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Chapter

Serum Creatinine, Muscle Mass, and Nutritional Status in Intensive Care

Gianlorenzo Golino, Vinicio Danzi and Silvia De Rosa

Abstract

Skeletal muscle places a vital role in regulating immune function, glucose disposer, protein synthesis, and mobility. This massive dynamic reservoir of proteins, minerals, and other metabolites could be cannibalized, and a loss of skeletal muscle may predispose impaired tissue hailing and few poor immune functions. Several studies had shown the reduced survival rates and the increased hospital lengths of stay of patients who have a poor nutrition status and low muscle mass. In addition, few studies have demonstrated the effect of muscle wasting on serum creatinine. There are no data available regarding its effect on serum creatinine, and moreover, ICU-acquired myopathy is rarely recognized because of insufficient diagnostic criteria or methodological limitations. Despite these limits, serum creatinine is still considered the standard for assessing acute changes in renal function. The present chapter details the existing evidence related to the effects of nutritional status and muscle wasting on serum creatinine based on recent evidences.

Keywords: serum creatinine, muscle mass, muscle wasting, nutritional status

1. Introduction

Skeletal muscle places a vital role in regulating immune function, glucose disposer, protein synthesis, and mobility. Unfortunately, critical illness is characterized by hypermetabolic and hypercatabolic states, which leads to an elevated resting energy expenditure rate, hyperglycaemia, altered substrate use, and increased oxygen consumption.

Among the patients who are previously well nourished before intensive care unit (ICU) admission, nutritional disorders develop rapidly because of the metabolic demands of illness, rapid fluid shifts, and the loss of specific vitamins and trace elements. Timely initiation of optimal nutritional support is important to slow the catabolic process and minimize adverse events such as prolonged mechanical ventilation, longer ICU stay, and increased risk of death [1]. The body's reaction to the illness (trauma, burns, inflammation, or surgery) includes an increase of energetic metabolism, hypersecretion of counter-regulatory hormones (glucagon, glucocorticoids, and catecholamines), and release of inflammatory mediators and other hormonal mediators (vasopressin) in the general setting of inflammation. Protein energy malnutrition is associated with muscle weakness, increased risk of infections, impaired wound healing, impaired coagulation

capacity, impaired gut function, reduced respiratory muscle function, and prolonged time to convalescence [2]. The present chapter details the existing evidence related to the effects of nutritional status and muscle wasting on serum creatinine (sCr) based on recent evidences.

1.1 Protein-energy nutritional status in intensive care

The assessment of caloric and protein requirements include clinical history, nutritional history, physical examination, laboratory test (like albumin, prealbumin, blood glucose, transferrin, and kidney and liver function), severity of the illness, body mass index (BMI), ideal body weight (IBW), resting energy expenditure (based on calorimetry), and protein requirements (based on nitrogen balance). The nutritional assessment could be performed by direct calorimetry, performed by placing the patient in a calorimetric chamber, thermally insulated, in order to be able to evaluate the heat that it gives off by radiation, convection, conduction, and evaporation; this heat is detected by a water-cooled heat exchanger. Unfortunately, this method cannot be applied to all hospitalized patients. In critically ill, the gold standard is represented by indirect calorimetry, a method that measures respiratory gases: the oxygen of a determined volume of inspired air and the carbon dioxide produced. Therefore, numerous equations have been developed with the measurements performed with the indirect calorimetry in mechanically ventilated patients (**Table 1**).

Such equations use dynamic physiological variables, which allow the recalculation of energy expenditure, in order to evaluate how much energy the body spends in the acute phase, and then, determine the minimum requests. Predictive equations are notoriously inaccurate for individual critically ill patients, due to large differences in disease-related metabolic rate, treatment, and interindividual factors. Many centers that do not have indirect calorimetry adopt a simple approach providing 25–30 kcal/kg/day. Guidelines of the European Society for Clinical Nutrition and Metabolism recommend an intake of 25 kcal/kg/day in critically ill patients, and for both females than for males, considering, however, a 10–20% increase in patients with SIRS and overweight (BMI > 25), considering the IBW for calculation of energetic requirements [3].

