REVIEW ARTICLE

Estimating Catabolism: A Possible Tool for Nutritional Monitoring of Patients With Acute Kidney Injury

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Hypercatabolism has been described as the main nutritional change in acute kidney injury. Catabolism may be defined as the excessive release of amino acids from skeletal muscle. Conditions such as fasting, inadequate nutritional support, renal replacement therapy, metabolic acidosis, and secretion of catabolic hormones are the main factors that affect protein catabolism. Given the imprecision of the methods conventionally used to assess and monitor the nutritional status of hospitalized patients, the parameters of protein catabolism, such as nitrogen balance, urea nitrogen appearance, and protein catabolic rate appear to be the main measures in this population. Considering the high prevalence of malnutrition in this population and important limitations in this clinical condition, such as the inflammatory state and altered fluid, catabolism parameters are accurate and reliable methods that could contribute to minimize adverse prognosis in this population.

Introduction

ACUTE KIDNEY INJURY (AKI) is a clinical condition in which there is a decrease in renal function. It is characterized by increased serum levels of creatinine and decreased urine output.[1] Epidemiological evidence supports the fact that small changes in these parameters are sufficient to cause deleterious clinical consequences, such as increased mortality.[2] Septic shock, major surgery, cardiogenic shock, and hypovolemia are the main causes of AKI in critically ill patients.[3]

AKI is defined as an increase in serum creatinine by at least 0.3 mg/dL within 48 hours or an increase in serum creatinine higher than 1.5 times baseline which is known or presumed to have occurred within the prior 7 days or urine volume reduction less than 0.5 mL/kg/hour for 6 hours according to KDIGO definition.[2]

AKI is staged for severity according to increase in serum creatinine and urine output. In stage 1 occurs an increase from 1.5 to 1.9 times in the baseline creatinine or increase of more than 0.3 mg/dL and a decrease in urine output to less than 0.5 mL/kg/hour for 6-12 hours. In stage 2, an increase of 2.0-2.9 times of the basal creatinine with reduced urinary output to less than 0.5 mL/kg/hour for more than 12 hours is observed. Finally, in stage 3, there was an increase of at least three times in the baseline creatinine or increase in serum creatinine to more than 4.0 mg/dL or reduced diuresis to less than 0.3 mL/kg/hour for more than 24 hours or anuria for at least 12 hours or initiation of renal replacement therapy (RRT).[2]

It is important to consider that higher stages of AKI are probably associated with more aggressive insults and higher risk of hypercatabolism. Therefore, patients at early AKI stages (1 and/or 2) tend to be lower catabolism, while stage 3 tends to present more severe hypercatabolism, mainly because AKI is also more severe and likely need dialysis.[4]

Usually present in the context of multiple organ failure, AKI converges to proinflammatory and oxidative states, causing not only primary consequences with the accumulation of nitrogen and liquid products, but also complete alterations in the metabolism of macronutrients.[4-6] Affecting around 5-6% of patients in intensive care units, the requirement for dialysis as well as their consumptive effects on nutritional status contributes negatively, supporting the scenario of high mortality rates in this population.[3,4]

Hyperglycemia, hypertriglyceridemia, and hypercatabolism are the triad of nutritional changes in AKI. Consequent to several mechanisms, one of the main causes is related to peripheral insulin resistance, protein catabolism activation, and the inhibition of lipolysis, which are etiologically involved in malnutrition pathogenesis. Insulin has anticatabolic effects, and its deficiency is related to the consumption of muscle mass protein consequent to a

reduction in protein synthesis and increased proteolysis.[7] The resistance to its action is the major stimulus for muscle protein catabolism in patients with AKI. Other factors are associated with catabolic state, such as metabolic acidosis, secretion of catabolic hormones (catecholamines, glucagon, glucocorticoids), hyperparathyroidism, suppression of growth hormone activity, and the release of proteases and inflammatory mediators.[4]

