

# Nutritional aspects in acute kidney injury

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## SUMMARY

Nutritional assessment is an indispensable tool for the evaluation and clinical monitoring of patients with acute kidney injury (AKI). Acute loss of renal function interferes with the metabolism of all macronutrients, responsible for proinflammatory, pro-oxidative and hypercatabolic situations. The major nutritional disorders in AKI patients are hypercatabolism, hyperglycemia, and hypertriglyceridemia. Those added to the contributions of the underlying disease, complications, and the need for renal replacement therapy can interfere in the nutritional depletion of those patients. Malnutrition in AKI patients is associated with increased incidence of complications, longer hospitalization, and higher hospital mortality. However, there are few studies evaluating the nutritional status of AKI patients. Anthropometric parameters, such as body mass index, arm circumference, and thickness of skin folds, are difficult to interpret due to changes in hydration status in those patients. Biochemical parameters commonly used in clinical practice are also influenced by non-nutritional factors like loss of liver function and inflammatory status. Although there are no prospective data about the behavior of nutritional markers, some authors demonstrated associations of some parameters with clinical outcomes. The use of markers like albumin, cholesterol, prealbumin, IGF-1, subjective global assessment, and calculation of the nitrogen balance seem to be useful as screening parameters for worse prognosis and higher mortality in AKI patients. In patients with AKI on renal replacement therapy, a caloric intake of 25 to 30 kcal/kg and a minimum amount of 1.5 g/kg/day of protein is recommended to minimize protein catabolism and prevent metabolic complications.

**Keywords:** Nutritional assessment; biological markers; anthropometry; nutritional requirements; acute kidney injury.

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Submitted on: 02/25/2011  
Approved on: 07/19/2011

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**Conflict of interest:** None.

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## INTRODUCTION

Nutritional assessment is an indispensable tool to monitor and follow-up patients with acute kidney injury (AKI). This is a complex syndrome and develops in different situations, with clinical manifestations that can vary from minimal elevations in creatinine until renal failure that needs dialysis<sup>1</sup>. Its incidence varies according to the clinical conditions of patients, being higher in the Intensive Care Unit (20% to 40%)<sup>2</sup>, where it has a high mortality rate of about 60%<sup>3</sup>. Recently, the expression acute renal failure has been substituted by AKI, which expresses the amplification of its concept, allowing its early diagnosis<sup>1</sup>.

AKI affects not only water, electrolytic, and acid-basic balance, but it also interferes with the metabolism of every macronutrient, responsible for proinflammatory, pro-oxidative, and hypercatabolic states. The consequences related to AKI are added to the contributions of the underlying disease and its complications, which can interfere with the nutritional depletion of those patients<sup>4</sup>.

Among the metabolic changes more common in AKI are included hypercatabolism, hyperglycemia, and hypertriglyceridemia<sup>4</sup>.

Factors like insulin resistance, circulation of inflammatory mediators, acidosis, increased secretion of catabolic hormones, and inadequate delivery of nutritional substrates are among the major causes of hypercatabolism in those patients, contributing for the marked loss of lean body mass through the activation of muscle-protein catabolism, gluconeogenesis, and changes in amino acid metabolism seen in those situations<sup>4</sup>.

Dialysis, which is necessary in many AKI patients, also shows a harmful interference with the nutritional status by leading to direct loss of nutrients in the dialysate and interfering with protein homeostasis, according to Ikizler et al.<sup>5</sup> in a study with patients on chronic hemodialysis. In that study, dialysis was responsible for a 133% increase in muscle protein degradation and sustained degradation of total body protein even after the end of the dialysis.

Due to several conditions that can have important contributions for the reduction of food ingestion and malnutrition of patients with AKI, the ISRNM Expert Panel (International Society of Renal Nutrition and Metabolism) proposed a more encompassing and adequate terminology. It is known that depletion of muscular and adipose tissue that characterizes malnutrition is a consequence of low or inadequate ingestion of nutrients. However, several conditions inherent to renal disease can also contribute to this depletion, even with adequate ingestion. Therefore, considering the several kidney disease-related influences on malnutrition, the use of the expression "protein-energy-wasting" (PEW) was considered more adequate to characterize this situation<sup>6</sup>. This expression better represents the negative metabolic consequences of acute loss of kidney function on the nutritional state.

