CHAPTER 74

Amino Acid Turnover, Protein Metabolism, and Nitrogen Balance in Acute Kidney Injury

Horng-Ruey Chua and Zudin A. Puthucheary

OBJECTIVES

This chapter will:

1. Discuss the concept, pathogenesis, and impact of protein energy wasting in a patient with critical illness and acute kidney injury.
2. Discuss the significance of muscle wasting in conjunction with protein catabolism early in critical illness.
3. Discuss the effects of acute kidney injury and renal replacement therapy on amino acid and nitrogen balance.
4. Relate these concepts with purported nutritional management strategies to optimize tissue protein metabolism and discuss their impact on patient outcomes.

The critically ill patient with an inflammatory milieu suffers from a state of adverse tissue metabolism, from increased hepatic gluconeogenesis, protein catabolism, and muscle wasting. Severe sepsis and cardiogenic shock contribute to the development of acute kidney injury (AKI), which occurs in as many as 67% of intensive care unit (ICU) admissions.[1,2] Worsening stages of AKI are consequent to increasing severity of underlying critical illness, and patients with AKI in need of renal replacement therapy (RRT) have prolonged hospitalization and high mortality in excess of 40%.[3,4] Therefore patients with critical illness and AKI experience the worst metabolic derangements in nutrition, the latter compounded by further inflammatory stress from nosocomial infections. RRT facilitates nutritional support

TABLE 74.1

Projected Protein (and Nitrogen) Balance for a 70-kg Adult in Metabolic Equilibrium

SUBSTRATES	ENTERAL INTAKE WITH CALORIES OF 1.5 kcal/mL AND PROTEIN CONTENT OF 70 g/L		EXCRETORY PRODUCTS AND SECRETIONS		BALANCE
Enteral intake volume[a]	60 mL/hr =	estimated 1.4 L/day	Urine:	e.g., 2.0 L/day	Net even balance
Other fluid intake		estimated 0.6 L/day			
Caloric content	30 kcal/kg/day =	2100 kcal/day	—	—	
Protein content	1.4 g/kg/day =	98–100 g/day	Back-calculated from N loss[b]:	6.25 × 16 = about 100 g/day	Net even balance
N content	16% × 98 g/day[b] =	16 g/day	Total of sub-losses:	16 g/day	Net even balance
—	—	—	Urine urea N (85%) (6 g/L =	12 g/day)	
—	—	—	Other urine N (15%)[c] (Estimated =	2 g/day)	
—	—	—	Fecal N[d] (Estimated =	1.5 g/day)	
—	—	—	Dermal and other N[d] (Estimated =	0.5 g/day)	

[a]Assuming 100% enteric absorption, which is almost impossible. It is also difficult to quantify protein content accurately in general dietary intake.
[b]Back-estimation based on physiologic understanding that N content is 16% of protein content (g).
[c]Other urinary N loss in form of ammonia, creatinine, uric acid, free amino acids, trace protein, etc. Can be calculated assuming urea N accounts for 85% of total N loss.
[d]Insensible loss that is very difficult to quantify except in tightly controlled experimental conditions, hence based on prior observations and assumptions.
Please Note: One can tell that these calculations to ascertain N balance are prone to inaccuracies resulting from assumptions in various steps. However, it is more likely to ***underestimate losses*** than overestimate intake because of incomplete enteric absorption and insensible losses that are unaccounted for.
N, Nitrogen.

by azotemic and volume control in acute uremic and oligoanuric states but may lead to undesired loss of nutrients of low molecular weight with extended therapy of high intensity, including glucose, amino acids, selected vitamins, and trace elements. An understanding of protein metabolism in these scenarios will help the clinician manage these patients in hope of optimizing muscle mass and physical function in the medium term for survivors.

NITROGEN, AMINO ACIDS, AND PROTEIN BALANCE

Nitrogen is the fundamental component of amino acids (AAs), and AAs form the molecular structure of proteins. Proteins are polymers of AAs linked by peptide bonds. They are major functional substrates in cells and tissues and are essential for body growth, maintenance, and recovery. Protein metabolism also generates calories, about 4 kcal/g, similar to carbohydrates. Protein degradation by enzymatic reactions releases nitrogen. Nitrogen is lost in body secretions and excreted in sweat, feces, and urine, the latter most notably as urea nitrogen that accounts for 85% to 90% of urinary nitrogen loss.[5] The remaining urinary nitrogen is lost as creatinine and ammonia that facilitates hydrogen ion excretion in renal tubular acid-base handling, and as a trace protein.

In a healthy adult human with *metabolic equilibrium,* stable protein intake and synthesis should be balanced by protein degradation and loss to maintain tissue integrity. *This should allow stable body muscle mass and anthropometry.* In simplistic terms, *nitrogen balance,* which infers the difference of nitrogen intake and nitrogen loss, can be measured in nutritional intake and excretory products to reflect overall protein balance, given physiologic understanding that most proteins and AAs are 15.6% nitrogen by weight.[6] These sound ideal in theory but are subjected to various assumptions and inaccuracies in quantification (especially with insensible body losses and gut bacterial turnover, etc.). See Table 74.1 for further illustration of this concept.