Hypercatabolism has been described as the main nutritional change in AKI. Generally, about 400 g of body proteins are synthesized and degraded every day as part of the continuous amino acid flow.[8] In AKI, especially during metabolic stress, the transport of amino acids to skeletal muscle is altered and the synthesis of proteins is inhibited. Conditions related to the critical condition, such as fasting and inadequate nutritional support, also contribute to the deamination and oxidation of amino acids for energy generation. Accordingly, around 125 g of tissue proteins are rapidly degraded, leading to a deterioration in cellular functions.[8-11]

Another important factor that affects protein catabolism is RRT. This therapy can activate catabolism mainly through amino acids losses to the dialysate and the release of cytokines, thereby activating the inflammatory state. Moreover, convection methods promote protein losses in the dialysate when compared to diffusion.[12] In general, 4–16 g of amino acids is lost in continuous hemodialytic therapies, depending on the facility and filter used.[13-20] Significant albumin losses around 15 g/session are observed with the use of high-cutoff filters.[21] In the extended modality, losses tend to be lower, ranging from 4 to 6 g.[12,18] However, a recent study showed that patients on hemodialysis with extended low-flow hemodialysis showed significant losses of amino acids (around 16 g/session), similar to continuous therapies.[19] In high-volume peritoneal dialysis (HVPD), approximately 4 g of total proteins is lost, with twofold higher values in the presence of peritonitis.[20]

Many authors have consistently shown the catabolic state of hemodialysis patients.[21-24] Ikizler et al.[22] showed that, during a conventional hemodialysis session, there was an increase of 96% in total body protein loss (muscle and visceral protein) and 164% in muscle protein. In addition, 2 hours after the end of the session, total body protein breakdown remained increased, resulting in persistently high hypercatabolism. Profound effects on protein homeostasis such as increased oxidation of amino acids and lipids at the expense of carbohydrate oxidation were also observed.[22]

Inflammatory cytokines activate protein catabolism, suppress appetite, increase lipolysis, and increase resting energy expenditure.[10] Acting on the central nervous system, neurotransmitters are regulated, inducing anorexia and the loss of lean body mass. Finally, cytokines facilitate efflux from skeletal muscle amino acids during hemodialysis, exacerbating the patient's hypercatabolic state.[24]

Catabolism may be defined as the excessive release of amino acids from skeletal muscle. This increased demand is due to an alteration in homeostasis, to the synthesis of new proteins, resulting in a large redistribution from muscle to the liver. Consequently, amino acids are extracted from the circulation by the liver, culminating in gluconeogenesis and increased urea production on a large scale. Finally, there is an imbalance in the plasma amino acid pool and intracellular fluid, resulting in misuse.[4]

Historically, there are three definitions of hypercatabolism. The first cited by Parsons et al.[25] in 1961 defines hypercatabolism as an increase of at least 60 mg/dL of blood urea in 24 hours. Later, Schier[26] defined hypercatabolic patients as showing an increase of at least 30 mg/dL in serum urea nitrogen and 1 mg/dL in serum creatinine, associated with the following factors: an increase of more than 1 mEq/L/day in serum potassium, serum uric acid levels above 15 mg/dL, serum phosphorus higher than 8-10 mg/dL, or reduction in serum bicarbonate greater than 2 mEq/L/day. More recently and more broadly, Druml[4] proposed the calculation of urea nitrogen appearance (UNA) as a measure to estimate the extent of catabolism of patients with AKI. So, the older definitions seem inadequate as blood urea rise cannot be a proper measure of catabolism because no quantification is possible from these values.