Formula	Energetic requirements predicted (kcal/day)	Mechanical ventilation
Harris-Benedict	Man: 66 + (13.7 × BW) + (5 × H) – (6.8 × Age) Woman: 65 + (9.6 × BW) + (1.7 × H) – (4.7 × Age)	No
Ireton-Jones (a)	Mechanical Ventilation: 1925 – (10 × Age) + (5 × BW) + (281 × Sex) + (292 × Trauma) + (851 × Burn) Spontaneous Breath: 629 – (11 × Age) + (25 × BW) + (689 × Obesity)	Yes
Frankenfield (b)	21,000 + (100 × RR) + (13 × Hb) + (300 × Sepsis)	Yes
Swinamer	(945 × BSA) - (6.4 × Age) + (108 × BT) + (24.2 × RR) + (817 × TV) - 4349	Yes
Faisy	(8 × BW) + (15 × H) + (32 × RR) + (94 × BT) – 4834	Yes

BSA, Body surface area; BW, body weight; H, height; Hb, hemoglobin; RR, respiratory rate; BT, body temperature; and TV, tidal volume; (a) Sex, 1 = man, 0 = female; Trauma, 1 = present, 0 = absent; Burn, 1 = present, 0 = absent; and Obesity, 1 = present, 0 = absent. (b) Sepsis, 1 = present, 0 = absent, based on clinical evidence of presumed infection, systemic inflammation, or organ dysfunction.

Table 1.
Predictive equations of energetic requirements (kcal/die) in critically ill patients.

1.2 Muscle mass

Skeletal muscle has emerged as a potent regulator of immune system function in regulating immune function, glucose disposal, protein synthesis, and mobility [4]. Skeletal muscle can be viewed as the dynamic storage depot of amino acid, which is sensitive to the fed and fasted states but also of minerals and other intermediate metabolites [5], which can be depleted to meet the need for other tissues involved in the inflammatory response. The loss of skeletal muscle and reduced protein storage may predispose to a relative glutamine deficiency, which is seen as impaired tissue healing, poor immune function, and reduced survival [5]. Significant changes in body composition occur with aging and are a consequence of imbalances between energy intake and needs associated with an increasingly sedentary lifestyle [6].

1.3 Lean body mass

The body composition is often divided into fat mass and lean mass, the latter also known as lean body mass (LBM). LBM, unlike the fat mass that stores energy in the form of adipose tissue, includes muscle and visceral proteins and is mainly composed of water, proteins, glycogen, and minerals.

In pathological conditions such as chronic kidney disease (CKD), which is characterized by the presence of a positive water balance, it is necessary to perform an assessment of the volume of body water separately from the other components of the LBM. About half of LBM is made up of skeletal muscle mass, so the LBM compartment can be defined as heterogeneous and influenced by fluctuations in the distribution of water and electrolytes, which are more dynamic in nature in patients undergoing renal replacement therapy. Recent studies suggest that greater muscle mass is associated with greater longevity in people with chronic renal failure and in other chronic disease states [7]. Specific to LBM in the ICU, critically ill patients suffer significant LBM loss, much of it in the first 7–10 days of ICU stay [8]. However, patients gain weight back following ICU stay as fat mass but not as functional LBM [9]. Data in literature demonstrate that the catabolic/hypermetabolic state following injury can persist for up to 2 years following discharge from hospital, and this can markedly hinder the recovery of patients' LBM and function following injury [9].

1.4 Serum creatinine

sCr is an endogenous substance generated by the nonenzymatic conversion of creatine and creatine phosphate, 95% of which is found in the muscles [10]. sCr is an uncharged, small molecular weight, unfilled substance (113 Da) which is not related to whey protein. It is filtered freely by the glomerulus without tubular resorption. sCr is also secreted by the kidney tubules only in small quantities. In clinical practice, levels of sCr are used to determine kidney function to estimate the glomerular filtration rate. Its rise usually indicates either acute kidney injury (AKI) or chronic kidney disease [11, 12]. Due to the correlation between sCr levels and muscle mass, sCr in the steady state has been used as a surrogate of muscle mass measurements [13].

Low sCr levels could be considered as a proxy of protein-energy wasting in some clinical situations [14]. Individuals' sCr levels can be influenced by diet. In fact, arginine and glycine are precursors of creatine, and for this reason, a low protein intake in the diet can limit the generation of sCr. The sCr levels can be considerably lowered in the presence of protein malnutrition. Factors associated with low sCr levels are low muscle mass (female gender, elderly, and chronic illness), malnutrition, vegetarian diet, pregnancy, advanced liver disease, fluid overload, and augmented renal clearance.

AKI is an event that commonly complicates the clinical course of critically ill patients, contributing to multi-organ failure and requiring appropriate nutritional interventions in a strategic treatment.

The metabolic and nutritional demands of AKI patients are affected not only from the uremic state but also from the underlying pathology and complications associated.

A personalized approach for each patient that involves an analysis of specific nutritional requirements for each patient and a consideration of renal replacement therapy (RRT) support used is therefore necessary to improve the outcome of these patients.

