are higher in AKI-on-CKD patients than in patients with neither AKI nor CKD but lower than in patients with AKI in the setting of normal baseline kidney function.[14,15] The interplay between AKI-on-CKD and long-term functional outcomes remains unknown.

ICU-Acquired Weakness: Definition, Incidence, Outcomes, and Risk Factors

ICU-AW is defined as muscle weakness and wasting (atrophy) resulting from critical illness.[16] The reported incidence of ICU-AW ranges from 40% in systematic reviews[17] to >80% in individual studies.[18] Muscle wasting occurs early and rapidly during critical illness.[19] We and others have reported that 3% to 5% of baseline rectus femoris muscle size is lost in the first day of ICU admission, with up to 30% lost in the first 10 days.[20-23] Importantly, ICU-AW may persist for years and is associated with mortality, hospital readmission, long-term functional impairment, and lower QoL.[24-26] Traditional risk factors (Fig 2) for ICU-AW include preexisting comorbidity, high illness severity, sepsis, acute respiratory failure, prolonged immobilization, hyperglycemia, advanced age, and prolonged exposure to corticosteroids, sedatives, or paralytics.[25,26]

Recent data suggest that ICU patients with AKI and AKI-KRT may also be at increased risk of ICU-AW. Specifically, a recent prospective multicenter cohort study of 642

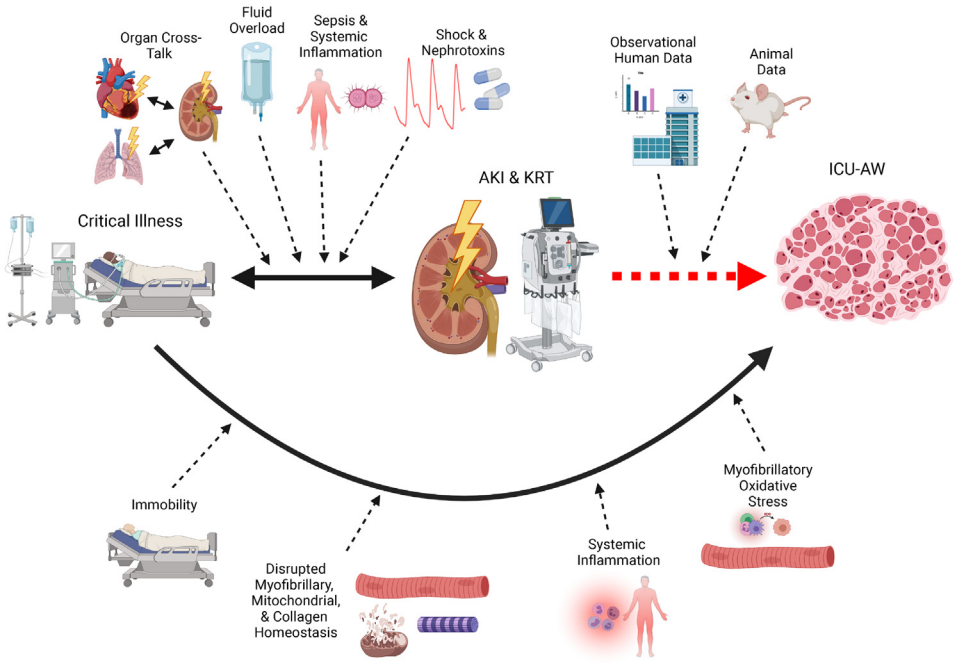

Figure 1. Framework for the relationship between critical illness, AKI-KRT, and ICU-AW. AKI frequently complicates critical illness. In addition to the traditional mechanisms of AKI in critical illness such as ischemia, sepsis, and nephrotoxin exposure, AKI and critical illness have a bidirectional relationship mediated by systemic inflammation, organ cross-talk, and fluid overload, combining to produce the high rates of morbidity and mortality characteristic of AKI in the ICU. Muscle wasting is a well-known complication of critical illness mediated by immobility; systemic inflammation; altered myofibrillary, mitochondrial, and collagen protein homeostasis; and myofibrillary oxidative stress. Though not considered a traditional risk factor for ICU-AW, emerging data—both observational human studies and experimental animal data—strongly imply that AKI and KRT may directly contribute to the development of ICU-AW. Abbreviations: AKI, acute kidney injury; ICU, intensive care unit; ICU-AW, ICU-associated weakness; KRT, kidney replacement therapy. Created with BioRender.com.

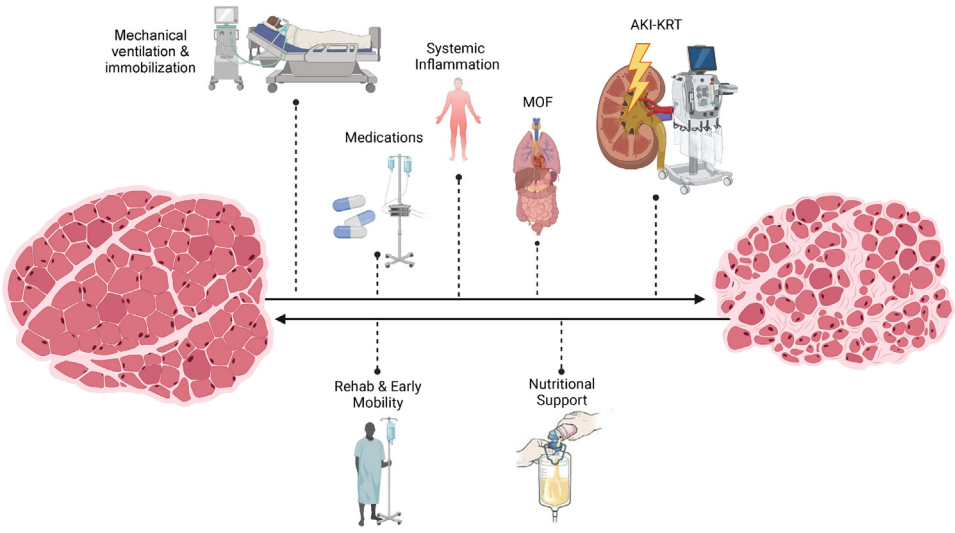

Figure 2. Risk factors for and management of ICU-AW. In addition to emerging data linking AKI and KRT to ICU-AW, risk factors for ICU-AW include prolonged immobilization, need for mechanical ventilation, use of certain medications (especially prolonged treatment with corticosteroids, sedatives, or paralytic agents), sepsis and other forms of systemic inflammation, multiorgan dysfunction, and high severity of illness. Though additional data are needed to better delineate and validate interventions to prevent and treat ICU-AW, early physical therapy and adequate nutritional support are felt to be the cornerstones of prevention and management. Abbreviations: AKI, acute kidney injury; ICU, intensive care unit; ICU-AW, ICU-associated weakness; KRT, kidney replacement therapy; MOF, multiorgan failure. Created with BioRender.com.