Different types of AAs may exert varying significance. Tissue protein is synthesized from an intracellular pool of 21 AAs, of which 9 are termed essential (EAAs), because these are from dietary sources and not synthesized de novo. Estimated daily requirements of individual EAAs in steady state are inferred from respective nitrogen balance or isotope studies. The other nonessential AAs (NEAAs) are interconvertible and synthesized in the body or from other dietary AAs[7] (Table 74.2). The reader may refer to more detailed biochemistry reviews on protein metabolism.[8]

PROTEIN AND MUSCLE TURNOVER

Increase in muscle activity stimulates the expression of insulin-like growth factor-1 (IGF-1), which is expressed ubiquitously in muscles and mitosis-competent cells. IGF-1 induces downstream autocrine and paracrine activities, including phosphoinositide 3-kinase (PI3K), downstream Akt (protein kinase B), and mTOR (mammalian target of rapamycin) phosphorylation-activations, to promote protein synthesis and muscle hypertrophy.[9] Protein synthesis is an energy-dependent process, with three phases, controlled in part by three groups of proteins: initiation (controlled by eukaryotic initiation factors, or EIFs), elongation (eukaryotic elongation factors, EEFs), and termination (eukaryotic release factors, ERFs). After termination, proteins undergo tertiary and quaternary structure development and folding.[10]

The reverse happens when Akt is downregulated via dephosphorylation, PTEN (phosphatase and tensin homolog), and SHIP (SH2-domain-containing inositol 5′-phosphatase). Breakdown is mediated through the ubiquitin-proteasome pathway, where proteins are ubiquitinated/conjugated and undergo proteasome-led recognition and degradation by proteasome.[11] Forkhead box group O-1 (FOXO1) translocation into the nucleus increases transcription of ubiquitin ligases (the most common is muscle ring finger protein-1 [MURF-1] and Atrogin-1 or Muscle Atrogen F-box protein 1 [MAFBx],

TABLE 74.2

List of Essential (Indispensible) and Nonessential (Dispensible) Amino Acids in Humans

LIST OF AMINO ACIDS (AAs)	COMMENTS ON RESPECTIVE SIGNIFICANCE	ESTIMATED DAILY REQUIREMENT (mg/kg/day)
Essential AAs	(Indispensible and not synthesized de novo, therefore required in diet)	
Histidine	Reduced hemoglobin concentration is observed with prolonged histidine-free diet	10
Leucine	Branched-chain AA. Most abundant AA in food proteins	39
Tryptophan	Precursor for metabolites such as serotonin and nicotinamide	4
Methionine	Metabolism of which yields cysteine	15 (including cysteine)
Phenylalanine	Metabolism of which yields tyrosine. Precursor of catecholamines and thyroid hormone	25 (including tyrosine)
Threonine		15
Lysine		30
Valine	Branched-chain AA	26
Isoleucine	Branched-chain AA	20
Nonessential AAs	(Synthesized de novo, but may become deficient in certain conditions or disease states)	
Arginine	Precursor of nitric oxide	
Cysteine	Synthesized from methionine, and is synthesized to taurine. Reduced in premature infants	
Selenocysteine	Synthesized from cysteine or dietary selenomethionine	
Tyrosine	Synthesized from phenylalanine, reduced in premature infants	
Glutamine	Constitutes > 60% of total free AA pool in skeletal muscle	
Others	Glycine, proline, alanine, asparagine, aspartic acid, glutamic acid, serine	

Please Note: Effective use of intakes of indispensible AAs at the lower end of requirement range can occur only with adequate amounts of dispensible AAs contributing to the overall nitrogen pool. However, consumption of excessive indispensible AAs paradoxically may consume dispensible AAs in detoxifying them. Therefore metabolism of indispensible or dispensible AAs are interdependent.
AAs, Amino acids.

and other newly discovered ones.[12,13] These ligases bind ubiquitin to proteins, forming an ubiquitin chain, targeting said proteins for proteolysis and AA release by the 20S proteasome. The ubiquitin-proteasome pathway is adenosine triphosphate (ATP) dependent, and in the setting of unstable patients other pathways may be activated such as the autophagic-lysosomal pathway. Myostatin, a member of transforming growth factor-β (TGF-β) superfamily, also works on downstream deregulation of Akt-mTOR pathways, as does nuclear factor-κβ, which may modulate the tumor necrosis superfamily receptor activation. Fig. 74.1 illustrates these interactions in maintaining protein metabolism and facilitating muscle turnover.[14]

PROTEIN ENERGY WASTING AND MUSCLE WASTING IN CRITICAL ILLNESS AND ACUTE KIDNEY INJURY

The inflammatory milieu during critical illness results in decreased protein synthesis, shifting the balance toward net protein catabolism. This is common across a range of factors associated with critical illness, including sepsis, trauma, and burns, and compounded by various comorbidities often present in an aging population. Immobilization further contributes to the impaired stimulus for muscle protein synthesis. Acquired insulin resistance secondary to impaired GLUT-4 membrane translocation contributes to hyperglycemia and inhibits protein synthesis.[15] Protein catabolism is driven by systemic inflammatory response syndrome,[16] oxidative stress, and catabolic hormones, including catecholamines and glucocorticoids.[17] Muscle protein degradation occurs along with increased hepatic gluconeogenesis and ureagenesis from AAs, as promoted by cortisol and glucagon, respectively, with stimulated hepatic diversion to production of acute phase reactants. The markedly reduced systemic concentrations of most AAs seen in sepsis may suggest enhanced hepatic extraction to fuel this process.[18]