Thus, PEW is a consequence of situations of malnutrition (low ingestion of nutrients), action of uremic toxins, inflammation, and hypercatabolism. And among the causes for these factors are several related to kidney disease, such as dialysis (dialysis membrane), loss of nutrients that occurs during this procedure, endocrine disorders, presence of comorbidities (diabetes, cardiovascular disease, infection, advanced age), anorexia, acidosis, increased inflammatory cytokine production, oxidative stress, hypervolemia, reduction in ingestion of nutrients, and prescription of restrictive diets<sup>6</sup>.

As a consequence of all factors that trigger this syndrome, one can observe reduced levels of albumin, prealbumin, and lipids, weight reduction, BMC and body fat, leading to higher rates of hospitalization and mortality<sup>6</sup>.

The data presented in this review originate from analysis of PubMed data base in the last 20 years by investigating AKI and assessment of nutritional status-related key words.

## NUTRITIONAL ASSESSMENT

Malnutrition in AKI patients is associated with a higher incidence of complications, longer hospitalizations, and higher mortality<sup>7</sup>. However, it is very difficult to obtain a reliable nutritional diagnosis considering, mainly, the influence of non-nutritional factors, such as inflammation and changes in hydration status, on the interpretation of available markers. Table 1 summarizes the main nutritional markers that can be used in AKI patients, as well as their limitations<sup>8</sup>.

## BIOCHEMICAL PARAMETERS

Laboratorial evaluation, composed mainly by visceral proteins (albumin, transferrin, and prealbumin), is a tool used in several pathologies to monitor the metabolic response to nutritional support. Factors like reduction of food ingestion, disruption of liver function, and inflammatory status can result in reduction in the levels of those proteins<sup>9</sup>.

Albumin, the classic malnutrition marker, can lose its accuracy in AKI patients, since the reduction in its levels is not always a consequence of the limited energy and protein substrate intake<sup>10</sup>. The presence of inflammation, which prioritizes the production of acute-phase proteins, can be intense in those patients, making albumin of little value as a nutritional marker<sup>9</sup>. However, its use as predictor of mortality has been described in patients with AKI. Chertow et al.<sup>11</sup> observed hypoalbuminemia as a predictor of mortality in patients with acute tubular necrosis. In this study, each 1 g/dL increase in serum albumin levels reduced by 44% the risk of mortality and dialysis. More recently, Obialo et al.<sup>12</sup>, in a retrospective study with 100 AKI patients, observed that, in the absence of multiple organ failure, patients with serum albumin levels lower than 3.5 g/dL had a relative risk of death of 3.6 regardless of the presence of sepsis. The use of this marker in critical AKI patients can be more useful

**Table 1** – Nutritional markers and their limitations in acute kidney injury patients<sup>8</sup>

Albumin, prealbumin, and cholesterol	May be reduced regardless of PEW (negative inflammation markers)
Leukocyte count	Low specificity
Changes in body weight	Total body water is increased in AKI Hypervolemia can mask changes in muscle mass
Anthropometry (triceps skin fold, arm circumference etc)	Influence by edema
Protein catabolic rate or protein equivalent of nitrogen emergence	Measurements require calculations based on urea kinetics during renal RRT + collection of the dialysate
Energy spending	Prediction formulas are not always accurate in critically ill patients (they are usually based on body weight)
Nutritional score (SGA and its modifications)	Most data are from patients with chronic renal disease
Other potential tools or under development	
Growth hormone and IGF-1 levels	Few data available on AKI
Inflammatory markers (CRP, serum interleukins, and etc)	Patient PEW prognostic/risk markers; non-nutritional parameters (they are not useful for nutritional diagnosis and monitoring)
Bioelectrical impedance analysis	No data available on AKI

AKI, acute kidney injury; PEW, protein energy-wasting; RRT, renal replacement therapy.

as a predictor of mortality than a marker of the nutritional status. The ISRNM recommends that levels below 3.8 g/dL of albumin can be used as a diagnostic parameter of PEW in AKI and chronic kidney disease<sup>6</sup>.