Table 1. Clinical and Research Tests to Diagnose ICU-AW or Assess Skeletal Muscle in the ICU

Test or Modality	Description	Limitations	Provider	Setting or Time Frame	Interpretation
Medical Research Council-sum score (MRC-ss)[28]	• Standardized manual muscle strength testing of 12 predefined bilateral muscle groups (shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, foot dorsiflexors) • 6-point ordinal scale (0: no contraction; 5: normal strength against full resistance) with total score of 0-60 • Gold standard and clinical standard for diagnosing ICU-AW	• Requires patient engagement and cognitive function • Ordinal scale may reduce sensitivity	• Physical therapist • Occupational therapist • Dietician • Physiatrist[a]	• Upon ICU awakening and repeated serially • Milestones[b]	<48/60, with no other etiology of weakness, constitutes a diagnosis of ICU-AW
Handgrip dynamometry (HGD)[29]	• Evaluates handgrip strength (concurrent strength of the elbow flexors and wrist extensors) • Standardized position recommended • Continuous outcome in kg or lb of force improves objectivity	• Requires patient engagement and cognitive function • Requires equipment	• Physical therapist • Occupational therapist • Dietician • Physiatrist[a]	• Upon ICU awakening and repeated serially • Milestones[b]	<7 kg (F) and <11 kg (M) suggests a diagnosis of ICU-AW
Handheld dynamometry (HHD)[110]	• Evaluates strength (force generated) of a selected muscle group (eg, knee extensors) • Standardized position recommended • Continuous outcome in kg or lb of force improves objectivity	• Requires patient engagement and cognitive function • Requires equipment	• Physical therapist • Occupational therapist • Dietician • Physiatrist[a]	• Rarely used in clinical practice • Commonly used in research	Score cutoffs not established for ICU-AW diagnosis
Muscle ultrasound[20-23,30]	• Ultrasonography to visualize and assess respiratory and peripheral skeletal muscles • Evaluates muscle quantity: thickness, cross-sectional area, and estimated mass • Evaluates muscle composition: pennation angle, fascicle length, elastography, and EI	• Requires equipment • Requires training • Heterogeneity in reported techniques, positioning, and landmarking	Trained sonographer[c]	• Variable use in clinical practice • Day 0 and repeated serially • Commonly used in research	• 20%-30% reduction in muscle size in first 10 d of ICU admit suggests ICU-AW • Increased EI associated with myofiber necrosis and worse patient outcomes
CT or MRI[30]	• Imaging modalities with precise and accurate measures of muscle mass and composition • Cross-sectional area of psoas by CT at L3 most commonly used	• Expensive • Requires significant planning in ICU for scheduling and for patient safety	Radiologist	• Rarely used for muscle assessment • Typically ordered for other purpose and muscle is a secondary assessment	Psoas major muscle mass appears representative of whole-body muscle and predictive of patient outcomes
EMG and evoked forces[111]	• Nonvolitional measurements of motor axon depolarization (evoked force) by either electrical or magnetic stimuli • Objective measure of evoked force using an ergometer	• Expensive • Requires training and equipment • Stimuli may cause discomfort	• Physiatrist[a] • Neurologist • Physical therapist with training	• Rarely used in clinical practice • Primarily used in research	• Compared to healthy controls or followed longitudinally • No standardized values

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Table 1 (Cont'd). Clinical and Research Tests to Diagnose ICU-AW or Assess Skeletal Muscle in the ICU

Test or Modality	Description	Limitations	Provider	Setting or Time Frame	Interpretation
Muscle biopsy[28]	• Most commonly obtained from vastus lateralis and performed with local anesthesia • Immunohistochemical, histochemical, and biochemical examinations of tissue	• Expensive • Invasive • Risk of complications	• Physician or AP provider with training • Pathologist	• Rarely used in clinical practice • Occasionally used in research	• Interpreted by pathologists • Norms established for certain parameters

Abbreviations: AP, advanced practice; AW, acquired weakness; CT, computed tomography; EI, echo intensity (a surrogate marker of muscle quality); EMG, electromyography; F, female; ICU, intensive care unit; L3, level of third lumbar vertebra; M, male; MRI, magnetic resonance imaging.
[a]Physiatrists are physicians specializing in physical medicine and rehabilitation.
[b]Patient milestones include any change in medical or functional status that requires re-evaluation (ie, clinical decompensation or fall); ICU and hospital discharge; and 1, 3, 6, and 12 months after discharge.
[c]Trained sonographer may be from any professional discipline who has received ultrasound-specific training; no current standard for muscle ultrasonography certification exists.

intubated patients identified days on KRT as an independent risk factor for ICU-AW.[27] Likewise, our group analyzed a cohort of 104 ICU survivors and found that patients with stage 2 or 3 AKI had increased severity of muscle weakness, lower health-related QoL, and impaired ability to return to work or driving.[13] However, additional data are needed to further investigate the link between the risk of ICU-AW and AKI, KRT, potential confounding factors such as ICU length of stay, and overall illness severity.

ICU-AW: Diagnosis

For this review, in concert with prior guidelines[28] we will use the term ICU-AW as a framework that encompasses muscle atrophy, weakness, and dysfunction in ICU patients. Muscle dysfunction (ie, impaired muscle performance) due to critical illness typically results from overlapping effects of myopathy and neuropathy; however, as we will outline, the studies linking AKI and ICU-AW are overwhelmingly centered on muscle rather than nerve function. Assessment of skeletal muscle in the ICU is influenced by a patient's ability to engage and follow simple commands and the time course and severity of their illness. With the emerging data linking AKI to ICU-AW, nephrologists practicing in the ICU should have foundational knowledge of the diagnosis and measures of ICU-AW to be able to interpret results and communicate effectively with intensivists, interprofessional team members, patients, and their care partners as part of patient-centered care (Table 1).

ICU-AW is diagnosed by assessing global muscle strength testing using the Medical Research Council–Sum Score (MRC-ss) in the appropriate clinical setting.[26,28] MRC-ss grades volitional strength in 12 predefined peripheral muscle groups (bilateral shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsiflexors). Handgrip dynamometry measures grip strength and has been proposed as a valid and reliable screening tool for ICU-AW, but like MRC-ss it requires patient participation.[29]

Imaging permits muscle assessment in patients who are unable to follow commands, potentially leading to earlier detection of ICU-AW. Computed tomography (CT) can quantify muscle size and quality but is rarely performed clinically for this purpose. Muscle ultrasound has similarly been proposed as a diagnostic tool to assess muscle size and quality and has been demonstrated in ICU patients to correlate well with CT-derived measures[30] and immunohistochemical analysis of muscle biopsy specimens.[22,23] However, whether ultrasound reliably predicts patient-relevant outcomes including ICU-AW requires further study. Electromyography (EMG), nerve conduction velocity studies (NCV), and muscle biopsy may be useful to diagnose ICU-AW but are relatively costly and invasive techniques typically reserved for complex neuromuscular disorders and research. Ultimately, imaging, EMG/NCV, and muscle biopsy are diagnostic adjuncts to strength testing by trained providers using MRC-ss; despite its