Urea Nitrogen Appearance

As nitrogen is the final product of protein degradation and most of the loss occurs through urine output, it is possible to estimate protein loss via urea nitrogen by collecting 24-hour urine plus the changes in blood urea nitrogen in body fluids with altering renal function. However, besides urea nitrogen, it is necessary to add the non–urea nitrogen present in the form of ammonia, creatinine, and uric acid and nitrogen lost in the stool. Mackenzie et al.[27] and Maroni et al.[28] showed that losses of non–urea nitrogen are around 2 g. To facilitate the final measurement, a fixed value of 2 g for nitrogen was defined for fecal losses and non–urea nitrogen, corresponding to insensitive losses, like sweat and via the skin.[10,27,28]

UNA is a less laborious measure to estimate the rate of protein catabolism and must evaluate the presence of urea in all body fluids such as blood, urine, and the dialisate.[10] In patients with AKI, UNA can be calculated using the formula shown in Figure 1.

In the presence of substantial losses through the gastrointestinal tract, blood urea nitrogen lost in feces, drains, or gastrointestinal fistulas must be considered, by multiplying the volume for nitrogen ureic serum (mg/dL) on the second day. In individuals on dialysis, nitrogen eliminated in the dialysate must necessarily be added to the final calculation of UNA.[4]

UNA (g/day) = urinary urea nitrogen excretion + changes in urea nitrogen pool

= (UUN x V) + (BUN2 - BUN1) x 0.006 x BW + (BW2 - BW1) x BUN2/100

Figure 1. Calculation of urea nitrogen appearance in patients with AKI.[4] AKI, acute kidney injury; BUN, blood urea nitrogen; BW, body weight; UNA, urea nitrogen appearance; UUN, ureic urinary nitrogen; V, urine volume (L).

It notes that the UNA calculation is entirely possible in AKI patients, on dialysis or not. Of course, in patient on dialysis, it requires accurate measurement of urea in the dialysate losses.

In no dialysis patient, losses in diuresis, variation of body serum urea, and insensible losses should be considered.

The nitrogen losses in urine may be obtained by urinary urea 24 hours or by urinary urea in urine sample (40 mL, e.g.) and multiplying by 24 hours of diuresis.

The variation of body serum urea should be measured by the change in serum urea in 24 hours. If the patient shows increased levels, this value will contribute to increase the UNA. It must be multiplied by 0.6 that represents total body water.

Finally, one should obtain the value of insensible losses (by multiplying the fixed amount by weight of 0.031) and fecal losses (fixed value of 2g).[4]

In dialysis patients, in addition to the measures explained above, the dialysate nitrogen loss must be obtained.

In patient undergoing hemodialysis, it is necessary to know the duration of the session, the dialysate flow, and ultrafiltration to obtain the total volume of ultrafiltrate generated. For example, in a 6-hour session (360 minutes), using dialysate flow rate of 300 mL/min and ultrafiltration of 3 L, it is known that at the end of the session, it will be produced 111 L of dialysate (300 mL $\times$ 360 minutes = 108 L + 3 L UF = 111 L).

For calculating the nitrogen dialysate, the urea dialysate should be measured at the beginning of the session (first minutes), in the middle of the session, and at the end of the session (last minutes). The average of these measurements must be multiplied by the total dialysate volume (111 L).

In the case of patients on HVPD, five isolated urea samples along the 24-h session should be measured. The average of these measures must be multiplied by the total volume prescribed adding the ultrafiltrate.

Therefore, it is possible to calculate UNA and nitrogen balance (NB) both days with or without dialysis. The collection of dialysate is the only difference. Considering the change in body serum urea is essential because in AKI patients, significant urea increases can occur in short periods of time (less than 24 hours), contributing significantly to increase the UNA.

Patients with AKI on continuous renal replacement therapy (CRRT) have a UNA ranging from 11 to 18 g/day, depending on modality,[29-33] which means degradation of 60-112 g of protein daily, even with adequate protein intake. Extended therapies or RRT with less time can lead to a higher UNA, reaching 25 g/day.[34,35]

NUU = urinary urea nitrogen (g/day).

V = urine volume (L).

NUS1 = nitrogen ureic serum (mg/dL) on the first day.

NUS2 = nitrogen ureic serum (mg/dL) on the second day.