Low cholesterol levels have also been described as predictors of complications and mortality. Extremely low cholesterol and LDL-cholesterol levels have been described in critically ill patients due to several factors, such as trauma, sepsis, hemodilution secondary to bleeding, and liver dysfunction<sup>13</sup>. In AKI patients, studies have demonstrated that cholesterol levels have a significant association with survival. Obialo et al.<sup>12</sup> identified a 50% reduction in survival of AKI patients who had cholesterol levels lower than 150 mg/dL on admission. More recently, Guimarães et al.<sup>14</sup>, in a study with 56 AKI patients admitted to the ICU, demonstrated that cholesterol levels below 96 mg/dL reduced significantly and independently the rate of survival in those patients. The ISRNM Expert Panel proposed cholesterol levels below 100 mg/dL among the criteria of biochemical assessment for the clinical diagnosis of PEW in AKI<sup>6</sup>.

Prealbumin (transthyretin), also used as a nutritional marker, has a half-life of about two days, inferior to that of albumin. Although its interpretation can also be hindered by the presence of infection, inflammation, and trauma, some authors have demonstrated interesting data of the use of this marker as a predictor of survival and marker of nutritional support. In a longitudinal study evaluating 161 AKI patients, Perez-Valdivieso et al.<sup>15</sup> demonstrated that level below 11 mg/dL of prealbumin was associated with greater mortality in patients with the same prognos-

tic index, classification, and treatment for AKI. Besides, a 5 mg/dL increase was associated with a 29% reduction in hospital mortality. As a marker of nutritional support, a prospective randomized controlled study with 120 critical patients in the ICU showed that, despite a reduction in length of hospitalization and mortality was not observed, those patients with greater caloric intake (25 kcal/kg x 11 kcal/kg) had a significant increase of 40 mg/L in prealbumin levels at the end of a 7-day follow-up<sup>16</sup>. However, data on its use as a marker of nutritional support in AKI patients were not found.

Insulin-like growth factor 1 (IGF-1) is a peptide analogous to insulin whose synthesis is influenced by hormonal and nutritional factors. Its reduction is associated to a lower survival in AKI patients, as shown by Guimarães et al.<sup>14</sup>. By evaluating 56 AKI patients, the authors observed that IGF-1 levels lower than 50.6 ng/mL showed a significant association to decreased survival regardless of the presence of sepsis. Patients with lower levels had up to 80% reduction in survival at the end of 28-day follow-up. The good correlation of this parameter with nutritional status, serum stability, and short half-life allow its use as an early and sensitive marker of mortality in critically ill AKI patients<sup>14</sup>.

#### HYPERCATABOLISM

Marked hypercatabolism is the main nutritional characteristic in AKI patients. Situations mentioned, such as insulin resistance, increased circulation of catabolic hormones, and acute phase reaction, are among the main factors responsible for this change<sup>4</sup>.

It is possible to estimate the extension of catabolism in those patients through a specific formula for patients with acute kidney disease. The calculus of the emergence of urea nitrogen, proposed by Wilfred Druml<sup>4</sup>, is a method that allows quantification of catabolic stress in AKI patients through the sum of the excretion of urine urea nitrogen and variation in body urea nitrogen. The author also associated this extension with the clinical picture of the patient, mortality rate, and need of dialysis. Thus, in patients with lower catabolism (loss of nitrogen exceeding up to 5 g the ingestion of dietary nitrogen), nephrotoxicity is usually the etiology of AKI, they have a low mortality rate (20%), and they rarely need dialysis. Surgery and infections are among the causes of AKI in patients with moderate catabolism (nitrogen losses exceeding 5 to 10 g/day) who have higher mortality rates (approximately 60%), and they may need dialysis. Finally, patients with marked catabolism are those with sepsis or severe injuries, with a high mortality rate (80%), and they frequently need dialysis.

Patients on dialysis, losses in the dialysate should be added to the total nitrogen losses to provide the final value for the classification of the catabolism<sup>6</sup>.

By calculating the difference between ingestion of dietary nitrogen and total nitrogen losses, we obtain the nitrogen balance, whose main objective is to evaluate nutritional nitrogen support. In stable patients, one tries to achieve a positive nitrogen balance between 4 and 6 g/day. Unfortunately, critically ill patients are hardly capable of maintaining a positive balance, especially while the situation of stress is not resolved. Besides, even higher delivery of dietary proteins can be insufficient to obtain a neutral or positive nitrogen balance in situations of marked catabolism, such as polytrauma and sepsis<sup>17</sup>. The main objective is the offer of adequate diet to obtain the least negative nitrogen balance possible to reduce protein catabolism in those patients.