Such catabolic effect of critical illness and multiorgan dysfunction probably overwhelms that from AKI alone.[19] AKI and tubular injury augment the inflammatory stress.[20] Proximal renal tubular epithelial cells secrete inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukins,[21] which potentially are upregulated in AKI. Metabolic acidosis (from acute illness and/or AKI) and hyperparathyroidism (with more prolonged AKI) worsen the catabolism, as inferred from studies in chronic kidney disease (CKD).[22,23] Anorexia and reduced nutrient intake before and during early hospitalization are worsened because of volume intake restriction in oligoanuric AKI and gastrointestinal intolerance during acute phase of critical illness. In patients who receive RRT, early generation regenerated cellulose (cuprophan) membranes are less biocompatible than modern synthetic membranes (e.g., polyamide, polysulfone, polyacrylonitrile), and the former invokes more complement activation with blood-membrane contact,[24,25] which may aggravate protein catabolism.[26–28] The term *protein energy wasting* (PEW), introduced by the International Society of Renal Nutrition and Metabolism in 2008 to describe this phenomenon in CKD, but similarly applicable in AKI, aptly describes the above condition[29] (Fig. 74.2).

Protein catabolism in critical illness with or without AKI translates to early and severe skeletal muscle wasting in patients. This was demonstrated elegantly in an observational study, which reported pronounced reduction in muscle bulk by ultrasonographic measurements, with consistent histologic features in muscle fibers and depressed protein to DNA ratio, *over the first week* of ICU care.[30]

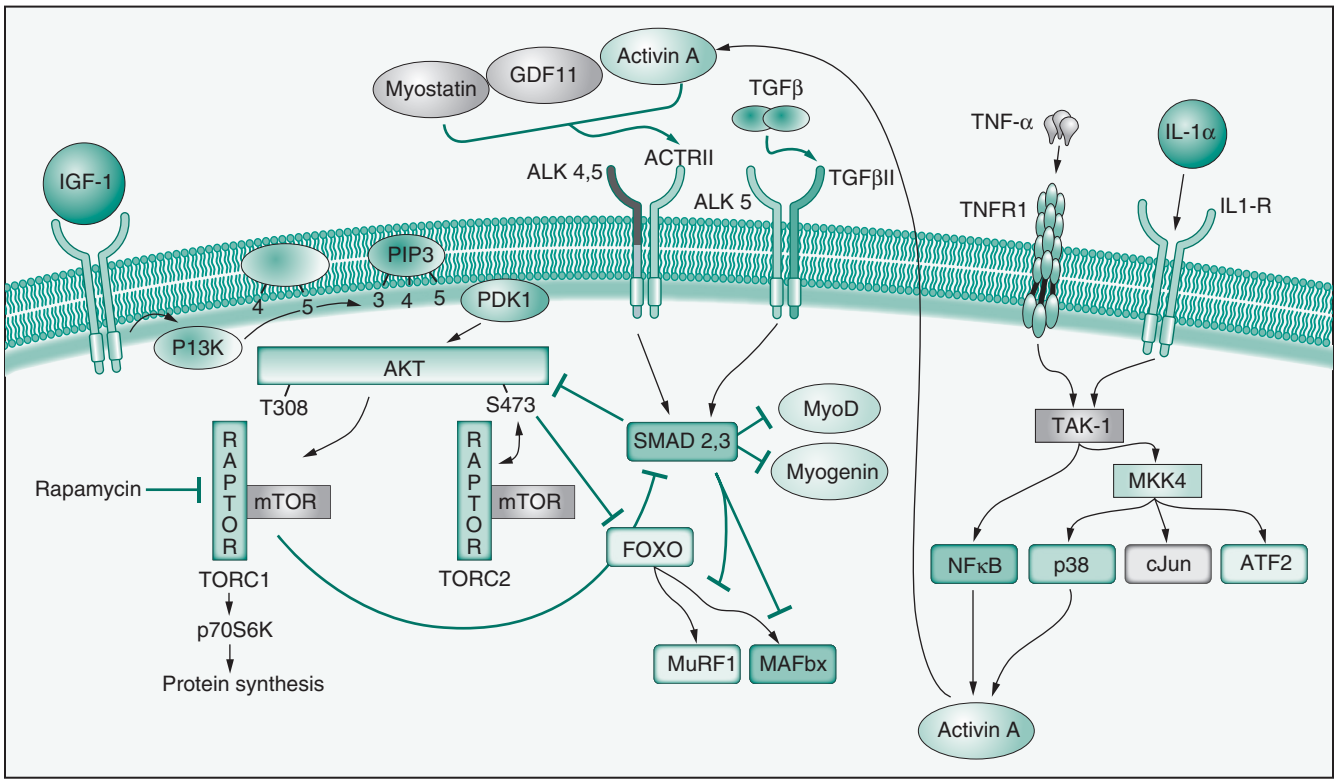

FIGURE 74.1 Muscle protein synthesis and degradation signaling pathways. From Fearon KC, Glass DJ, Guttridge DC. Cancer Cachexia: Mediators, Signaling, and Metabolic Pathways. *Cell Metabolism.* 2012;16(2):153–166.