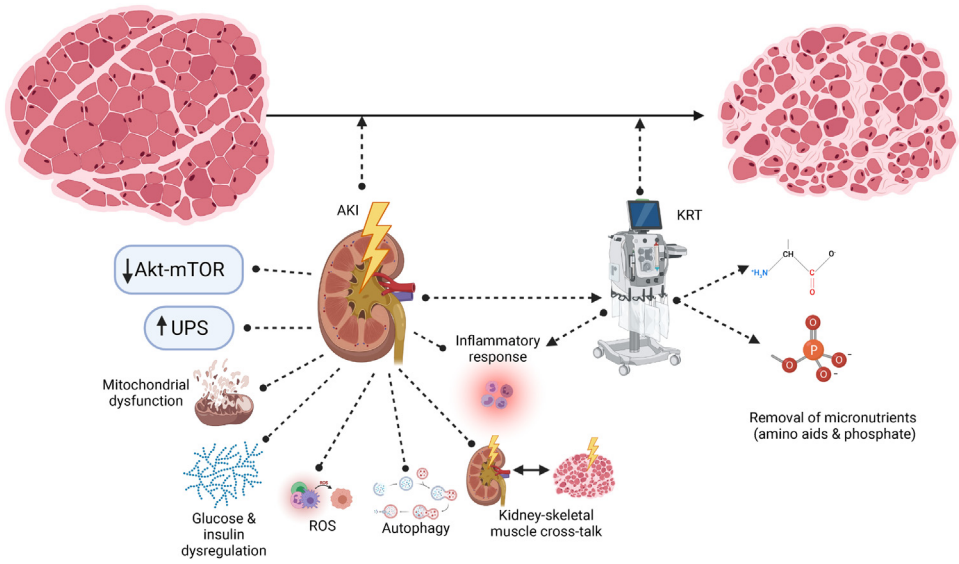

Figure 3. Potential mechanisms of muscle atrophy in critically ill patients with AKI and AKI-KRT. Experimental data have demonstrated that AKI within 24 hours causes muscle wasting by rapid activation of protein degradation via the UPS. This is followed as soon as 48 hours after AKI onset by impaired protein synthesis which is mediated in part by downregulation of the Akt-mTOR kinase pathway that normally functions to promote muscle anabolism in response to physiologic stimuli such as leucine. Abnormal glucose metabolism and insulin response have also been demonstrated in AKI, with AKI appearing to impair the normal ability of insulin to stimulate muscle anabolism, glucose utilization, and glycogen synthesis. AKI itself induces an intense systemic inflammatory response that has been shown to cause tissue damage, inflammation, and dysfunction of multiple distant organs including the heart, and a similar effect on skeletal muscle as has been demonstrated in cardiac muscle may partly mediate AKI-induced muscle wasting. IL-6 in particular may be a central mediator of this effect, as this cytokine has been shown to play a prominent role in the systemic inflammation and organ cross-talk that follows AKI, to mediate muscle wasting in many other clinical settings, and to be upregulated in muscle tissue after AKI. Likewise, AKI and ICU-AW may be linked by oxidative stress as AKI has been shown in animal studies to induce oxidative stress of distant organs, including the heart, and oxidative stress has been associated with skeletal muscle wasting and dysfunction in multiple non-AKI models of ICU-AW. Animal data also implicate possible roles for abnormalities in mitochondrial number and function and dysregulated autophagy. In addition to stimulating inflammation, KRT (especially CKRT) may directly contribute to ICU-AW via the nonselective clearance and the resulting depletion of muscle stores of amino acids, peptides, and small proteins as well as phosphate and other metabolites. Abbreviations: AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ICU, intensive care unit; ICU-AW, ICU-associated weakness; IL-6, interleukin 6; KRT, kidney replacement therapy; mTOR, mammalian target of rapamycin; UPS, ubiquitin-proteasome system. Created with BioRender.com.

limitations, strength testing remains the gold standard and most practical method to diagnose ICU-AW.

ICU-AW: Pathophysiology

Multiple mechanisms have been proposed for ICU-AW (Fig 1). Critical illness is associated with a significant inflammatory response, which has been demonstrated in experimental studies to alter mitochondrial, myofibrillar, and collagen protein homeostasis and to trigger myofibrillary oxidative stress.[19] Additional animal, space flight, and human research has shown that disuse or immobility lead to muscle atrophy through mechanical silencing—the process of inducing myosin loss and atrophy through the removal or reduction of internal (ie, muscle contraction) or external (ie, loading or weight-bearing) stimuli.[31] Patients requiring mechanical ventilation with deep sedation are therefore at the greatest risk of muscle dysfunction. We propose that AKI and AKI-KRT may independently contribute to ICU-AW.

Proposed Mechanisms of Muscle Wasting in AKI

Though muscle wasting in CKD, including in kidney failure, has been studied for decades,[32,33] less is known about muscle wasting in AKI. Some of the mechanisms underlying muscle wasting in CKD may apply to AKI, including systemic inflammation, metabolic acidosis, defective insulin signaling, and malnutrition stimulating mediators of muscle protein catabolism including the ubiquitin-proteasome system (UPS), caspase 3, lysosomes, and myostatin.[34] However, unrelated mechanisms may contribute to muscle wasting in AKI, as AKI and CKD are distinct clinical processes, with AKI having drastically worse prognosis in the ICU.[8,14,15]

The experimental data linking AKI to muscle wasting are summarized in Figure 3 and outlined in detail in Table 2. Collectively, animal studies suggest that AKI of multiple etiologies causes muscle wasting by rapid activation of protein degradation via UPS, subsequently followed by impaired protein synthesis via, in part,

Table 2. Studies in Animal Models Investigating the Mechanisms of Muscle Wasting in AKI