BW1 = body weight (kg) at the end of the session.

BW2 = body weight (kg) at the beginning of the session.

To determine the loss of protein equivalents, the UNA is multiplied by 6.25. To assess the loss of lean mass from skeletal muscle, this value must be multiplied by 5, since muscle contains about 20% protein.[4]

Protein Catabolic Rate

The protein catabolic rate (PCR) is a measure of protein degradation obtained by multiplying UNA by 6.25; this represents the equivalent protein, since protein is 16% nitrogen.[9,10] The final result can estimate the protein intake of clinically stable individuals. In critical and unstable patients, the rate of protein catabolism will reflect the intensity of catabolism because the product of urea metabolism is not only from the ingested protein, but also from muscle protein degradation.[30] Dividing the PCR by dry weight, you get the standard PCR (nPCR), which allows the clinician to determine the best way to rate individual patient catabolism and estimate the minimum protein intake necessary to meet the demands of this rate.[10]

Many studies have shown that nPCR in CRRT patients ranges from 1.4 to 1.8 g/kg/day[29-31,35-36] according to Table 1. Therefore, similar or superior protein intake becomes necessary to minimize energy and protein consumption. There have been few studies evaluating nPCR in

Table 1. Values of Normalized Protein Catabolic Rate in Patients With AKI Undergoing Different Renal Replacement Therapy Modalities

Author/Year	RRT Modality	Number of Patients	Protein Intake (g/kg/d)	nPCR (g/kg/d)
Chima/1993	Continuous arteriovenous hemofiltration	19	1.4 ± 0.5	1.7 ± 0.7
Macias/1995	Continuous venovenous hemofiltration	40	1.0 ± 0.4	1.4 ± 0.5
Leblanc/1998	Venovenous continuous renal replacement therapy	38	26 patients: 1.0-1.2 g/kg; 12 patients: fasting	1.75 ± 0.82
Marshall/2002	Sustained low-efficiency dialysis	9	0.57 ± 0.32	1.40 ± 0.63
Fiaccadori/2005	4h hemodialysis or 8 h sustained low efficiency hemodialysis	10	1.5	1.47 (0.97-1.80)

AKI, acute kidney injury; nPCR, normalized protein catabolic rate; RRT, renal replacement therapy.

patients undergoing extended TRS, with studied values around 1.5 g/kg/day.[35]

Given the etiologic diversity of patients with AKI, the calculation of nPCR becomes extremely useful and applicable in clinical practice in order to minimize errors in calculations and future nutritional impairment. However, it is important to emphasize that, for greater accuracy, the calculations should be based on the kinetics of urea and total dialysate collection.[4,10]

Nitrogen Balance

Nitrogen balance (NB) allows the clinician to estimate the protein used by the body and the degree of catabolism. It can be obtained simply by calculating the difference between nitrogen intake and losses. NB is achieved when the supply of protein is sufficient to replace the nitrogen losses in urine, fecal volume, scarring, peeling of skin cells, and sweat.[10] When supply equals or exceeds these losses, the patient reaches neutral or positive NB. A lower supply leads the patient to use other energy substrate sources, such as muscle mass.

As nitrogen is released during protein catabolism and the majority is excreted in urine as urea, it is plausible that NB can be a powerful method to identify the intensity of protein degradation.[10] In stable patients, the desired NB should be maintained between 4 and 6 g/day. However, in critically ill patients, these values are virtually unattainable. Therefore, keeping the NB minimally negative becomes the most suitable option in these patients. Despite nutritional support not sustaining the AKI patient in anabolism, a minimally negative NB can certainly reduce the intensity of the loss of body cell mass, greatly reducing the risk of death.[9,10]

To rate the intensity of catabolism in AKI patients, Druml.[4] proposed three levels of classification: mild hypercatabolism (NB between 0 and −4.9 g/day), moderate (between −5.0 and −10.0 g/day), and severe (greater than −10 g/day). Currently, determining the degree of catabolism in AKI is considered an important nutritional tool.[4]