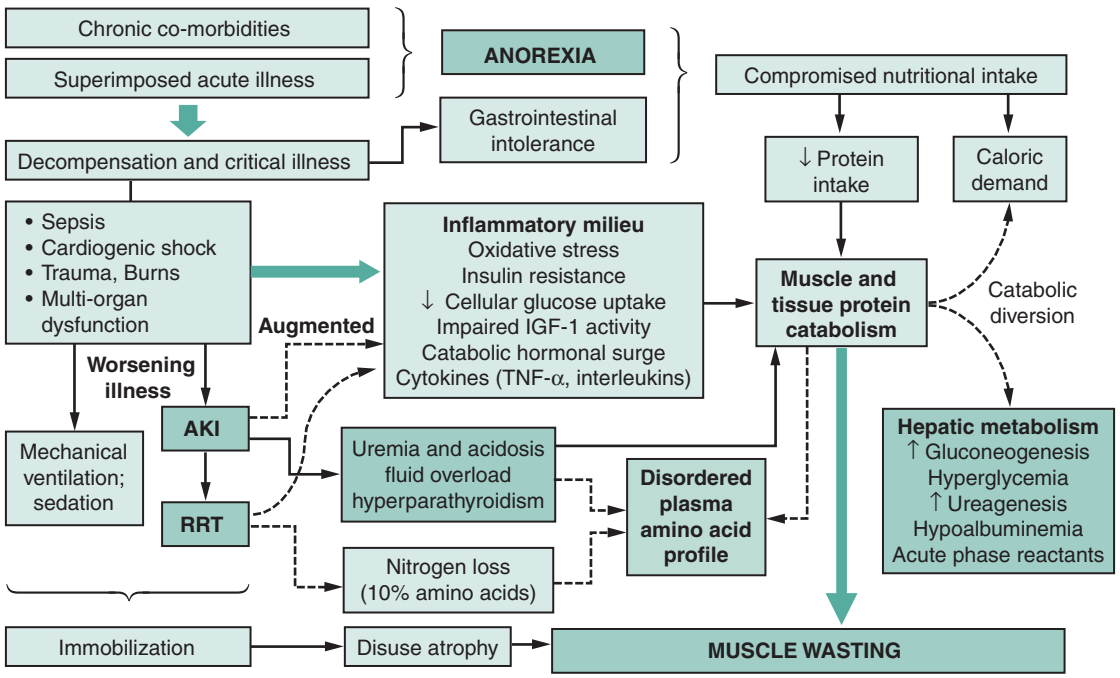

FIGURE 74.2 Protein catabolism in critical illness and acute kidney injury-renal replacement therapy. Modified from *Cell Metabolism* 2012;16:153–66 (Figure 3).

Muscle protein synthesis was depressed to levels seen in healthy fasting state initially, rising to rates comparable with healthy fed state by 1 week, *but yet remained in net catabolism*. The degree of muscle wasting was significantly worse in patients with multiorgan failure (vs. single organ). Older age, metabolic acidosis, and lower ratio of PaO_2 to FiO_2 were associated with greater loss of muscle mass. Interestingly, no clear single molecular mechanism based on physiologic understanding, correlated with muscle loss and proteolysis, suggesting incomplete understanding of molecular signaling in muscle protein turnover in critical illness.

AMINO ACID AND NITROGEN BALANCE IN ACUTE KIDNEY INJURY AND RENAL REPLACEMENT THERAPY

Plasma Profile of Amino Acids in Acute Kidney Injury

AA metabolism also is affected by impairment of renal metabolic function. Under physiologic conditions, various AAs are synthesized or converted by the kidneys and released into the circulation, including arginine, tyrosine, cysteine, methionine (from homocysteine), or serine.[31] This balance can be disrupted in acute illness and AKI, rendering the usual NEAA conditionally indispensible. It also implies imbalance in plasma and intracellular AA pool in AKI. For example, plasma concentrations of essential AAs such as methionine and phenylalanine are elevated, whereas levels of valine, leucine, threonine, tryptophan, and lysine are either at lower limits or decreased, compared with respective reference ranges.[32,33] These plasma AA levels are generally lower than benchmark in patients who are fasted versus those receiving enteral nutrition (EN) (Fig. 74.3).[33] In AKI-RRT studies with administration of total parenteral nutrition (TPN), plasma AA levels tend to be higher than or normal compared with reference range or controls in patients with protein intake of more than 2 g/kg/day,[34,35] versus lower levels when protein intake is less.[36,37] The significance of these observations is unclear, because elevated levels do not necessarily translate to improved tissue utilization for protein anabolism.