Study	AKI Model & Timing	Findings	Implications
Mitch (1981); Clark & Mitch (1983); May et al (1985)[112-114]	Rat, 24-48 h after bilateral ureteral ligation	• Lower serum AA levels • AA release from perfused rat hindquarter • Findings exaggerated in rats deprived of food and water • Increased protein degradation without changes in synthesis at 24 h • Increased degradation and impaired synthesis present by 48 h • Changes in protein metabolism correlate with changes in insulin-mediated protein synthesis, glucose utilization, and glycogen synthesis	• AA release in AKI is of peripheral/nonhepatic source • Muscle protein degradation occurs soon after AKI, with impaired synthesis occurring later • Dietary changes may exacerbate AKI-induced AA release • Suggests role of defective insulin-induced muscle synthesis and glucose utilization
Flugel-Link et al (1983)[115]	Rat, 30 h after bilateral nephrectomy	• Greater net urea generation • Lower plasma/muscle levels of most AAs • Increased muscle protein degradation • Unchanged or slightly decreased muscle protein synthesis • Net release of phenylalanine, tyrosine, alanine, total AAs, potassium, and phosphate from perfused hemicorpus	• Replicates prior studies with a nephrectomy model of AKI
Baliga & Shah (1991)[116]	Rat, gentamicin-induced AKI, assessed day after 7-d gentamicin exposure	• Net muscle protein degradation significantly increased in AKI rats, but only those fed a high-protein diet • Muscle protein synthesis not affected • Insulin reduced net protein degradation in AKI rats fed low- or normal-protein diet but protein degradation continued despite insulin in AKI rats on high-protein diet	• Replicates possible role of insulin in AKI-induced muscle wasting in nephrotoxic AKI • Confirms changes in net muscle protein balance in early AKI due mostly to increased degradation rather than impaired synthesis • Suggests dietary protein intake may increase risk of AKI-induced muscle wasting in nephrotoxic AKI (not replicated in other models)
Price et al (1998)[117]	Rat, 40 h after bilateral ureteral ligation	• Lower or unchanged serum plasma levels of BCAA • Activity of BCKAD (mitochondrial enzyme and rate limiting step in BCAA catabolism) in muscles increased by >17-fold • Increase in BCKAD activity partly suppressed by correction of acidemia with supplemental sodium bicarbonate • Change in BCKAD activity not due to changes in muscle BCKAD mRNA or protein content	• Suggests AKI-induced catabolism of BCAA partly but not fully mediated by acidosis • Suggests (as serum levels of BCAAs decreased or remained unchanged despite significant increase in BCAA catabolism by BCKAD) serum AA levels can change independently of muscle AA levels in AKI
Andres-Hernando et al (2014)[36]	Mice, 7 d after bilateral IRI (22 min of renal pedicle clamping)	• Using serum glutamate levels as a marker, demonstrated increase muscle catabolism at 7 d after IRI	• Demonstrates AKI-induced muscle catabolism for the first time in ischemic AKI and in a mouse model • Muscle catabolism persists up to 7 d after AKI
McIntire et al (2014)[61]	Rat, 44 h after bilateral ureteral ligation	• Disrupted phosphorylation of mTOR by Akt (which normally stimulates muscle anabolism induced by the BCAA leucine) • Increased muscle levels of IL-6 mRNA, LC3B-II (marker of autophagy), and UPS components (atrogin 1, MuRF)	• Possible mechanism for AKI resulting in muscle wasting resistant to nutritional supplementation • Suggests roles for IL-6–mediated inflammation, autophagy, Akt-mTOR pathway, and UPS in AKI-induced muscle wasting

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Table 2 (Cont'd). Studies in Animal Models Investigating the Mechanisms of Muscle Wasting in AKI

Study	AKI Model & Timing	Findings	Implications
Aniort et al (2016)[62]	Rat, gentamicin-induced AKI, assessed at last day of 7-d gentamicin exposure	• Muscle atrophy (decreased muscle weight) in extensor digitorum longus but not soleus • Activation of UPS components (MuRF-1, atrogin 1) • Downregulation of Akt-mTOR pathway	• Replicates roles of UPS and Akt-mTOR pathway in nephrotoxic AKI • Suggests AKI may preferentially affect phasic muscles rather than postural muscles
Nagata et al (2020)[63]	Mice, 7 d after IRI (15 min of renal pedicle clamping in contralateral nephrectomized rats [AKI + uremia] *or* 35 min of clamping in rats with intact contralateral kidney [AKI without uremia])	• Muscle wasting (decreased weight, myofiber cross-sectional area, and mitochondrial density) and decreased maximal running time in AKI + uremia • Increased muscle tissue expression of mediators of muscle wasting (myostatin, atrogin 1) in AKI + uremia • Decreased Akt phosphorylation in AKI + uremia • Changes in AKI + uremia group partially prevented by regimen of regular treadmill exercise and BCAA supplementation • In AKI without uremia, atrogin 1 expression increased on d 1 but not d 7; muscle weight same as control	• Replicates roles of Akt-mTOR pathway and UPS in ischemic AKI • Suggests role of disordered mitochondrial function/number in AKI-induced muscle wasting • First study to relate biochemical or structural changes to measurable deficit in function • Implies exercise and nutritional supplementation with BCAAs may mitigate muscle wasting in AKI • Implies uremia may be needed for induction of muscle wasting in AKI

Atrogin 1 is also known as muscle atrophy F-box (MAFbx). Abbreviations: AA, amino acid; AKI, acute kidney injury; AMP, adenosine monophosphate; BCAA, branched chain amino acid; BCKAD, branched-chain ketoacid dehydrogenase; IL-6, interleukin 6; IRI, ischemia-reperfusion injury; mTOR, mammalian target of rapamycin; MuRF, muscle RING-finger protein; UPS, ubiquitin-proteasome system.

downregulation or disruption of activation (phosphorylation) of the protein kinase mTOR (mammalian target of rapamycin) by the kinase Akt. The Akt-mTOR signaling pathway has been shown in other settings to promote muscle synthesis and inhibit muscle degradation in response to stimuli such as insulin and insulin-like growth factor 1 (IGF-1).[35] These studies also implicate roles for dysregulated autophagy, mitochondrial dysfunction, and inflammatory mediators, especially interleukin 6 (IL-6).

The ability of AKI to induce systemic inflammation and predispose to skeletal muscle wasting may be considered a form of organ "cross-talk." Notably, such kidney–skeletal muscle cross-talk has been proposed to mediate muscle wasting in CKD.[33] AKI is increasingly recognized as a systemic inflammatory state associated with multiorgan dysfunction induced by tumor necrosis factor α (TNF-α), IL-1, IL-6, and other mediators.[7,36–38] These systemic effects are hypothesized to mediate the high mortality of critically ill patients with AKI and the worse outcomes of ICU patients who are receiving KRT for AKI rather than for chronic kidney failure.[1,7] Specifically, renal ischemia-reperfusion injury has been shown in animal models to induce cardiac oxidative stress, amino acid depletion, cardiomyocyte apoptosis, and systolic and diastolic dysfunction.[37,38] Similar effects of AKI on skeletal muscle may occur. IL-6 specifically has been shown in other animal models to induce or augment muscle catabolism,[39] thereby providing another plausible mechanistic link between AKI and muscle breakdown. However, data to support the theory that direct inflammatory cross-talk between kidney and skeletal muscle mediates AKI-induced muscle wasting remain limited.