Nitrogen is a fundamental component of the amino acids that make up the molecular structure of proteins. Proteins are the major functional substrate for cells and tissues and are essential for body growth and also for the maintenance and recovery. Protein metabolism generates calories (about 4 kcal/g). Nitrogen is released from protein degradation, which is also lost from secretions or excreted in sweat, feces, and urine. In particular, urea nitrogen represents 85–90% of the urinary nitrogen loss.

In the ICU patient, the greater non-urinary loss occurs through the intestine, severe burns, RRT, and/or by abdominal drains. The nitrogen balance becomes negative (from −5 to −30 g day), reflecting the important protein catabolism.

The nitrogen balance is calculated as the difference between the nitrogen intake and output, according to the following equation:

$$\text{N balance} = \left[\text{protein intake}\left(\text{g / die}\right) / 6.25\right] - \left[\text{urinary nitrogen}\left(\text{g / die}\right) + \text{skin / stool losses}\right]$$

where skin/fecal losses are approximately 2–4 g per day, while urinary losses can be recorded in the urine for 24 h (or by sampling for at least 4 h). The equivalence between urea in mmol/l and g occurs via two parameters: urea (g) = urea (mmol)/20.36, and then through the fact that 6.25 g of protein contains 1 g of nitrogen (**Table 2**).

In the setting of inflammatory state, acute loss of kidney homoeostatic function plays a central role in the worsening of the dysmetabolic state of the condition of critical illness. The stress response also induces changes in the use of substrates:

- Cellular insulin resistance acquired and secondary to the reduction of translocation of GLUT4 transporters on the plasma membrane, contributing to hyperglycaemia and alteration of cellular energy

	Non-catabolic state	**Catabolic state**
Proteins (g/kg/day)	0.8–1.0 (KDIGO 2012)	Minimum 1.0 (expert opinion)
Energy	Energetic support is not influenced by AKI. Some authors suggested 20–30 kcal/kg/day (KDIGO 2012). Others suggested 25–30 kcal/kg/day (Cano 2009, Brown 2010, Gervisio 2011, McClave 2016)	
Fluids	Fluid balance and daily body weight must be monitored carefully. Fluid intake varies according with patient's critical state, body weight, and fluid balance	
Electrolytes	Electrolytes should be monitored frequently and corrections vary according to the critical state and type of treatment	
Micronutrients	Evidences in this regard are scarce and not well documented. Usually, the levels of fat-soluble vitamins (Vit. A, Vit. D, Vit. E, Vit. K, and Vit. F) are low. CRRT has a negative effect on the balance of some vitamins and trace elements. It is not known whether micronutrient supplementation improves results	

Table 2.
Nutritional support in AKI patients.

- Increased use of fatty acids as the use of glucose becomes inefficient
- Switch from protein anabolism to catabolism (net negative nitrogen balance)

2. Assessment of muscle mass and nutritional status in intensive care

Critically ill patients require a muscle mass assessment during their ICU stay. Unfortunately, the tools used to assess nutritional status are poor indicators of malnutrition in the critically ill population. A sarcopenic obesity, characterized by excess fat and fluid retention of 10–20% of the patient's body weight can mask the skeletal muscle wasting in the ICU [15]. Many ICU patients are edematous, and the measured weight, the BMI, and anthropometric measurements (mid-upper arm circumference and triceps skinfold thickness) may not reflect the real body muscle mass and could have limited results [16, 17]. In the ICU setting, albumin is also a poor marker of nutritional status not only due to changes in intravascular volume but also due to the impact of acute infection, inflammation, hepatic function, etc. [18]. Concerning the use of tools that assess muscle mass and nutrition, such as Nutrition Risk in Critically Ill Score [19], are difficult to perform and hence they cannot uniformly identify patients at risk of malnutrition. The bioelectrical impedance vector analysis is a useful method not only to evaluate tissue hydration but also to detect muscle mass variations in sarcopenic indictviduals, and it is able to discriminate sarcopenic individuals from sarcopenic obese individuals. However, the bioelectrical impedance vector analysis has some limitations: estimation of hydration status is related to fat-free mass, which basically means muscle mass (in the limbs). Whereas, the limbs contribute roughly 90% to whole body impedance, only 6–12% are contributed by the trunk which, however, provides roughly 50% of the body weight and stores most of the surplus volume [20]. A baseline muscle mass assessment in the acutely critically ill patient is challenging. Muscle ultrasound is an attractive emerging technique able to offer qualitative analysis [21], inexpensive, and readily available at bedside. Unlike computed tomography (CT), however, international consensus does not exist on methodology, with significant differences between the techniques [21]. Although CT scans provide a reliable measure of muscle mass in these medically ill populations, CT scans are not performed on every critically ill patient due to cost and radiation exposure [22].