Impact of Renal Replacement Therapy on Amino Acid Clearance

The molecular weight of proteins ranges from 55 to 220 kDa, well above the cutoff of standard dialyzer membranes. Therefore protein or high molecular weight peptide losses during RRT occur mostly via membrane adsorption, the latter being influenced by electrostatic interactions, hydrophilicity, and hydrophobicity. These include albumin (66 kDa) and inflammatory cytokines.[38,39] Adsorption on polymethylmethacrylate membranes results in in vitro albumin loss of 2.5 g over 12 hours, but less so (<0.5 g) with polysulfone or polyacrylonitrile membranes.[40]

AA molecular weight is about 110 Da (75–204 Da) and AAs are lost in effluent with diffusive and convective clearances. The majority of AAs have high sieving coefficient (SC) near 1.0, such as cysteine, arginine, alanine, and glutamine, except for glutamic acid (0.25–0.5).[36,41] Glutamic acid has a low isoelectric pH, and it assumes a negative surface charge at physiologic pH.[42] Such AAs may be repelled by the negative surface charge on most synthetic membranes, thus resulting in a low SC.[41] AA clearances range from 30 to 70 mL/min during prolonged intermittent RRT (PIRRT),[33] to 20 to 45 mL/min during continuous RRT (CRRT),[34,36,37,43] and can be 30% to 40% higher with continuous hemofiltration versus hemodialysis.[41] There is, however, no consistent trend in extent of clearance for EAA or NEAA, but more recent studies on PIRRT identified relatively higher clearances for EAA, such as lysine, leucine, phenylalanine, (about 50 mL/min),[33] and highest for valine (140 mL/min).[44]

Protein, Amino Acid, Nitrogen Loss During Renal Replacement Therapy

AA balance in AKI-RRT is studied primarily in the context of TPN and less with EN, because enteric absorption is impossible to measure accurately. AA losses account for 5% to a substantive 20% of daily AA intake,[34–37,41,43,45,46] and AA/protein loss seems less with lower protein intake.[43,45,47] For example, protein intake of more than 1.5 g/kg/day is associated with AA loss of about 12 g/day.[34,41,46] This is because higher intake generally leads to higher plasma AA levels, and plasma levels correlate well to corresponding loss with RRT.[35,43,45,46] *However, fractional AA loss (relative to intake) reduces instead with increasing protein intake,* with the most optimal nitrogen balance achieved at protein intake of 2.5 g/kg/day.[34,35] There is weak evidence that AA loss is marginally higher with convective versus diffusive techniques, and with higher therapy intensity.[36,48] There are also selective AA losses. NEAAs, including alanine and especially glutamine, consistently are reported to be lost in greater absolute amounts,[33,34,44,49] and tyrosine has the highest fractional loss per intake.[34,35] These may contribute to their conditional indispensability. EAAs, including valine, lysine, phenylalanine, are lost in larger amounts but not consistently.

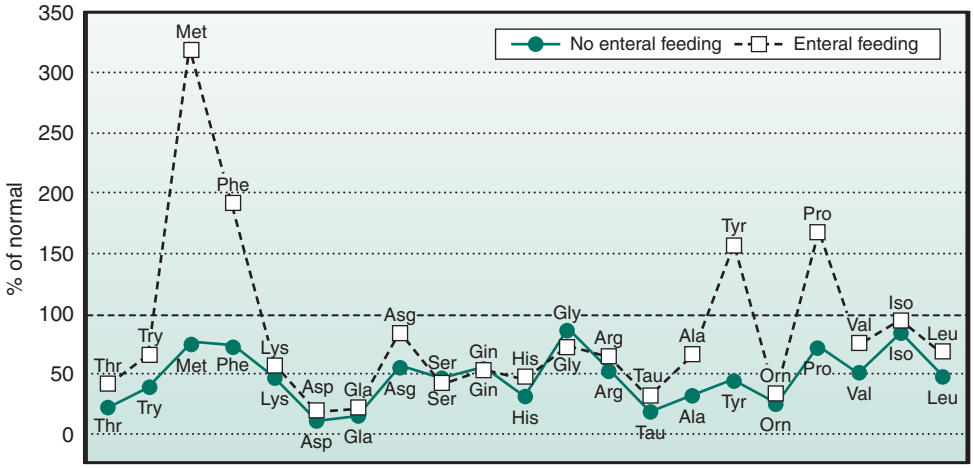

FIGURE 74.3 Plasma amino acid profile in critical illness and acute kidney injury. *Ala,* Alanine; *Asg,* asparagine; *Asp,* aspartic acid; *Arg,* arginine; *Gla,* glutamic acid; *Gln,* glutamine; *Gly,* glycine; *His,* histidine; *Iso,* isoleucine; *Leu,* leucine; *Lys,* lysine; *Met,* methionine; *Orn,* ornithine; *Phe,* phenylalanine; *Pro,* proline; *Ser,* serine; *Tau,* taurine; *Thr,* threonine; *Try,* tryptophan; *Tyr,* tyrosine; *Val,* valine. From Chua, HR et al. Amino acid balance with extended daily diafiltration in acute kidney injury. *Blood Purif.* 2012;33:292-299. (DOI: 10.1159/000335607).