Proposed Mechanisms of Muscle Wasting in AKI-KRT

Although AKI itself may promote ICU-AW, AKI-KRT may compound muscle dysfunction by additional mechanisms (Fig 3). The effects of KRT on muscle have been extensively studied in kidney failure, but far less is known about the impact of AKI-KRT on muscle. A recent systematic review on the short-term effects of hemodialysis on skeletal muscle, which included 14 studies of patients with kidney failure, reported variable effects on muscle perfusion and function but consistently found that hemodialysis causes acute muscle protein breakdown and net protein loss, induces markers of muscle protein breakdown (caspase 3 activity and polyubiquitin), and triggers inflammation, especially IL-6.[40]

Hemodialysis and hemofiltration remove unbound water-soluble molecules nonselectively. Therefore, the effects of KRT on muscle may be mediated by nonselective removal of amino acids, peptides, or small proteins. Studies decades ago demonstrated substantial removal of amino acids by intermittent hemodialysis (IHD) in the setting of kidney failure.[41,42] Similar significant dialytic losses of amino acids, peptides, and small proteins have subsequently been demonstrated in AKI-KRT (Table 3).[43–56]

Table 3. Studies in Humans With AKI-KRT Demonstrating Depletion of Amino Acids, Peptides, Proteins, and/or Other Nutrients

Study	Setting	KRT Modality & Approximate Dose	Key Study Features and Findings
Davenport & Roberts (1989)[43]	8 pts on TPN, mechanical ventilation	High-flux CVVH (1 L/h)	• ~2-4 mmol/d of AAs lost in effluent
Davies et al (1991)[44]	8 pts (6 on TPN)	CAVHDF (Qd 1-2 L/h; variable UF)	• Total effluent losses represented ~10% of daily protein input and up to 112% of AA input for specific AAs (eg, tyrosine)
Frankenfield et al (1993)[45]	17 pts (+15 non-KRT controls), trauma with SIRS on TPN	CAVHDF or CVVHDF (Qd 15 or 30 mL/min; variable Qr)	• AA losses (mean: 6.6 g/12 h) 2-3 times higher in CKRT pts than controls; increased with higher Qd and higher serum AA levels but did not correlate with AA intake
Mokrzycki & Kaplan (1996)[46]	7 pts (22 effluent samples; 12 during TPN infusion, 1 during enteral feeding)	CVVH and CVVHDF	• Protein loss of 1.2-7.5 g/d • Protein loss higher in CVVH vs CVVHDF despite lower total effluent dose (mean of ~1,400 vs 1,800 mL/h)
Kihara et al (1997)[47]	6 pts on TPN, on 40 g/d of AAs	PIKRT (slow HD with Qd 20 mL/min for 10 h/d)	• Mean of 6.2 g of AAs eliminated in dialysate per treatment (16% of daily intake; accounting for 43% of the daily negative nitrogen balance)
Novak et al (1997)[48]	6 pts on TPN (4 with multiorgan failure, 2 with isolated AKI); also, 16 healthy controls	CVVHDF (Qd 1 L/h)	• Daily AA nitrogen loss of 0.6 g/d (4.5% of daily input, including 0.2 g/d of nitrogen as glutamine) • Serum levels of most AAs lower than controls but stable during 5 d of CKRT except for glutamine (dropped on d 2 but then returned to baseline)
Scheinkestel et al (2003)[49]	11 pts; anuric; on TPN, mechanical ventilation	CVVHD (with Qd 2 L/h)	• 17% of infused AAs lost in the dialysate • With protein intake <2.5 g/kg/d, 14%-57% of serum AA levels below reference range, but all levels were in reference range when protein intake raised to 2.5 g/kg/d
Chua et al (2012)[50]	7 pts (4 on enteral nutrition, none on TPN)	PIKRT (EDHDF, 8 h/d with Qb 100 mL/min, Qr 21 mL/min, and Qd 280 mL/min)	• AA loss of 4.2 g/d (4.5% of intake in patients on enteral nutrition, accounting for 6.5% of negative nitrogen balance of 10.7 g/d)
Schmidt et al (2014)[51]	5 pts (3 on TPN); 10 KRT sessions	PIKRT (extended dialysis, 10 h per treatment with Qb and Qd of 150 mL/min)	• 10.5 g of AAs removed in effluent per each 10-h treatment, with glutamine accounting for 30% of the AAs removed • Despite removal, pre- and post-KRT serum AA levels did not differ significantly
Umber et al (2014)[52]	5 pts (2 on IV nutrition)	PIKRT (12-h SLED sessions with low-flux dialyzer and Qb 200 mL/min and Qd 100 mL/min)	• Mean AA loss per treatment of 15.7 (range, 10-57) g, including mean of 5.3 g of glutamine • Albumin loss negligible
Stapel et al (2019)[53]	10 pts (8 on enteral nutrition, 1 on parenteral nutrition)	CVVH (high-flux membrane, Qb 180 mL/min, predilution Qr 2.4 L/h)	• 13.4 g/d of AA lost, including 10.4 g in effluent and 2.9 g assumed to be lost by adsorption • Degree of adsorption varied by AA; some seemed to be "generated" (ie, levels higher in effluent than in postfilter blood)
Oh et al (2019)[54]	60 pts (mix of ward and ICU pts; majority malnourished but nutritional input NR)	27 on IHD (2-3 h, Qb 200-250 mL/min; Qd 400-500 mL/min); 12 on PIKRT (SLEDf, 6-8 h daily, Qb 200 mL/min, effluent 200 mL/min); 21 on CVVH (35 mL/min)	• First 1-2 sessions of KRT studied • Micronutrient loss: CVVH >> SLEDf > IHD (eg, mean total AA loss of 18.7, 8.2, and 5.1 g, respectively, per 24-h of CVVH or per IHD/SLEDf treatment) • Differences in modality persisted when correcting for AA plasma concentration and KRT dose; differences attributed to modality (ie, convection vs diffusion vs both) not dose • Serum AA levels dropped with KRT, but rebounded within 2 h of stopping • Variable but marked loss of non-AA trace elements (eg, copper, zinc) • B vitamins undetectable in effluent

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Table 3 (Cont'd). Studies in Humans With AKI-KRT Demonstrating Depletion of Amino Acids, Peptides, Proteins, and/or Other Nutrients

Study	Setting	KRT Modality & Approximate Dose	Key Study Features and Findings
Griffin et al (2020)[56]	11 pts (+2 KF); 7 after cardiac surgery; nutritional input NR	CVVHD (25 mL/kg/h)	• 22/101 measured metabolites decreased in serum by d 2 • Serum levels declined for only 3/20 AAs (alanine, proline, cysteine); other metabolites with significant serum reductions included phosphate and lactate • AAs detected in the effluent in all patients with most sieving coefficients approaching 1 • Reductions largely seen at 24 h after baseline, but no further reduction beyond 48 h, suggesting serum levels of AAs or other metabolites are maintained despite removal by CKRT at the expense of muscle or total body stores
Ostermann et al (2020)[55]	55 pts (31 treated with CKRT); on full-dose enteral nutrition (TPN excluded)	CKRT (mean total effluent dose of 46 L in first 24 h)	• Significant depletion of serum AA levels noted even before CKRT start; depletion of nutrient levels common in both CKRT and non-CKRT groups • All AAs, trace elements, vitamin C, and folate detectable in effluent fluid, but plasma levels of only citrulline, glutamic acid, and carnitine were significantly lower at 24 h in the CKRT vs non-CKRT pts and only the difference in glutamic acid levels persisted to d 6