3. Muscle wasting and serum creatinine

After 10 days from the intensive care unit (ICU) admission [23, 24], a dynamic clinical state characterizes a "cascade" of new clinical problems [25]. This transition point is defined as "persistent critical illness" based on the point "beyond which diagnosis and severity of illness at admission are no more predictive of in-hospital mortality than are simple premorbid patient characteristics" [23]. Characterized by persistent inflammation, neurohumoral alterations, and prolonged immobilization, this catabolic state is not suppressed by nutrition [26, 27]. Catabolism results in muscle wasting and associated weakness, which impairs outcome [26–28]. Currently, there is no routine biomarker available with acceptable sensitivity and specificity which is able to monitor catabolism. Accurate monitoring of nitrogen losses and balances is not easy, but the presence and severity of catabolism often becomes clear once muscle loss and weakness are established. SCr is a metabolite of creatine phosphate, an energy store found in skeletal muscle, and in normal subjects it is produced at a constant rate. Particularly, a prolonged immobilization could decrease the plasma volume, bone mass, and skeletal muscle mass [29, 30]. A decrease in muscle

mass could theoretically be associated with changes in the metabolism of urea and sCr. Indeed, a muscle mass reduction could increase the urea generation because the muscular tissue has a high protein content and urea is the final catabolite of endogenous protein breakdown [31]. Disorders associated with dehydration/hypovolemia or with hypercatabolism increase plasma urea [32, 33]. In addition, skeletal muscle mass is the main determining factor of creatinine generation since creatinine is the final catabolite of muscle energy metabolism [34]. A decrease in muscle mass could decrease SCr levels, and conversely, SCr may be falsely increased with higher muscle mass. In addition, creatinine generation is low among individuals who have more diminutive muscle mass, either constitutionally or disease-related [13]. Due to the correlation between SCr levels and muscle mass, SCr in the steady state has been used as a surrogate of muscle mass measurements [35].

3.1 Muscle strength and sarcopenia index

Sarcopenia is a skeletal muscle disorder that is characterized by the loss of strength and mass together with impairment in physical function [36]. Sarcopenia is a complex syndrome that is associated with muscle mass loss, alone or in conjunction with increased fat mass. Since 2018, sarcopenia is not only considered as a debilitating condition that involves loss of muscle mass and function but also as a muscle disease. However, challenges in understanding the current evidence of the role of nutrition is represented by the number of different aspects of muscle health that have been considered as outcomes, both in observational and interventional study. New guidelines, which aim to improve consistency in the identification of sarcopenia in clinical care, identify muscle strength as the key characteristic of sarcopenia. This new guidance may also offer a useful structure within which to evaluate the influences on muscle health, including the effects of differences in diet [37]. Thus, a low muscle strength leads to a diagnosis of probable sarcopenia [37]. Sarcopenia is associated with frailty, poor surgical outcomes, prolonged need for mechanical ventilation, increased hospital cost, depression, decreased quality of life, increased risk of fall, nursing home residence, and a higher risk of death [38]. Evaluation of patients with sarcopenia could be really difficult as often physical function assessment is not performed and the measurement of muscle mass requires expensive and complex radiologic technique [39]. In addition, BMI, serum albumin levels, prealbumin levels, and physical examination lack in sensitivity and specificity to be used as surrogates for muscle mass. As previously reported, a low baseline sCr value is associated with a worse outcome and has been proposed as an indicator of low muscle mass [recently, a method to estimate muscle mass, named sarcopenia index (SI), was developed using the differential origin of two molecules cleared by the kidney: sCr (skeletal muscle cells) and cystatin C (nucleated cells) [40, 41], assuming steady kidney function]. The SI was calculated as (sCr value/cystatin C value) × 100. The SI not only significantly correlates with imaging but also it has a superior performance compared with sCr alone in estimation of muscle mass, as reported by recent evidence [42].

3.2 Urea:creatinine ratio

The lack of validated and routinely available biomarkers of catabolism to some extent hampers the epidemiological and interventional studies on this topic. The initial decreases in sCr may be from altered metabolism and reflect bioenergetic failure. The subsequent continued fall in sCr reflected the length of ICU stay and length of hospitalization, and it is due to skeletal muscle loss (decreasing creatinine production) [43, 44]. Particularly, from 3 to 4 days after ICU admission, urea progressively rises, with a higher peak and greater duration of elevation in those patients remaining longer