Recently, Fiaccadori et al.[6] proposed protein (g/kg/day) requirements for patients with AKI according to the degree of catabolism. These recommendations emphasize the importance of quantifying the extent of the catabolic state of the patient in order to provide an adequate nutritional supply. Unprecedented work with the dietary route was also nominated as the degree of catabolism of the patient. The enteral or parenteral route is suggested for patients with moderate to severe catabolism, with protein needs ranging from 1.2 to 2.0 g/kg/day. The oral route is generally observed in those with mild or no catabolism, with requirements from 0.8 to 1.0 g/kg/day.[6]

Chua et al.,[33] evaluating AKI patients on extended daily hemodialysis (8 hours/session), showed severe initial hypercatabolism, evidenced by NB −10.7 g/day. However, protein intake was extremely low, ranging from 1 to 12 g protein/day. Furthermore, very high UNA values (25 g) indicated important protein degradation in these patients. Only Fiaccadori et al.[35] showed a positive NB (0.30 g/day) in patients receiving parenteral nutrition with 1.5 g/kg protein and 30 kcal/kg of energy undergoing extended (8 hours) or conventional (4 hours) RRT daily. Other studies in patients on CRRT offered different amounts of protein, with NB ranging from −2 to −7 g/day.[18,29,30]

Goes et al.[20] studied AKI dialysis patients and found less severe levels of catabolism when assessing 208 sessions of HVPD. A positive NB ranging from 0.5 to 1.4 g/day was observed in patients regardless of the presence of peritonitis. Minimally negative NB was associated with an adequate dose of Kt/V (around 3 weekly), ischemic AKI, and dialysis due to fluid overload. Ponce et al.[37] showed similar results evaluating 150 patients on HVPD for seven continuous sessions. The authors observed a mean NB of −7.2 ± 2.4 g/day in the first session, progressing positively to −1.1 ± 0.7 g/day in the sixth (last) session. Patients had Kt/V of 3.5 ± 0.7 weekly and a prevalence of ischemic acute tubular necrosis (50%) in survivors, factors that may have contributed positively to the gradual improvement in catabolism.

Figure 2 shows the calculations required to determine and estimate the degree of catabolism in patients with AKI.

It is important to highlight that nitrogen is equivalent to 46.7% of the urea molecule. Therefore, to find it, the value must be multiplied by 0.467. To calculate NB, total nitrogen losses must be subtracted from the amount of ingested dietary nitrogen. Nitrogen intake is obtained by the amount of protein diet converted to grams of nitrogen, dividing the protein content (in grams) by 6.25 (since 6.25 g of protein generates 1 g of nitrogen).

In patients with AKI, nitrogen losses can be higher than in stable chronic patients. However, other nitrogen losses in the range of 4-6 g/day could include nitrogen loss during dialysis, in stools, through drainage and other minor nitrogen losses through skin and sweat.[10] When calculating NB, it is suggested that ureic urinary nitrogen must be corrected for the nonurea increasing component by the ureic urinary nitrogen measured by 20%.[38]

Absolute nitrogen output requires measurement of nitrogen content from all body fluids excreted. However, due to collection difficulties, urine and feces are most commonly collected as representative portions of nitrogen loss. These portions are then subtracted from the net nitrogen input.[38]