Abbreviations: AA, amino acid; AKI, acute kidney injury; CAVH, continuous arterio-venous hemofiltration; CAVHDF, continuous arteriovenous hemodiafiltration; CKRT, continuous kidney replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; EDHDF, extended daily hemodiafiltration; HD, hemodialysis; ICU, intensive care unit; IHD, intermittent hemodialysis; IV, intravenous; KF, kidney failure; KRT, kidney replacement therapy; NR, not recorded; PIKRT, prolonged intermittent kidney replacement therapy; pts, patients; Qb, blood flow rate; Qd, dialysate flow rate; Qr, replacement fluid rate; SIRS, systemic inflammatory response syndrome; SLED, sustained low-efficiency dialysis; SLEDf, sustained low-efficiency diafiltration; TPN, total parenteral nutrition; UF, ultrafiltration.

The losses are progressively greater in IHD, prolonged intermittent KRT, and continuous kidney replacement therapy (CKRT),[54] paralleling the cumulative clearance (ie, standardized Kt/V_{urea}) typically provided by each modality.

While KRT clearly removes amino acids, how significantly this contributes to negative protein or nitrogen balance is unclear.[50,55] For example, a recent study of ICU patients with AKI, including 31 CKRT patients and 24 non-KRT patients, measured serum levels of all amino acids at days 1 and 6.[55] Effluent levels of all amino acids were also measured in the CKRT group. However, significant depletion of serum amino acid levels was noted before CKRT initiation, and glutamic acid was the only amino acid with significantly lower levels in CKRT patients than in non-KRT AKI patients.[55] The authors concluded that these findings refute the hypothesis that losses during KRT are the main reason for altered micronutrient profile in AKI patients.[55] However, serum levels of substances do not necessarily reflect total body levels. An alternative hypothesis is that, although AKI alone does indeed result in significant disruption in amino acid metabolism, the added nonselective clearance of amino acids by KRT may aggravate catabolism and total body depletion of amino acids as serum levels are maintained at the expense of muscle breakdown.

Similarly, we performed an analysis of serum and effluent levels of 101 metabolites, including amino acids, in 13 CKRT patients. Despite detecting amino acids in the effluent with most dialyzer sieving coefficients approaching 1, we found reductions in serum levels of only 3 of 20 amino acids.[56] Notably, the reductions were seen at 24 hours after baseline, but thereafter no further reduction in amino acid levels was seen at 48 or 72 hours,[56] again suggesting that serum amino acid levels may be maintained despite ongoing removal by CKRT at the expense of total body/muscle stores.

In addition to amino acids, KRT removes other nutrients, minerals, and metabolites that could potentially affect muscle function.[54-56] Of these, the most studied is phosphate (Table 4). Though readily cleared from the vascular compartment by hemodialysis or hemofiltration, the kinetics of phosphate removal by IHD and CKRT differ dramatically. Because phosphate is primarily intracellular and slowly re-equilibrates with the extracellular compartment, IHD clears a relatively small amount of total-body phosphate with each treatment. CKRT, by virtue of being continuous, overcomes the slow re-equilibration between the intracellular and extracellular compartments.[57] CKRT ultimately removes phosphate so effectively that after 2 to 4 days hypophosphatemia requiring repletion is a near-universal complication when using traditional phosphate-free CKRT solutions.[57]

Phosphate depletion may lead to significant and long-term effects on muscle function. For example, phosphate depletion during CKRT has been linked with decreased erythrocyte levels of 2,3-diphosphoglycerate,[58] which, especially if coupled with hypophosphatemia-induced cardiovascular dysfunction,[59,60] could lead to impairment in oxygen delivery to skeletal muscle. Furthermore,

phosphate depletion also could directly impair the function of kinases in the Akt-mTOR pathway and other signaling pathways responsible for stimulating muscle protein synthesis.[35,61-63]

Data linking hypophosphatemia directly to muscle weakness in general ICU populations are limited.[64] However, multiple observational studies have found hypophosphatemia to be associated with worse outcomes in CKRT patients and suggest that it may contribute to respiratory muscle dysfunction. Specifically, CKRT-induced hypophosphatemia has been independently associated with prolonged mechanical ventilation or increased need for tracheostomy, and, to a lesser degree, with increased hospital length of stay, with variable but generally neutral effects on mortality.[60,65-70]

Unlike phosphate, most standard CKRT solutions contain physiologic or near-physiologic concentrations of potassium, calcium, and magnesium. As such, hypokalemia, hypocalcemia, and hypomagnesemia—though present in a substantial minority of CKRT patients—develop less frequently than hypophosphatemia,[9,10] and fewer data exist on the impact of depletion of these electrolytes on outcomes. As citrate chelates magnesium and calcium, CKRT using regional citrate anticoagulation can cause hypocalcemia and hypomagnesemia,[71] which have both been associated with respiratory muscle weakness in small studies.[72,73] Furthermore, limited data have found associations of hypomagnesemia and hypocalcemia with increased ICU mortality and morbidity, including respiratory failure and/or need for mechanical ventilation,[74-76] potentially implicating respiratory muscle dysfunction. By contrast, hypokalemia developing during CKRT was not found to be associated with mortality in a recent single-center study of >1,200 patients.[77] The relative impacts of CKRT-induced hypokalemia, hypocalcemia, or hypomagnesemia on ICU-AW remain unclear.

Interventions to Mitigate Micronutrient Loss During KRT

Use of amino acid–containing dialysate has been studied in kidney failure, though the impact on outcomes and clinical uptake have been limited.[41,42] There are no studies of amino acid–containing CKRT solutions for AKI-KRT. Studies of amino acid supplementation in CKRT have been performed but with limited impact on outcomes apart from maintenance of serum amino acid levels.[49]

Based on the available data, prevention of hypophosphatemia is a reasonable intervention to mitigate ICU-AW in CKRT patients.[57] The options include adding phosphate to CKRT solutions or using commercially available dextrose-free solutions containing phosphate. Multiple centers, including those using regional citrate anticoagulation, have reported that either option can effectively mitigate hypophosphatemia without effects on solute control apart from modest degrees of hypocalcemia, hypoglycemia, and metabolic acidosis.[67,78,79] Moreover, in a retrospective before-and-after study at one of our centers, the use of phosphate-containing CKRT solutions was independently associated with decreased durations of mechanical ventilation and ICU and length of stay without impact on mortality.[67,78] Though promising, prospective interventional data on phosphate-containing CKRT solutions and outcomes are needed. An alternative to adding phosphate to CKRT solutions to mitigate CKRT-induced hypophosphatemia is to implement preemptive enteral or intravenous phosphate replacement as soon as serum phosphate levels fall to within normal limits, often 24-48 hours after CKRT initiation.[57]

The optimal approach to replacement of other electrolytes in CKRT patients appears less clear. Though typically standard of care, data on the benefits of treating or preventing CKRT-induced hypomagnesemia, hypocalcemia, or hypokalemia—beyond normalizing serum levels—are lacking.[80,81] Interestingly, some animal and observational human data suggest harm from calcium supplementation in the setting of sepsis or general critical illness,[82-84] but the relevance of these observations to KRT patients is unclear.