In the literature, the association of this parameter with the clinical prognosis in AKI patients on dialysis has been reported. Scheinkestel et al.<sup>18</sup> observed that the nitrogen balance was inversely associated with hospital and ICU outcomes. Besides, an increase of 1 g/day in nitrogen balance caused a 21% increased in survival of those patients.

### ANTHROPOMETRY

Anthropometry, which is easy to apply and low cost, is one of the methods used more often in nutritional evaluation. Although measurements like arm circumference and skin folds are used as representative of adipose and muscular tissue body compartments<sup>10</sup> in several types of patients, its use in critically ill patients is very limited, since it seems to reflect more total body water rearrangement than modifications in body composition<sup>19</sup>.

On the other hand, Fiaccadori et al.<sup>7</sup> were able to demonstrate that AKI patients with prior malnutrition,

according to the diagnosis of the Subjective Global Assessment (SGA), also have anthropometric markers, such as triceps skin fold and circumference of the arm, below normal for the population investigated had higher mortality rates.

However, the difficulty to standardize those measurements in critically ill patients, as well as the interference of factors related to changes in the hydration status, make the use of these data not trustworthy as a tool for nutritional follow-up.

### BODY MASS INDEX (BMI)

The increase in body mass is classically described as one of the main risk factors for increased mortality and worse prognosis in the general population. However, among AKI patients, the presence of reverse epidemiology, also observed in other pathologies, such as chronic kidney disease, chronic obstructive pulmonary disease, and congestive heart failure, also seems evident. In those patients, higher BMI values seem to have more advantage in survival and clinical prognosis<sup>20</sup>.

A prospective study that analyzed the data of 5,232 AKI patients on dialysis showed that patients with a BMI between 30 and 35 kg/m<sup>2</sup> had a 20% reduction in the survival probability. In this study, despite obesity being an independent risk factor for the development of AKI, patients with higher BMI had higher survival rate compared to those with BMI lower than 25 kg/m<sup>2</sup><sup>20</sup>. One should consider that the BMI is not a perfect measure of body composition, since it is influenced by the presence of edema.

### BIOELECTRICAL IMPEDANCE ANALYSIS (BIA)

Bioelectrical impedance analysis is a non-invasive method of body evaluation, easy to use, and low cost. Its analysis is based on the resistance of the body to the flow of low amplitude (800 mA) and high frequency (50 KHz) electrical current, providing results like impedance, resistance, reactance, and phase angle. To estimate total body water, lean body mass, cellular body mass, and body fat, BIA assumes the concept that hydration of bodily tissues is constant in all individuals, and the human body is similar to a cylinder that conducts electrical current homogeneously. These are the main reasons why it is difficult to use it in critically ill patients, since they have frequent changes in tissue hydration as a consequence of edema, ascitis, IV fluids, and diuretics<sup>21,22</sup>. 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.

### SUBJECTIVE GLOBAL ASSESSMENT (SGA)

Used as an independent predictor of survival in several diseases, SGA is a simple method based on loss of body weight, changes in food ingestion, gastrointestinal symp-

toms, functional capacity, and physical exam for loss of fat and body mass<sup>23,24</sup>. Fiaccadori et al.<sup>7</sup>, applied this evaluation in 309 AKI patients, of which 67% needed dialysis; it identified 58% who were malnourished, of which 16% were moderately malnourished (SAG B class) and 42%, severely malnourished (SAG C class). Patients who were severely malnourished had anthropometric and biochemical parameters, and immunologic nutritional indices significantly reduced compared to those who were well nourished (SAG A class). Besides, they were also twice as likely to die regardless of the presence of acute and chronic comorbidities and complications during hospitalization. These data demonstrate that the diagnosis of malnutrition, according to the SGA, is an important risk factor for mortality, regardless of the severity of baseline disorders in AKI patients.

### NEED OF MACRONUTRIENTS

Nutritional support of AKI patients should be similar to that of other patients in catabolic situations to achieve optimal energy, protein, and micronutrient requirements to prevent PEW, preserve muscular mass, improve healing, improve immunologic function, and reduce the mortality rate<sup>25</sup>.