Two important studies evaluated the association between NB and mortality. Scheinkestel et al.[39] showed that the NB of patients on continuous TRS and receiving a high protein supply was directly associated with better hospital and intensive care unit prognosis. For each increase of 1 g/day in the NB of these patients, the likelihood of survival increased by 21%. More recently, Ponce et al.[37] evaluated the indications and limitations of HVPD and found stabilized NB values
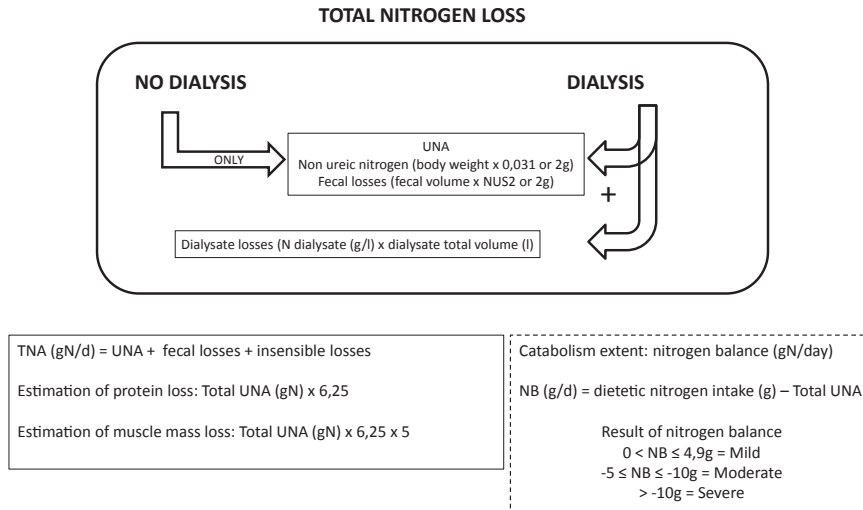
Figure 2. Calculation of catabolism degree.[4] NB, nitrogen balance; TNA, total nitrogen appearance; UNA, urea nitrogen appearance.

after the fifth session. In addition, the evaluation of 150 patients showed a 31% reduction in the risk of death after three sessions of HVPD. Berbel et al. also found that, at the end of 14 days of nutritional counseling, on average, reduced NB during the follow-up of patients with AKI requiring dialysis was a risk factor for higher mortality.[40]

Many factors can interfere in UNA and NB values, such as conditions which can lead to higher serum urea (dehydration, corticoids, infectious processes, inflammatory, and dietary low intake). The time to stop the hypercatabolism and the generation of urea is unpredictable. Therefore, it is important to interpret the results of the UNA, considering all causes of hypercatabolism. As soon as insult AKI is controlled, less hypercatabolic the patient remains and smaller fluctuations in urea occur. In the short term, nitrogen equilibrium can be achieved in 5-7 days with adequate energy and protein intake.[10]

Although laborious, mainly depending on the availability of the team, it is recommended daily calculation of UNA and NB in hemodynamically unstable and weekly at stable patients to strictly monitor the catabolism and dietary adequacy.[4]

To calculate the target of protein and caloric intake, the underlying process, preexisting comorbidities, and current complications should be considered because AKI rarely exists as an isolated organ failure in critically ill patients.

A table with current protein and calories recommendations for AKI patients follows below or is shown in Table 2.

The current energy and protein recommendations for AKI patients are based on the catabolism degree, emphasizing the importance of using this method.

In 2013, Fiaccadori et al., in their review, reported that patients without catabolism associated (usually not on dialysis) have protein needs similar to healthy subjects. As long as catabolism increases, often accompanied with the need of dialysis, the requirements for more protein increase. As shown in Table 2, only patients without associated catabolism (usually with AKI due to nephrotoxicity) require low protein intake. Individuals with severe catabolism, usually septic requiring continuous dialysis therapies, may require 2.0 g/kg/day of protein.[6]

This year, the American Society for Parenteral and Enteral Nutrition confirmed in its guidelines that AKI patients may require significantly high protein intake. Importantly, the protein intake must be accompanied by adequate caloric intake in order to ensure proper and optimum metabolism.[41]

Conventional Nutritional Methods in AKI Patients

As with other diseases, there is no single method for nutritional diagnosis in AKI patients because it is a clinical condition with important limitations, such as the

Table 2. Recommendations for Protein and Energy Provision in Patients With Acute Kidney Injury

