A general overview of malnutrition in normal kidney function and in chronic kidney disease

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In adult patients, the main nutrition-related diseases are obesity, diabetes type 2 and dyslipidaemia and on the other hand malnutrition. Malnutrition can be defined as the imbalance between intake and requirement which results in altered metabolism, impaired function and loss of body mass [1]. Such a definition includes both the so-called protein–energy malnutrition (PEM) and inadequate micronutrient status. Although macro- and micronutrient deficiencies are most often associated, most studies on ‘malnutrition’ or undernutrition usually address PEM. The purpose of the present review is to give a general overview of PEM and its assessment methods in normal kidney function and in renal patients. Recently, an expert panel from the International Society of Renal Nutrition and Metabolism proposed the term ‘protein energy wasting’ (PEW) to designate malnutrition in kidney diseases and gave its definition and a pathophysiological basis [2].

Protein–energy malnutrition in normal kidney function

Protein–energy malnutrition subtypes

Several PEM subtypes have been described according to the respective deficiencies in protein and/or energy intakes, the presence of inflammation and the speed of the constitution of PEM. Acute PEM, which is observed in stressed conditions, such as severe acute kidney disease, will not be developed in this review [3].

Marasmus is the consequence of a prolonged partial starvation with a similar reduction of both protein and energy intakes. In marasmic patients, hormonal changes, mainly characterized by a decrease in the insulin/glucagon ratio, make it possible to adapt to starvation. This adaptation consists in a progressive switch in the use of energy substrates from glucose to ketone bodies, together with a decrease in gluconeogenesis from amino acids and an increase in fatty acid release from adipose tissue. The clinical picture of marasmus is a depletion of both fat and fat-free mass without noticeable water retention. In these patients, albumin synthesis is preserved and no oedema is observed.

Kwashiorkor is the consequence of prolonged insufficient intakes predominating on protein supply. Most often, kwashiorkor is associated with inflammation due to chronic intestinal or cutaneous infections and malabsorption. In this setting, because of inflammatory cytokines and hormonal-related changes, the decrease in the insulin/glucagon ratio cannot occur. The adaptation to starvation is no more possible, leading to an increased use of muscle protein stores for gluconeogenesis. Such protein malnutrition is associated with hypoalbuminaemia, oedemas and sometimes ascites.

In clinical practice, a lot of intermediate nutritional pictures can be observed between marasmus and kwashiorkor. In patients with chronic disease, the presence of both insufficient intakes and inflammation can be responsible for protein malnutrition mimicking kwashiorkor. The prevalence and causes of PEM in chronic diseases are given in Table 1. In hospitalized patients, PEM is found in 20–50% of patients depending on criteria for malnutrition and clinical settings [4]. Protein malnutrition, as characterized by the presence of hypoalbuminaemia, is associated with higher rates of complications and mortality together with an increase of hospitalization length and overall costs [4–6].