Similarly, though nutrition is essential supportive care in the ICU, the optimal nutritional approach to mitigate ICU-AW in patients with AKI or AKI-KRT is unclear. Despite some data suggesting that standard approaches to estimating nutritional needs perform poorly in critically ill AKI patients,[85] guidelines recommend, based on low-quality evidence, that AKI patients receive the same targets as other ICU patients for protein (1.2-2 g/kg/d) and total calories (25-30 kcal/kg/d).[86] In patients requiring CKRT or frequent KRT, additional protein supplementation up to 2.5 g/kg/d is recommended to counteract amino acid loss.[86] Notably, secondary outcomes of some large RCTs of nutrition in the ICU suggest that earlier initiation of supplemental nutrition and/or higher caloric intake may be associated with prolonged need for KRT or delayed kidney recovery.[87,88] Furthermore, higher protein intake has not been convincingly associated with improved outcomes in general ICU populations, with a recent meta-analysis demonstrating attenuation of muscle loss but no impact on measured muscle strength, QoL, discharge destination, or mortality.[89] Likewise, a recent study of 15 ICU patients demonstrated impaired incorporation of nutritional amino acids into skeletal muscle despite normal enteral protein digestion and absorption.[90] High-quality prospective data on optimal nutrition for ICU patients with AKI or AKI-KRT are needed.

Physical Rehabilitation/Early Mobilization to Mitigate ICU-AW in Patients With AKI

Early mobilization, physical rehabilitation, and exercise are the primary approaches to reducing the detrimental effects of prolonged immobilization or bedrest.[91] Multiple factors have been proposed as barriers to early mobilization in the

Table 4. Studies of Hypophosphatemia Induced by KRT and Clinical Outcomes

Study	Setting	Key Findings
Demirjian et al (2011)[66]	321 AKI pts on CVVHD for >2 d	• Hypophosphatemia (<2 mg/dL) in 27% • Decline in serum phosphate independently associated with higher rate of prolonged respiratory failure requiring tracheostomy (OR, 1.81) but not 28-d mortality
Yang et al (2013)[69]	760 AKI pts on CVVH	• Incident hypophosphatemia (<2.5 mg/dL) not associated with outcomes in overall cohort • In subgroup of 521 (69%) pts with hypophosphatemia, ratio of total days with hypophosphatemia over total CVVH days independently associated with 28-d mortality (OR, 1.45; $P = 0.008$)
Bellomo et al (2014)[70]	1,441 pts on CVVHDF (either 25 or 40 mL/kg/h of total effluent dose; ratio of Qd and postfilter Qr of 1:1)	• Post hoc analysis of RENAL trial[9] (comparing 2 doses of CKRT for AKI in ICU) • Hypophosphatemia (<0.6 mmol/L) developed in 32%, peak incidence on CKRT d 2 and 3 • Hypophosphatemia not independently associated with 90-d mortality
Sharma et al (2015)[58]	20 CKRT pts (19 on mechanical ventilation; 4 on parenteral nutrition, 10 on enteral nutrition); also, 10 controls (surgical pts mostly without AKI)	• Mean RBC 2,3-DPG level decreased after 2 d of CKRT; associated with lower oxygen carrying capacity (ie, mean P_{O_2} required for 50% Hb saturation) • Reduction in 2,3-DPG levels reached 29% in the 3 pts still on CKRT at d 7 • Reductions in 2,3-DPG correlated with negative phosphate balance despite maintenance of normal serum phosphate levels • Greater reduction in 2,3-DPG associated with increased HR for death
Lim et al (2017)[60]	96 AKI pts (64 [67%] on mechanical ventilation; 44 had CKRT only, 28 IHD only, and 24 both)	• Secondary analysis of single-center cohort study • 25 pts developed hypophosphatemia and had longer duration of vasopressor support and mechanical ventilation, with the latter persisting on multivariable analysis (AOR, 14); no difference in ICU mortality
Hendrix et al (2020)[68]	72 pts (60 AKI; 12 KF); all had ≥12h of CKRT	• Hypophosphatemia (<2.5 mg/dL) in 45 (63%) • Hypophosphatemia associated on univariable analysis with increased ICU LOS ($P = 0.014$) but not with hospital LOS, AKI recovery, duration of mechanical ventilation, or ICU mortality
Sharma et al (2020)[65]	907-pt subset of ATN trial on mechanical ventilation, 80% started KRT with CVVHDF, 15% with IHD, 4.5% with SLED	• In post hoc analysis of ATN trial[10] of KRT intensity in AKI, pts randomized to more-intensive (vs less-intensive) KRT had a lower rate of successful extubation (HR, 0.67; $P < 0.001$), or 1 fewer ventilator-free day over 14 d • More intensive KRT resulted in more hypophosphatemia • Statistically significant interaction between effect of treatment group on extubation rates and tertiles of baseline phosphate, with pts in lowest tertile (≤4.3 mg/dL) having 43% lower hazard rate of successful extubation if assigned to intensive group • Effect of treatment intensity statistically significant in pts treated with CKRT and SLED but not in pts treated with IHD
Thompson-Bastin et al (2021)[78]	1,396 CKRT pts (511 had phosphate-free solutions; 885 had phosphate-containing solutions)	• Single-center retrospective before-and-after study • Hypophosphatemia (<2.5 mg/dL) in 21% of those treated with phosphate-containing CKRT solutions vs 62% of those treated with phosphate-free solutions, with phosphate-free solutions associated with 8× higher adjusted incidence of hypophosphatemia ($P < 0.001$) • Phosphate supplementation requirement higher in nonphosphate group ($P < 0.001$)
Thompson-Bastin et al (2022)[67]	992 intubated CKRT pts (343 had only phosphate-free CKRT solutions; 649 had only phosphate-containing solutions)	• Single-center retrospective before-and-after study of only mechanically ventilated patients • Treatment with phosphate-containing CKRT solution independently associated in multivariable analysis with 12% more ventilator-free days, 17% fewer ICU days, and 20% fewer hospital days • Reduction in ventilator-free days reproduced in propensity score analysis of 303 pairs of pts • No impact on mortality

Abbreviations: AKI, acute kidney injury; AOR, adjusted hazard ratio; CKRT, continuous kidney replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; 2,3-DPG, 2,3-diphosphoglycerate; Hb, hemoglobin; HR, hazard ratio; ICU, intensive care unit; IHD, intermittent hemodialysis; KF, kidney failure; KRT, kidney replacement therapy; LOS, length of stay; OR, odds ratio; P_{O_2}, partial pressure of oxygen; Qd, dialysate flow rate; Qr, replacement fluid rate; RBC, red blood cell; SLED, sustained low-efficiency dialysis; TPN, total parenteral nutrition.