TABLE 74.3

Summary of Renal Replacement Therapy Studies Examining Amino Acid and Nitrogen Balance in Critical Illness and Acute Kidney Injury

STUDIES	NUTRITION	PROTEIN/AA INTAKE	MODE	AA CLEARANCE (mL/min)	AA LOSS	FRACTIONAL LOSS OF DAILY PROTEIN/AA INTAKE	NITROGEN LOSS
CRRT Studies							
Frankenfield 1993 (n = 19)[46]	TPN	2.2 g/kg/day	CAVHDF/ CVVHDF	NR	10–16 g/day (Gln 2 g/day)	6%–9%	NR
Novak 1997 (n = 6)[37]	TPN	1.2 g/kg/day	CVVHDF	Gln: (19)	NR	5%	27 g/day (0.6 g from AA)
Maxvold 2000 (Paeds n = 6)[41]	TPN	1.5 g/kg/day	CVVH/ CVVHD	Cys: (75); Arg: (46)	12 g (HD), 13 g (HF) - daily/1.73 m^2. (highest with Gln, Lys, Pro)	11%–12%	22 g/day/1.73 m^2. (2 g from AA)
Bellomo 2002 (n = 7)[34]	TPN	2.5 g/kg/day	CVVHDF	Tyr: (45); Asg: (24)	12 g/day (highest with Ala, Val, Lys)	5%–21% (highest % loss for Tyr)	24 g/day
Scheinkestel 2003 (n = 11)[35]	TPN	Up to 2.5 g/ kg/day	CVVHD	NR	NR	17% (87% loss for Tyr)	NR
Ganesan 2009 (n = 25)[47]	Mostly EN	0.6 g/kg/day	CVVHDF	NR	(Protein) 1.6 g/kg/ day	NR	11 g/day (urea)
Kritmetapak 2016 (n = 70)[80]	58%–85% EN	0.5–0.7 g/kg/ day	CVVH	NR	(Protein) 2.1 g/kg/ day (including urine)	NR	Negative balance by -11 g/day
PIRRT Studies			**(mL/min)**				
Kihara 1997 (n = 6)[43]	TPN	40 g/day	Qb 80; Qd 30	Cys: (36); Leu: (25)	6 g (per session). (highest with Gln/Gla, Ala)	16%	8 g/day (≈ 1 g from AA)
Chua 2012 (n = 7)[33]	Mostly EN	≈ 92 g/day	Qb 100; Qd 280; Qf 21	Ser: (60); Lys: (53); Leu: (49); Gln: (48); Phe: (45)	4 g (per session). (highest with Gln, Pro, Phe)	5%	25 g/day, negative balance by -11 g/day (0.7 g from AA)
Schmidt 2014 (n = 5)[44]	Mostly TPN	1.2 g/kg/day	Qb 150; Qd 150	Val: (140); Arg: (95); Gly: (94); Cys: (93); Ser: (91)	10 g (per session). (highest with Gln, Pro)	15%	NR

Amino acids: *Ala,* alanine; *Arg,* arginine; *Asg,* asparagine; *Cys,* cysteine; *Gla,* glutamic acid; *Gln,* glutamine; *Gly,* glycine; *Leu,* leucine; *Lys,* lysine; *Phe,* phenylalanine; *Pro,* proline; *Ser,* serine; *Tyr,* tyrosine; *Val,* valine.
AA, Amino acid; *AKI,* acute kidney injury; *CRRT,* continuous renal replacement therapy (*A,* arterio; *V,* venous; *HD,* hemodialysis; *H,* hemofiltration; *HDF,* hemodiafiltration); *EN,* enteral nutrition; *NR,* not reported; *Paeds,* pediatrics; *PIRRT,* prolonged intermittent renal replacement therapy; *Qb,* blood flow; *Qd,* dialysate flow; *Qf,* replacement fluid flow; *TPN,* total parenteral nutrition.

However, AA nitrogen loss during RRT in general only contributes to less than 10% of total nitrogen loss.[37,41,43] The latter adds up to 20 to 25 g/day during RRT.[33,34,37,41] Therefore the majority of nitrogen loss is from protein catabolism and ureagenesis. This corresponds to a protein loss of

$$6.25 \times 25 \text{ g/day} = 156 \text{ g/day}$$

which infers an estimated protein loss of 2.2 g/kg/day for a 70-kg patient. Such severe protein loss may have to be considered during nutritional intake assessment.

Relevant studies on the above are summarized in Table 74.3.

OTHER NUTRIENT BALANCE AFFECTING PROTEIN OR MUSCLE TURNOVER

Inadequate caloric substrate will lead to undesired catabolic diversion of AAs into endogenous gluconeogenesis. Glucose has a molecular weight of 180 Da and is lost at 40 to 80 g/day if glucose-free CRRT fluids are used,[50,51] for which greater loss occurs with higher dialytic dose. This translates to a calorie deficit of 160 to 320 kcal/day (based on 4 kcal/g). Insulin loss during CRRT is trivial (1%), compared with endogenous secretion or exogenous administration rates and is unlikely to be clinically relevant.[52]

Phosphate is the source of high-energy phosphate bonds in ATP and a key component in nucleic acids and proteins. Hypophosphatemia can contribute to diaphragmatic muscular weakness and rhabdomyolysis in critically ill patients.[53,54] Hypophosphatemia during extended and high-dose CRRT is common and associated with impaired respiratory weaning.[4,55] The former can be addressed via ad-hoc intravenous phosphate replacement but results in variability in phosphatemia and need for frequent monitoring. Off-label addition of phosphate to CRRT solutions to maintain a fluid concentration of 1.2 mmol/L has been reported with good clinical efficacy.[56] Modern CRRT fluids premixed with phosphate at 1.2 mmol/L and bicarbonate at 30 mmol/L are available, but their sole use has been associated with mild metabolic acidosis and hyperphosphatemia compared with

conventional CRRT fluids.[57,58] The ideal fluid phosphate content is likely lower but remains to be clarified.