Causes of malnutrition in chronic diseases

The causes of PEM in chronic diseases are given in Table 1. Schematically, PEM can be explained by insufficient nutrient intake (primary malnutrition) and/or an increase in nutrient needs due to disease-related metabolic abnormalities leading to increased energy expenditure, increased protein degradation and negative protein balance (secondary malnutrition). Insufficient nutrient intake can be due to mechanical obstructions of the digestive tract, disease-induced anorexia, depression and low socioeconomic status.
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Numerous methods have been used for assessing nutritional status. Dietician consultation is of primary importance in chronically ill patients both for assessing nutritional intakes and providing nutritional counselling. Among anthropometric measurements, body weight and height, and body mass index (BMI, body weight/height\(^2\)) are routinely used. BMI and body weight loss were reported as independent markers of survival in chronic respiratory and renal diseases [2,7]. In the absence of water retention, triceps skinfold thickness (TSF) reflects fat stores and arm muscle circumference (AMC = arm circumference – 3.14 × TSF) muscle mass. TSF and AMC should be considered according to reference values for age and gender [8]. Serum concentrations of albumin and transthyretin (prealbumin) are determined both by nutritional variables, namely protein–energy intakes, and by non-nutritional variables such as inflammation, liver function, hydration status, gender, age and, regarding to serum albumin, urinary losses [9,10]. However, in chronically depleted patients, these serum proteins also reflect protein intake and nutritional status [2,11]. Both serum albumin and transthyretin exhibit a high prognostic value in chronically ill patients as well as in patient undergoing surgical interventions [10,12,13]. The subjective global nutritional assessment (SGA), using variables derived from history and physical examination, has been validated in numerous medical and surgical settings [14]. Body impedance analysis (BIA) using the 50-kHz frequency makes it possible to assess fat mass and fat-free mass. Multifrequency BIA is required for measuring the ratio of extracellular water to total body water in subjects with end-stage renal disease [15]. However, BIA results should be interpreted with caution in patients with body water changes. DEXA is the reference method for body composition measurement, which makes it possible to measure fat mass and fat-free mass, including mineral mass [16]. The association of DEXA with multi-frequency BIA makes it possible to assess body cell mass.

Among these methods used to assess nutritional status, BMI, body weight loss and serum protein measurements appeared more useful for detecting high-risk patients requiring nutritional intervention. Buzby et al. proposed a nutritional risk index (NRI) based on serum albumin and the ratio of present to usual body weight:

\[
NRI = 1.519 \times \text{serum albumin} + 0.417 \\
\times (\text{present/usual by weight/100}).
\]

According to this index, patients can be classified as non-malnourished (NRI > 97.5), moderately malnourished (97.5 > NRI > 83.5) and severely malnourished (NRI < 83.5). This index, validated in surgical patients, is now widely used for the nutritional assessment of hospitalized patient [12].

**Particularities of chronic kidney disease patients**

*Prevalence of protein–energy wasting*

The term ‘protein–energy wasting’ (PEW) in acute, and chronic kidney disease (CKD) has been recently proposed...
by an expert panel for the loss of body protein mass and fuel reserves. PEW should be diagnosed if three characteristics are present: low serum levels of albumin, transthyretin, or cholesterol; reduced body mass defined by low or reduced BMI, fat mass or weight loss with a reduced intake of protein and energy; and reduced muscle mass defined by muscle wasting or sarcopenia and reduced mid-AMC [2].

The prevalence of PEW progressively increases during the evolution of CKD. It has been reported that 40% of the patients present with symptoms of PEW at the entrance in dialysis [17]. Adequate data are lacking to compare nutritional status in peritoneal dialysis (PD) and haemodialysis (HD). In one Italian report, maintenance HD patients >76 years were more likely to be malnourished than PD patients. In patients <65 years of age, PEW was more likely to be present in PD patients than in HD patients [18]. In HD patients, the prevalence of PEW varies from 20% to 60% according to the indicators used [11]. In a European series of 7123 HD patients, albumin, transthyretin and normalized equivalent of total nitrogen appearance (nPNA) were below the high-risk threshold of 35 g/L, 300 mg/L and 1 g/kg/day in 20%, 36% and 35%, respectively [11]. Similarly, in DOPPS II Study, 20.5% of US patients had a serum albumin level <35 g/L [19]. The prevalence and severity of PEW increase with the number of years of dialysis and are more pronounced in older patients [11]. As compared with non-diabetics, diabetic HD patients are characterized by decreased lean body mass, serum albumin and transthyretin and increased BMI and serum cholesterol [20]. Such an alteration of protein status is associated with accelerated loss of lean body mass during the first year of renal replacement therapy [21].