Author/Guideline/Year	Clinical Condition	Protein (g/kg/d)	Energy (kcal/actual weight/d)
Fiaccadori E, 2013	No catabolism, no RRT	0.8 (max. 1.0)	25 (max 30)
	Moderate catabolism, on RRT	1.2-1.5	
	Severe catabolism, on RRT (CRRT or SLED)	1.7-2.0 g	
ASPEN, 2016	Critically ill with AKI	1.2-2.0	25-30

AKI, acute kidney injury; ASPEN, American Society for Parenteral and Enteral Nutrition[41]; CRRT, continuous renal replacement therapy; RRT, renal replacement therapy; SLED, sustained low efficiency dialysis.

inflammatory state and altered fluid conditions.[42-44] However, considering the high prevalence of malnutrition in this population, that is, around 60% as a diagnosis of subjective global assessment, proper nutritional intervention is fundamental to minimize adverse prognosis in this population.[42,44] Among the existing methods, laboratory markers such as albumin, prealbumin, and cholesterol are most commonly used in clinical practice; however, these markers may be reduced independently of malnutrition, thus acting as acute phase markers.[45,46]

The total lymphocyte count has low specificity, while changes in body weight, an important measure of the nutritional routine of any patient, become unreliable in AKI, as the change in water status may overestimate the actual weight and show no loss of lean body mass. Anthropometric measurements, such as skinfold thickness and arm circumference, are also heavily influenced by the degree of edema.

It is known that obesity diagnosed by body mass index (BMI) increases the risk of developing AKI. However, individuals with AKI and a BMI between 30 and 35 kg/m^2 present a 19% reduction in the risk of mortality during hospitalization.[47] Despite the proven benefit of increased body weight in this situation, using this measurement as a parameter of nutritional monitoring is questionable due to the difficulty in determining the dry weight of patients.

The calculation of resting energy expenditure must be carried out, preferably by indirect calorimetry, but it is rarely used in the hospital routine due to its high cost. Substitution with predictive formulas may overestimate the actual rate, given the difficulty in estimating the dry weight.[42,48]

The Subjective Global Assessment is a nutritional diagnostic method established in AKI due to its association with important clinical outcomes; it is easily applied.[40,44] Although differences between evaluators can occur, nutritionist training can reduce the subjectivity errors inherent in the method. However, the Subjective Global Assessment is used for the initial diagnosis and may not be used for nutritional monitoring during the hospitalization of these patients.

Members of the International Society of Nutrition and Renal Metabolism have proposed protein–energy wasting criteria for patients with chronic kidney disease and AKI patients considering some objective criteria, such as albumin levels lower than 3.8 g/dL, total cholesterol levels lower than 100 mg/dL, and a BMI lower than 23 kg/m^2.[49] However, Berbel et al.,[40] after evaluating 133 patients with AKI, found no association between these separate parameters and mortality. The influence of inflammation and changes in volume status surely contributes to the poor specificity of these methods as nutritional parameters in this population.

There are many reasons why it is difficult to use bioelectrical impedance in critically ill patients, since they have frequent changes in tissue hydration because of edema, ascitis, intravenous fluids, and diuretics. Due to the lack of validation of the predictive equation specific for acute situations, there are very few studies in the literature that have used this tool for nutritional diagnosis and follow–up in AKI patients.[42]

Conclusions

Given the imprecision of the methods conventionally used to assess and monitor the nutritional status of hospitalized patients, such as BMI, skinfold measurements, arm circumference, and biochemical tests, the parameters of protein catabolism (NB, UNA, and nPCR) appear to be the main measures in this population. However, exact calculations and perfect collection of the dialysate are essential for proper interpretation of the results.

Practical Application

This review discusses an alternative method of nutritional management in patients with AKI. Faced with the limitations of conventional nutritional assessment methods, catabolism parameters such as NB, UNA, and nPCR seem more efficient and reliable in determining the optimal protein support and estimate the degree of catabolism of these patients.

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