ICU including vasopressor and sedative use and, in AKI-KRT patients, the presence of vascular catheters and ongoing KRT.[92] However, clinical practice and recent research have demonstrated that these barriers can be overcome.[93-95] Strategies that we and others have reported include disconnection from the KRT circuit during

mobilization, extensions placed on KRT lines, portable batteries to mobilize patients with KRT machines, and temporarily adjusting the KRT prescription (eg, to recirculation mode or to pause net ultrafiltration) to facilitate rehabilitation.[94]

Catheter type (ie, nontunneled vs tunneled) and access site (ie, femoral vs jugular) may influence the perceived feasibility of mobilizing KRT patients.[93] However, in one prospective study, 77 patients with a total of 92 femoral venous or arterial catheters suffered no catheter-related complications during mobility sessions including hip flexion.[96] Another study of 101 ICU patients with femoral catheters receiving 253 therapy sessions, including standing, walking, sitting, supine cycle ergometry, and in-bed exercises, reported no catheter-related adverse events.[97] Collectively, these data suggest that mobilization of ICU patients with femoral catheters is feasible and safe.

We recently performed a systematic review analyzing adverse events, both major (ie, catheter dislodgement, accidental extubation, bleeding, fall, hemodynamic emergency) and minor (ie, desaturation, hypotension, bradycardia, tachycardia), reported in 10 observational studies involving 840 mobility sessions during CKRT and found pooled rates of 1.6% and 0.2% for minor and major adverse events, respectively.[95] Finally, the 2014 expert recommendations on safety criteria for active mobilization of mechanically ventilated adults concluded that in-bed or out-of-bed exercises can be performed during CKRT with low risk of adverse events.[98] Though it seems probable that early mobilization in CKRT patients would have a meaningful benefit on outcomes, randomized trials to prove this hypothesis are lacking.

Postdischarge Care for ICU-AW in AKI Survivors

Advancements in intensive care have led to increasing survival over the past 2 decades,[99] but ICU survivors also often face significant impairments in cognitive, emotional, and physical health. Post-intensive care syndrome (PICS) encompasses the development or exacerbation of symptoms or impairments after critical illness in the cognitive,[100] psychiatric,[101] or physical[25] domains and has become an increasing focus of postdischarge care being provided in multidisciplinary PICS clinics. Though some benefit in terms of decreased readmissions and posttraumatic stress disorder has been demonstrated,[102,103] no studies thus far have demonstrated improvements in functional status through rehabilitation provided by these clinics.

Similarly, dedicated post-AKI clinics have increased in number over the past decade, and tailored outpatient nephrology follow-up evaluation has been advocated as an intervention to improve post-AKI outcomes.[104] Observational data[105,106] suggest that early nephrology follow-up evaluation after AKI improves outcomes, though prospective studies thus far have been scarce and have produced mixed results,[107] supporting the need for further interventional trials.

No data exist on how to best address persistent ICU-AW in AKI survivors, but we propose that nephrologists providing post-AKI ambulatory care should, at a minimum, recognize these patients as being at high risk of long-term functional impairment and, where feasible, consider referral to physical and occupational therapy for evaluation and treatment. Future studies should therefore investigate whether providing rehabilitation is useful in addressing long-term physical impairments in AKI survivors and, if so, how to best deliver such care. One novel model could be to provide post-AKI nephrology visits within or in coordination with multidisciplinary PICS clinics, which could potentially improve the feasibility of providing systematic post-AKI care.[107] Alternatively, for AKI patients requiring postdischarge outpatient KRT, providing rehabilitation services or exercise training during hemodialysis, similar to interventions that have proven to some degree to be beneficial in kidney failure,[108] could prove effective.

Conclusions and Future Directions

Critically ill patients who develop AKI are at high risk of skeletal muscle loss and dysfunction and associated long-term impairments in physical function and QoL. The need for KRT during the hospital stay likely further exacerbates the risk of ICU-AW. Nephrologists must work with ICU teams to address potentially modifiable risk factors for ICU-AW and coordinate multidisciplinary care to optimize delivery of rehabilitation. The development of KRT quality assurance teams[109] to advocate for excellence in KRT and create protocols to prevent complications such as hypophosphatemia, optimize nutritional support, and enhance delivery of physical therapy may mitigate the burden of ICU-AW in patients with AKI-KRT.

Furthermore, though data to support such approaches remain limited, advances in proteomics and metabolomics may further enhance our understanding of how ICU patients adapt to extracorporeal therapies that nonselectively clear solutes. Specifically, improved characterization of the resulting metabolic derangements through analyses of tissue, blood, and effluent could promote the development of precision medicine approaches to reestablishing homeostasis in critically ill patients with AKI-KRT. In conclusion, additional experimental research and clinical trials are direly needed to better understand the mechanisms that link critical illness, AKI, and KRT to ICU-AW and to ultimately develop and validate treatment strategies to prevent and mitigate ICU-AW in these high-risk patients.

Article Information

Authors' Full Names and Academic Degrees: J. Pedro Teixeira, MD, Kirby P. Mayer, DPT, PhD, Benjamin R. Griffin, MD, Naomi George, MD, MPH, Nathaniel Jenkins, PhD, C. Anil Pal, MD, Felipe González-Seguel, PT, MSc, and Javier A. Neyra, MD, MSCS.

Authors' Affiliations: Division of Nephrology, Department of Internal Medicine (JPT, CAP), Center for Adult Critical Care (JPT, NG), and Department of Emergency Medicine (NG), University of New Mexico,

Albuquerque, New Mexico; Department of Physical Therapy, College of Health Sciences, University of Kentucky, Lexington, Kentucky (KPM); Division of Nephrology, Department of Internal Medicine (BRG), and Department of Health and Human Physiology (NJ), University of Iowa, Iowa City, Iowa; Servicio de Medicina Física y Rehabilitación, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Santiago, Chile (FG-S); and Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama (JAN).

Address for Correspondence: J. Pedro Teixeira, MD, University of New Mexico School of Medicine, MSC10-5550, 1, University of New Mexico, Albuquerque, NM 87131 (email: jteixeira@salud.unm.edu) or Javier A. Neyra, MD, MSCS, Heersink School of Medicine, Division of Nephrology, 638 Zeigler Research Bldg, 703 19th St S, Birmingham, AL 35294 (email: jneyra@uabmc.edu).

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