Prognostic impact of PEW

PEW and survival. PEW is recognized as an independent determinant of morbidity and mortality in HD and PD patients. Prospective studies have also shown a strong association between nutritional parameters and the 1-year morbidity and mortality among HD patients, with serum albumin and transthyretin showing the strongest predictive value at the respective thresholds of 35 g/L and 300 mg/L [22–27]. In Western Europe, according to serum albumin and transthyretin, it can be estimated that 25% of HD patients present with malnutrition compromising their 1-year survival [11]. The relative risk of mortality after 2 years has been shown to be decreased by 5% per unit of 1 g/L of serum albumin and by 14% per unit of 100 mg/L of serum transthyretin [25]. Changes in nutritional variables over a few weeks provide additional prognostic information [28]. Low serum albumin and transthyretin, reduced urea nitrogen appearance, decreased lean body mass, low serum creatinine and low nutrition scores assessed by the subjective global assessment are also associated with high morbidity and mortality in PD patients [29]. It can be estimated that yearly mortality rates in malnourished HD patients are ~25–30% [25]. PEW is not usually a direct cause of morbidity and mortality but rather contributes to a fatal outcome by worsening the adverse effects of cardio-vascular and infection diseases which are the most common causes of death in HD patients [30].

BMI and long-term survival. In the general population, the lower death risk is observed in subjects with BMI values from 20 to 25 kg/m², and an increased death risk occurs when BMI is lower or higher than these values [31]. In HD patients, BMI was established as an independently important predictor of mortality [32]. Since a few years, the relationships between BMI and mortality risk have drawn special attention. An observational study in a HD patient series showed that for every unit increase in BMI, the relative risk (RR) of mortality was reduced by 10%. Similarly, in patients entering dialysis, of the three body-size groups, the lowest BMI group (<23.2 kg/m²) had a 42% higher 2-year mortality risk than the highest BMI tertile (≥27.8 kg/m²) after adjusting for age, gender, GFR and comorbidity [33]. This particular relationship between BMI and survival in HD patients was called ‘reverse epidemiology’. The reverse epidemiology was also reported in healthier or younger end-stage CKD patients: in patients <45 year with low comorbidity, the survival benefit observed in overweight patients (BMI from 25 kg/m² to 29.9 kg/m²) was even greater in obese patients (BMI >30 kg/m²) [31], as in all subgroups of age, sex, race, dialysis vintage, serum albumin and Kt/V [34]. Such a reverse epidemiology was also described regarding to other conventional risk factors of cardiovascular disease such as blood pressure [35], serum cholesterol [36] and homocysteine [34]; high values for these risk factors are paradoxically protective and associated with improved survival in HD patients [37]. The protective effect of high BMI on morbidity and mortality risk, which is independent of serum albumin, indirectly confirms the importance of nutritional factors in the outcome of HD patients [38]. Several explanations have been proposed to explain this reverse epidemiology linked to BMI in HD patients (for review [39]). One of them appears as particularly relevant: the duration of the follow-up greatly differs in HD patients as compared with healthy subjects (3–5 years versus more than 15 years). In order to study the impact of the follow-up duration, De Mutsert et al. studied the relationships between BMI and survival in 722 HD and 2436 control subjects of comparable age during an equal follow-up of 7 years [40]. Adjusted hazard ratios of BMI categories were calculated with a BMI of 22.5–25 kg/m² as the reference category within each population. In 7 years of follow-up, standardized mortality rates were ~10 times higher in the HD population than those in the general population. Compared with the reference category (BMI = 22.5–25 kg/m²), the hazard ratios of BMI <18.5 kg/m² were 2.0 in the HD population and 2.3 in the general population and only 1.2 in the HD population and 1.2 in the general population for obesity. Thus, a HD population and a general population with comparable age and equal duration of follow-up showed similar mortality risk patterns associated with BMI [40]. This means that when the life expectancy is limited to a few years, low BMI represents a higher risk of death than high BMI. These data are coherent with other findings of ‘reverse epidemiology’ found in old people and in other chronic diseases such as chronic obstructive pulmonary disease (COPD) [41]. However, it should be mentioned that protein wasting can be present in obese patients and is associated with inflammation and poor survival [42]. Although both lean body mass and fat mass were reported to account for increased
survival associated with high BMI values in HD patients [43,44], the protective effect of muscle mass seems to be the pre-eminent factor [43].