IMPLICATIONS ON NUTRITIONAL MANAGEMENT

Early Optimal Nutrition Versus Permissive Underfeeding

Early feeding with balanced caloric to protein delivery is assumed to be essential to prevent protein malnutrition. EN is generally the preferred route of nutritional therapy in critical illness[59,60] and is associated with reduced infections, cumulative cost, and length of stay, compared with TPN.[61,62] However, best practice guideline approaches to promote either early EN initiation or optimal delivery duration versus standard care were examined in large cluster RCTs and did not demonstrate reduced patient mortality.[63,64] The belief that adequate caloric intake attenuates early protein catabolism is challenged by the concept of *permissive underfeeding*. *Short-term* and *initial* hypocaloric feeding at 40% to 60% versus 70% to 100% of projected requirement but *without compromising recommended protein intake, for up to 2 weeks* during critical illness, demonstrated favorable glycemic profile, and similar protein-nutritional indices, nitrogen balance, 90-day mortality, and hospitalization days.[65] The EDEN trial of trophic feed versus full feeding demonstrated no difference not only in 60-day mortality but also between groups in health-related quality of life at 1 year.[66,67]

Early Supplemental Parenteral Nutrition

Early supplemental PN in patients not tolerating EN does not lead to improved clinical outcomes.[68] A multicenter RCT showed that late (after day 8) compared with early (within 48 hours) supplemental PN for insufficient EN was associated with reduced ICU stay and hospitalization days, infections, healthcare cost, duration of mechanical ventilation, and RRT days.[69] Although some concerns may be raised regarding enteral absorption of calories and protein, the CALORIES trial of enteral versus parenteral feeding again did not demonstrate superiority of route.[70] Further, as of 2016, international consensus has yet to be achieved regarding definition of "failure" of EN initiation requiring TPN, with variation in timing seen between European (3 days), and more recent American (7 days) guidelines.[71,72]

Likewise, the above evidence should extend to critically ill patients with AKI-RRT. This is consistent with understanding that initial hypercatabolism with acute illness and AKI cannot be simply overcome by increasing protein or calorie intake.

Assessing for Severity of Protein Energy Wasting

Baseline screening tools such as the NRS (Nutritional Risk Screening) 2002 and the more recent NUTRIC (Nutritional Risk in Critically Ill) scores[73,74] use risk assessment based on indices including age, preceding anorexia, comorbidities, illness severity index, and organ dysfunction(s). These may lack discriminatory value in the subcohort of patients with critical illness and AKI, who will almost certainly be scored high risk. Ultrasound of rectus femoris echogenicity correlates well with myofiber necrosis and helps identify subsequent muscular dysfunction[75,76] but demands technical expertise. Computed tomography assesses sarcopenia and quantifies adipose tissue depots but is limited by radiation risk and logistics of care.[77] Bioimpedance techniques apply current flow from arm to leg or specific body segments and use differential reactance and resistance by cells and tissue water to provide lean body mass and body cell mass as objective nutritional indices. These are simple and readily reproducible at bedside, but muscle mass can be overestimated in volume overload states as inferred from CKD studies.[78,79] However, these are more objective measures indicating extent of tissue/muscle wasting, and ongoing research in these areas may provide the missing link between the extent of nutritional support and ability to trend clinical efficacy.

Nitrogen Balance During Acute Kidney Injury and Renal Replacement Therapy

The extent of negative nitrogen balance may not be appreciated, unless frequent monitoring of total nitrogen appearance and protein catabolic rate are performed. Simplified equations for practical application are presented in Table 74.4. These involve assessing for urea nitrogen appearance over 24 hours in RRT effluent and body excretory fluids, with up-estimations made to account for insensible and other nitrogenous losses. As discussed, estimated protein loss of more than 2 g/kg/day is possible in patients on CRRT or PIRRT.[33,80]

Individualized Management to Manage Protein Energy Wasting of Acute Kidney Injury

Permissive underfeeding does not equate to total or prolonged avoidance of nutritional therapy beyond 2 weeks, which otherwise remains physiologically unsound.[81,82] It can be inferred from above assessments that cumulative negative protein balance and muscle wasting are substantial. We suggest that more deliberate nutritional management may apply to patients in the recovery phase of critical illness and AKI, especially with extended RRT. The flexibility of adjusting protein intake is limited by the composition of standard nutritional formulas, in the modern era of EN. For example, intake of 30 kcal/kg/day, of an EN formula containing 1.5 kcal/mL of calories and 16.9 g of protein per 250 mL, only delivers 1.4 g/kg/day of protein. Supplementation with either enteral protein powder preparations or parenteral AA nutrition is needed to meet a protein intake of 1.5 to 1.8 g/kg/day suggested with AKI and RRT. Higher protein intake of up to 2.5 g/kg/day can result in a near positive nitrogen balance,[34,35] but there is no evidence to suggest this improves patient survival or functional outcomes and cannot be recommended routinely.