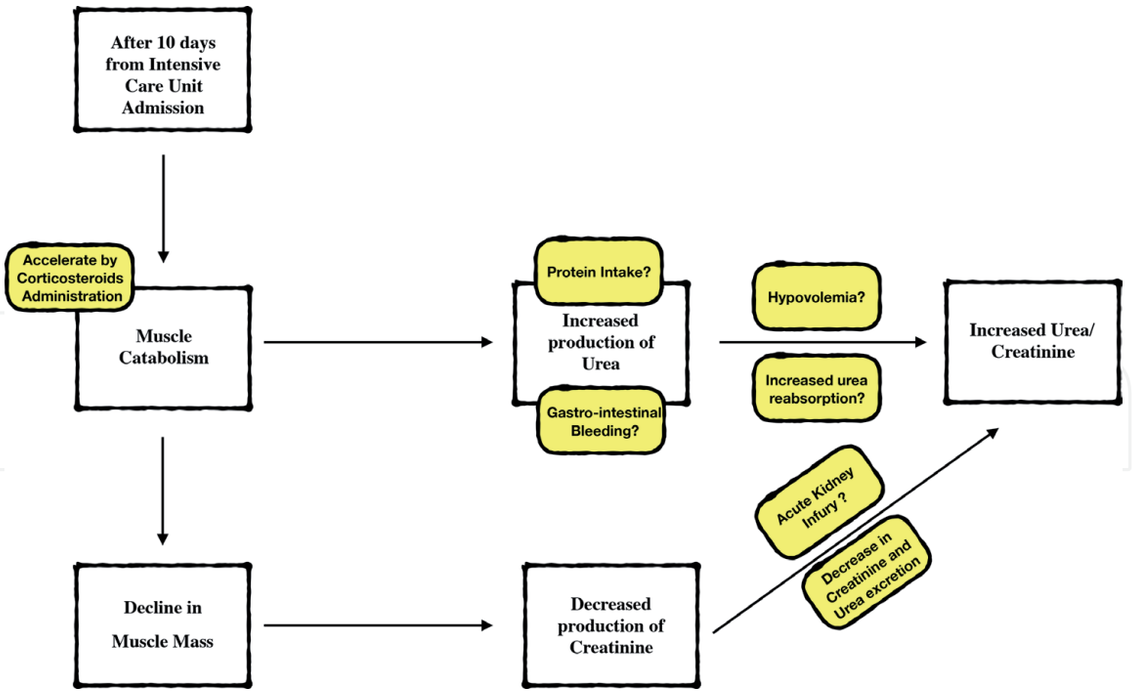


Figure 1.
Urea:creatinine ratio in critical illness.

in ICU. Recently, it was suggested that a persistent elevation in urea might reflect increased production from muscle catabolism, amino acid liberation, and metabolism. Based on the observed trajectory of urea, this catabolic state appears to persist throughout ICU admission [27]. For this reason, elevated urea:creatinine (UCR) may reflect a combination of muscle bioenergetic failure, muscle catabolism/altered protein homeostasis, and persistent muscle wasting, providing a metabolic signature of the effects of prolonged critical illness [27, 45, 46]. Although the potential role of UCR in future studies, clinical usability seem limited, as other factors such as the following may increase UCR independent of catabolism: decreased effective blood volume, protein intake or gastrointestinal bleeding, and acute kidney injury (**Figure 1**).

Particularly, despite altered tubular reabsorption of urea (normally 40–50%) can affect the serum urea:creatinine, classically increased urea retention occurs during severe dehydration with preserved tubular function. Conversely, tubular injury in AKI will lessen the concentrating capacity, thereby lessening urea:creatinine [47].

4. Conclusions

Critically ill patients suffer significant LBM loss, much of it in the first 7–10 days of ICU stay, requiring adequate timing initiation and optimal nutritional support to slow the catabolic process and to minimize adverse events such as prolonged mechanical ventilation, longer ICU stay, and increased risk of death. Due to the correlation between SCr levels and muscle mass, SCr in the steady state has been used as a surrogate of muscle mass measurements. However, SI could be considered a useful tool with a superior performance compared with sCr alone in the estimation of muscle mass, while the clinical usability of UCR seems limited and influenced by other factors such as decreased effective blood volume, protein intake or gastrointestinal bleeding, and also acute kidney injury. However, muscle wasting, often present in critically ill patients, can influence SCr and mask a diagnosis of AKI, decreasing the sensitivity of SCr for the early detection of AKI. Future studies should address the effect of muscle wasting on the true SCr concentration.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

AKI	acute kidney injury
BMI	body mass index
CT	computed tomography
IBW	the ideal body weight
ICU	intensive care unit
LBM	lean body mass
RRT	renal replacement therapy
sCr	serum creatinine
SI	sarcopenia index
UCR	urea:creatinine

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