Nutritional assessment in renal patients

According to the National Kidney Foundation Clinical Practice Guidelines for Nutrition in Chronic Renal failure, nutritional status should be assessed with a combination of valid, complimentary measures rather than any single measure alone [45]. Dietary interviews should be performed every 6 months during 3-day records including one dialysis day and one weekend day [45,46]. This first step of nutritional assessment is of first importance to evaluate nutrient intakes, to detect nutritional deficiencies and for nutritional counselling. Anthropometric measurements usually include body weight, height, percentage of usual and standard body weight and BMI. The follow-up of body weight is of great interest to detect PEW. In PD patients, clinical observations suggest that overhydration is a usual feature. Because of overhydration and expense of body fat due to the glucose load through dialysis fluid, protein wasting can coexist with stable body weight [47]. In CKD patients, in the absence of oedema, TSF and AMC are reliable clinical tools for assessing fat stores and muscle mass. Handgrip strength has been recently proposed as a cheap and simple method that agrees reasonably well with other measures of nutritional status and predicts outcome [48,49].

It can be assumed that the relationships between nutritional parameters are due to a mutual dependence on nutritional status. According to this assumption, parameters exhibiting the tightest correlations with the others can be considered to be the most representative of nutritional status. Thus, serum albumin and transthyretin (prealbumin) appeared as major tools for evaluating protein–energy status, although their concentrations are also dependent on such non-nutritional variables as liver function, hydration and inflammatory status. In HD patients, these proteins should be measured before a HD session. Serum albumin was shown to be correlated with multiple markers of protein–energy status such as nPNA, lean body mass, serum creatinine, transferrin, cholesterol, insulin-like growth factor-I and transthyretin [11,22,50,51]. Transthyretin should be interpreted with caution in the CKD patient and only considered as a nutritional marker in condition of stable renal function [13]. In maintenance HD patients, serum transthyretin is recognized as a valid and clinically useful measure of protein–energy status [22,45,52]. Indeed, serum transthyretin correlates with many other markers of protein–energy status including protein and energy intake, nPNA, body weight, BMI, AMC, TSF, lean body mass, serum creatinine, albumin, transferrin and IGF-I [11,22,50,51]. It has been recommended that the outcome goal for transthyretin is a value >300 mg/L in dialysis patients [22,45,52]. Both serum albumin and transthyretin have been demonstrated to be independent predictors of mortality in maintenance dialysis [26]. In protein–energy wasted HD patients, transthyretin was recently shown to be of particular value for the monitoring of patients receiving a nutritional support and more specifically for predicting the morbidity and mortality response to nutritional support [53]; an increase by 30 mg/L of serum transthyretin after 3 months was associated with a more than 2-fold increase in the 2-year survival.

Although serum cholesterol is not properly considered to be a classical tool for monitoring protein–energy status in CKD patients, individuals with low or declining serum cholesterol should be investigated for possible nutritional risk factors that promote PEW [2,45].