Parenteral supplementation of standard AA solution to maximum of 2 g/kg/day of protein intake, in critically ill patients with 12% to 18% renal dysfunction at baseline, did not improve duration of renal dysfunction, RRT rates, or other hospital outcomes.[83] There is also no evidence to support specific administration of EAA.[84] Intravenous glutamine supplementation was thought to be beneficial in critical illness,[85,86] and it was opinion based that higher supplementation may be useful during CRRT.[87] However, a multicenter RCT reported higher in-hospital and extended mortality with supplementation of glutamine versus none, in a cohort with majority having shock and higher than

TABLE 74.4

Estimation of Daily Total Nitrogen Appearance and Protein Catabolic Rate During Acute Kidney Injury and Renal Replacement Therapy

CONCEPTS AND ASSUMPTIONS			
Example: 70 kg male with anuric AKI on CRRT with effluent rate of 2.5 L/hr			
1.	Urea nitrogen appearance	(urine urea N) + (RRT effluent urea N) + (change in blood urea N or BUN)	Calculations
	(i)	Urine urea N = $[\text{urea N}]_{\text{urine}}$ × urine volume over 24 hr	Anuric, hence urine N assumed negligible
	(ii)	Effluent urea N = $[\text{urea N}]_{\text{effluent}}$ × RRT effluent volume over 24 hr	*Sampled* $[\text{urea N}]_{\text{effluent}}$ = 0.25 g/L; hence effluent urea N/day = (0.25 × 2.5 × 24) = 15 g/day
	(iii)	Change in BUN = $([\text{BUN}]_{D2} - [\text{BUN}]_{D1})$ × estimated TBW*	Change in BUN negligible as CRRT allows plasma solutes in steady state.
		where $[\text{BUN}]_{D1}$ is the BUN done *post-RRT session*, and $[\text{BUN}]_{D2}$ is the latest BUN done following day; and the difference is the rise in BUN after dialysis over 24 hr	*(Rise in BUN calculation applies more to patients on intermittent RRT.)*
		*: Total body water (TBW) is estimated by various anthropometric-based equations, or simply (0.6 × body weight) for males, or (0.5 × body weight) for females.	Therefore UNA is estimated at 15 g/day.
2.	Others:	Other urinary N (from AA/protein, creatinine, ammonia, etc.) + insensible losses	
	(Other nitrogen appearance)		
	(i)	AA N loss with RRT is estimated at <10% of total N appearance.	*(These are not routinely measured and just estimated for practicality purpose.)*
	(ii)	Given the difficulty in measuring other sources of N loss routinely, we assume that UNA constitutes an estimated 75% of total N appearance.	
3.	Total nitrogen appearance (TNA)	UNA ÷ 0.75 (as inferred from above)	TNA = (15 ÷ 0.75) = estimated 20 g/day
4.	Protein catabolic rate (PCR)	TNA × 6.25	PCR = (20 × 6.25) = estimated 125 g/day
	(i)	Back-calculation, assuming N is 16% of protein by weight (g)	(PCR = 1.8 g/kg/day for a 70-kg male)
5.	Net protein balance = Protein intake – PCR (g/day)		If protein intake is 1.5 g/kg/day, the patient will be in negative protein balance of 0.3 g/kg/day, assuming 100% enteric absorption of macronutrients.

AKI, Acute kidney injury; *CRRT,* continuous renal replacement therapy; *N,* nitrogen.

30% incidence of renal dysfunction.[88] Therefore routine supplementation cannot be recommended.

Individualized nutritional management in the medium term based on ongoing protein balance and objective tissue/muscle mass assessments may be desirable. There is growing interest in early mobilization of critically ill patients with participation in active exercises to improve muscle strength and expedite functional recovery. Such deliberate therapy remains undersubscribed, and mechanical ventilation, sedation, and indwelling femoral catheters, remain its biggest deterrence,[89] but it remains possible even during CRRT.[90] However, the intensity and type of exercises and perceived health benefits are uncertain.[91]

Key Points

1. Net protein catabolism in patients is consequent to the inflammatory milieu in critical illness, which is augmented by AKI. These occur early in acute illness and result in muscle wasting and cannot be suppressed by provision of conventional nutritional substrates alone.
2. PEW results in obligatory nitrogen loss in the acute phase of illness, which can be quantified from RRT effluent and excretory products predominantly as urea nitrogen, albeit with inaccuracies resulting from insensible losses. However, this also implies underestimation of loss and further signifies the severity of negative protein balance.
3. Increasing overall protein intake, meeting necessary caloric demand, and avoidance of iatrogenic RRT nutrient losses with necessary supplementation are believed to be beneficial to optimize nitrogen balance but will need intensified azotemic and volume control with RRT to facilitate its unrestricted nutritional support. These concepts have not translated to improved patient-centered outcomes, and optimal body nitrogen balance also does not imply optimal tissue/muscle protein balance.
4. The optimal timing, delivery, and intensity of nutritional therapy in critical illness and AKI-RRT to arrest protein malnutrition remain uncertain. An individualized management approach, guided by continued protein balance estimation and

objective tissue/muscle mass assessments, may be desirable, especially in the recovery phase of disease and with extended RRT support.

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