To achieve the nutritional needs of AKI patients, first, we should consider the severity of the disease, prior nutritional status, presence of complications, and the type and intensity of RRT. Those factors have more important role in determining the supply of nutrients than AKI itself<sup>25,26</sup>.

### CALORIES

Acute renal injury by itself does not cause an increase in energy spending, and the recommended supply should not exceed 130% of baseline energy spending<sup>5,27,28</sup>. To determine energy requirements, indirect calorimetry should be applied. Whenever this tool cannot be used, 25 to 30 kcal/kg/day should be supplied<sup>8,25,29</sup>. Greater supplementation does not bring any advantages when their effects on nitrogen balance and metabolic complications in AKI patients on RRT are analyzed. Fiaccadori et al.<sup>30</sup>, comparing individual on diets of 30 kcal/kg and 40 kcal/kg, both with 1.5 g/kg/day of protein, demonstrated that the higher intake was not associated with advantages regarding significant improvement in nitrogen balance, contributing with negative factors, such as hyperglycemia, hypertriglyceridemia, greater need of insulin, and greater volume of fluid intake.

According to the European directives, recommendations for lipids range from 0.7 to 1.5 g/kg/day<sup>29</sup>. Other authors recommend the use of about 30% or 1/3 of total non-protein calories, both using lipid emulsions composed of medium- and long-chain triglycerides<sup>8,31</sup>. Since fatty acid oxidation is decreased in AKI, serum triglycerides should be closely monitored, and the administration of the diet should be discontinued whenever their levels exceed 400 mg/dL<sup>8</sup>.

Regarding carbohydrates, the recommendations suggest that 2/3 of total non-protein calories or between 2 to 5 g/kg/day of glucose should be administered<sup>8,29</sup>. Note that AKI patients on peritoneal dialysis can absorb approximately 40% to 50% of the total prescribed glucose in the dialysate, which is an important contribution to the supply of glucose and it should be considered when calculating total requirements<sup>32</sup>.

### PROTEINS

Considering that the catabolic rate of protein in AKI patients on RRT ranges from 1.4 to 1.8 g/kg, the objective of the upper recommended dose of 1.5 g/kg/day is to minimize nitrogen loss in those patients<sup>8</sup>. Fiaccadori et al.<sup>31</sup> suggest that protein supply should be based on the degree of catabolism, according to Table 2.

### MICRONUTRIENTS

There are very few studies on the requirements of minerals and vitamins in AKI patients. The majority of the studies are on patients with chronic kidney disease. In AKI patients, losses during dialysis are among the most important causes of micronutrient depletion. Studies have shown plasma levels of C vitamin, thiamin, and folic acid below normal in AKI patients on RRT<sup>33</sup>. Table 3 shows nutrient losses during RRT, as well as the recommended intake.

To conclude, there are very few studies in the literature assessing the nutritional status of AKI patients. Although prospective data on the behavior of nutritional markers are lacking, some authors were able to demonstrate associations with clinical outcomes. The use of parameters like albumin, cholesterol, prealbumin, IGF-1, ASG, and calculus of the nitrogen balance seem to be useful as screening parameters for worse prognosis and higher mortality in AKI patients. In AKI patients on RRT, a calorie intake of approximately 25 to 30 kcal/kg and a minimum intake of 1.5 g/kg/day of proteins is recommended to minimize protein catabolism and metabolic complications.

**Table 2** – Protein recommendations for acute kidney failure patients<sup>31</sup>

Protein (essential and non-essential amino acids)	
Conservative treatment – low catabolism	0.8 g/kg/day
On extracorporeal therapy – moderate hypercatabolism	1.0 to 1.5 g/kg/day
Extended or continuous hemodialysis – severe hypercatabolism	1.5 to 2.0 g/kg/day



**Table 3** – Micronutrient dialysate losses and recommendations<sup>33</sup>

Micronutrients	Mean dialysate losses/24 hours	Recommendations (parenteral nutrition)
Chrome	25 µmol	15 µg
Copper	0.41 mg	1.0 to 1.2 mg
Selenium	110 µg	60 µg
Zinc	0.2 mg	6.5 mg
Vitamin B1	4.1 mg	3 mg
Vitamin C	10 mg	100 mg
Vitamin E	ND	10 IU

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