In HD patient, the normalized protein equivalent of total nitrogen appearance (nPNA, g protein/kg/day) is calculated from the interdialytic changes in serum urea nitrogen and the urea nitrogen content in urine and dialysate. It should be noticed that the most commonly used method for calculating nPNA does not include dialysate and interdialytic urine collection. In the absence of dialysate collection, urea production is approximated from pre and post-HD serum urea concentrations and the theoretical estimates of urea dilution space. The lack of estimation of residual renal function may underestimate urea nitrogen output, mainly in recently dialysed patients. As a matter of fact, data on renal residual function in HD patients showed that 1–2% of patients presented with urine output >500 mL/day after 1 year [18,54]. In clinically stable conditions, nPNA provides a valid estimate of protein intake and is correlated with lean body mass, serum albumin and serum transthyretin [11]. Normalized PNA also predicts patient outcome [55,56]. In PD patient, nPNA is also an estimate of dietary protein intake, validated and simple to use in the clinical setting [57]. However, it should be underlined that nPNA approximates dietary protein intake only when the patient is at nitrogen equilibrium or steady state. As a consequence, nPNA is influenced in anabolic or catabolic situations and in circumstances of marked variation in protein intake. Thus, nPNA exceeds protein intake in catabolic patients and may overestimate dietary protein intake when the protein intake is <1 g/kg/day, possibly due to protein catabolism. Furthermore, normalizing PNA to body weight can be misleading in obese, malnourished and oedematous patients [58]. Predialysis serum creatinine and the creatinine index reflect the sum of endogenous creatinine production and dietary intakes of creatinine precursors. Low predialysis serum creatinine and creatinine index reflect low protein intake and/or decreased muscle mass and indicate a need for assessment of protein–energy status assessment. Both variables have been shown to be correlated with outcome in chronic HD patients [22,23,25,59]. In a clinical trial involving 187 HD patients, using multivariate analyses, serum transthyretin appeared to be the most predictive biological marker of non-cardiovascular death, and the creatinine index was most predictive of cardiovascular death [60]. In PD patients, the reliability of creatinine kinetics to evaluate lean body mass has been debated [61,62]. The SGA has been proposed as an inexpensive and easy-to-apply method using variables derived from history and physical examination [14]. SGA is now considered to be a valid indicator of PEW in uraemic patients and is proposed as a component of the systematic monitoring of PEW in chronic HD and PD patients [45,46,52,62].

BIA using a mono-frequency procedure, makes it possible to assess fat mass and fat-free mass. Multifrequency BIA makes it possible to measure the ratio of extracellular
water to total body water in subjects with end-stage renal disease [63]. In HD patients, body cell mass estimated by BIA was shown to be highly correlated with body cell mass determined by dual-energy x-ray absorptiometry (DEXA) and NaBr [64]. BIA measurements vary to a considerable extent according to the point in time chosen for performing BIA, but remain constant and highly reproducible during the first 120 min following the end of HD, that is, in a dry-weight state [65,66]. BIA results should be interpreted with caution in patients with body water changes. Moreover, in order to ensure reproducible results, a standardization of formulas used for calculation as well as a clear definition of the acceptable times to perform BIA is required. Similarly, in PD patient BIA offers reliable estimates of total body composition but population-specific equations are needed. Because DEXA estimates lean body mass as body mass minus fat and bone masses, it can be noticed that the estimation of lean body mass includes possible changes in the hydration state. Nevertheless, in HD as well as in PD patients, according to present guidelines, DEXA remains the reference method for the precise measurements of body composition and bone mineral density [45,67–70]. The precision of DEXA for fat mass measurement is ~3%, in HD and PD patients [67].

The recommended variables for the routine follow-up of dialysis patients are given in Table 2.

## Conclusion

PEM is widespread among patients with chronic organ failure, usually as a consequence of both low nutrient intakes and abnormal nutrient metabolism. In these patients, nutritional status is an independent predictor of morbidity and mortality. Therefore, the detection and treatment of PEM appears as a major challenge in the care of chronically ill patients. In routine clinical practice, the detection of malnourished patients most often relies on simple tools such as dietary records, height and weight measurements, history of weight changes, BMI and measurement of serum albumin and transthyretin. The subjective global assessment of nutritional status has been validated in several chronic diseases, including CKD. In selected cases, body composition measurements can be useful. In CKD patients, PEW has recently been defined as the association of low serum markers of malnutrition, together with indicators of decreased fat and fat-free mass. The fact that PEW compromising the 1-year survival is found in ~25% of dialysis patients underlines the necessity of a close dietary and nutritional management of these patients.

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## References

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56. Kalantar-Zadeh K, Supasynnd O, Lehns RS et al. Normalized protein nitrogen appearance is correlated with hospitalization and mortality in
hemodialysis patients with Kt/V greater than 1.20. J Ren Nutr 2003; 13: 15–25


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