Nutritional status assessment: a neglected biomarker in persons with end-stage kidney disease.

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Abstract

Purpose of review: Malnutrition is a frequent complication and risk factor for adverse outcomes in the dialysis population that is often underrecognized and neglected. This article reviews published literature on the associations between malnutrition, mortality, quality of life and hospitalisations in persons on dialysis in order to raise awareness of the importance of preventing and treating it.

Recent findings: All methods of nutritional assessment namely serum biochemistry, body composition, dietary intake, handgrip strength and nutritional scoring tools are independently associated with increased mortality in dialysis populations. Malnutrition severely affects physical and mental measures of quality of life and increases the number and length of hospitalisations in persons receiving dialysis, resulting in increased healthcare costs. Worsening of nutritional status is also associated with poor survival and higher rates of hospitalisations in this patient population.

Summary: Malnutrition is an unacceptably common complication in dialysis patients that is substantially associated with adverse outcomes and higher hospital costs. Further interventional studies assessing the impact of preventing and treating malnutrition on clinical outcomes are warranted and should be considered a priority.

Keywords: adverse outcomes, end-stage kidney disease, dialysis, malnutrition, nutritional status assessment.

Introduction

Malnutrition is a major and frequent complication in persons with end-stage kidney disease (ESKD) receiving dialysis that results from the interaction between psychosocial factors, decreased functional capacity, and multiple ESKD-related mechanisms, including uremic toxicity, metabolic acidosis, loss of appetite, inadequate dietary intake, presence of comorbidities, nutrient losses during dialysis, and increased systemic inflammation and oxidative stress, which together lead to increased energy expenditure, muscle wasting and hypoalbuminaemia [1]. A number of terms have been used to refer to malnutrition and in 2008 the International Society of Renal Nutrition and Metabolism therefore suggested a single term, "Protein-Energy Wasting" (PEW), which provided a more accurate description of the association between muscle and energy wasting, inadequate dietary intake, systemic inflammation, oxidative stress, hypercatabolism and other metabolic abnormalities [2]. For the purpose of this review, the term "malnutrition" will be used as synonymous with "PEW".

According to a meta-analysis of 90 studies conducted in dialysis populations, the global prevalence of malnutrition varies between 28% and 54% (median 40%), which highlights the magnitude of the problem in this patient population [3**]. Despite the fact that malnutrition has been shown to be an independent and strong predictor of increased mortality, poor quality of life and higher rates of hospitalisations, resulting in increased hospital costs [3**-5], it continues to be underrecognized and neglected in the context of ESKD. In order to raise awareness of the importance of preventing and treating malnutrition in persons receiving dialysis, we reviewed the increasing body of evidence surrounding its association with adverse clinical outcomes.

Methods for nutritional status assessment and associations with mortality

Multiple methods have been developed for the assessment of nutritional status. These vary in their dependence on laboratory testing, specialised equipment and staff time but most have been validated by confirmation of an association with increased mortality in persons receiving dialysis (Table 1).

1. Biochemistry

The main biochemical markers used for nutritional assessment in the dialysis population are serum albumin, prealbumin, total cholesterol and serum creatinine [2]. Among these, hypoalbuminaemia has been the most extensively studied marker of malnutrition in persons on dialysis, mainly because of its strong association with increased all-cause and cardiovascular mortality [4], and because serum albumin levels can be improved by different dietetic interventions [1]. Even though prospective studies have not yet investigated whether improvements in serum albumin (or any other biochemical markers of malnutrition) result in reduced mortality, there is evidence suggesting that a substantial percentage of deaths occurring during the first year of haemodialysis (HD) treatment could potentially be prevented by modifying important clinical risk factors, including hypoalbuminaemia [6*]. An analysis of data from 15,891 incident and 51,565 prevalent HD patients in the Dialysis Outcomes and Practice Patterns Study (1996-2015) investigated population-attributable fractions (PAF), which consider both the strength of association (hazard ratio, HR) and the prevalence of a risk factor, of 12 predictors of mortality to determine the percentage of deaths that could theoretically be prevented if the risk factor was modified. After dialysis catheter use, serum albumin <3.5 g/dL

and serum creatinine <6 mg/dL had the largest PAF for 1-year mortality in the incident HD population (19% and 12%, respectively). In the prevalent HD cohort, hypoalbuminaemia had the highest PAF (15%). More importantly, the combined PAF for malnutrition (i.e. hypoalbuminaemia + low serum creatinine) was even higher than the combined PAF for inflammation (i.e. high white blood cell count + high ferritin) in the incident (29% vs 8%) and prevalent HD populations (20% vs 4%). Additionally, in a subgroup analysis of 3,596 incident HD patients who had C reactive protein (CRP) measured, the largest PAF was observed for CRP >10 mg/dL (21%), followed by dialysis catheter use (20%) and hypoalbuminaemia (19%) [6*].

2. Dietary intake

In the dialysis population, food diaries conducted usually over 3 or 7 days are the preferred method for the assessment of energy, macronutrient and micronutrient intake, while 24-hour dietary recalls and normalised protein catabolic rate (nPCR) are alternative methods (Table 1) [4]. Inadequate dietary intake is another important marker of malnutrition and predictor of increased mortality in the dialysis population [7, 8]. For example, in a 44-month observational study conducted in 305 incident peritoneal dialysis (PD) patients, dietary protein intake <0.73 g/kg/d was independently associated with a 66% increase in overall mortality and a 2.6-fold increase in cardiovascular death [8]. In a 10-year retrospective observational study conducted in 144 prevalent HD patients, energy intake <25 kcal/kg/d and protein intake <0.8 g/kg/d were significantly associated with increased mortality in univariable analysis; however, only energy intake <25 kcal/kg/d was identified as an independent determinant of all-cause mortality (HR 1.86, 95%CI 1.02–3.39; p=0.04)

in a multivariable analysis adjusted for age, sex, Kt/V, diabetes and Charlson comorbidity index [7].

3. Body composition

The most common techniques used for the assessment of body composition in the dialysis population are anthropometry and bioelectrical impedance analysis (BIA; Table 1). Anthropometry refers to the standard and systematic measurement of weight, height, skinfold thicknesses and circumferences to calculate different anthropometric indexes and percentages, such as body mass index (BMI), body fat percentage and mid-arm muscle circumference. BIA is a technique that can directly measure and differentiate between body water, body fat mass and lean body mass (i.e. muscle mass) according to their electrical conductivity properties [4].

Decreased body fat and muscle mass are considered risk factors for higher mortality in persons receiving dialysis. For example, a 24-month multicentre longitudinal study conducted in 2,527 persons on HD observed that low body cell mass index (BCMI), which is a marker of muscle mass, was an independent determinant of higher mortality (HR 1.7, 95%CI 1.14–2.50; p=0.009), after adjustments for confounders [9]. Lower lean tissue index (LTI) and fat tissue index (FTI), markers of muscle and fat mass, respectively, have also been shown to be independent predictors of poor survival in persons performing PD [10].

Although BMI is a poor marker of malnutrition when used in isolation [4], some studies have shown an independent association between low BMI and poor survival [11, 12]. For instance, in a 36-month observational study conducted in 173 persons

on maintenance HD, BMI <23 kg/m^2 was independently associated with an 85% higher risk of death, after adjusting for confounders [11]. In a multicentre prospective observational study, 697 HD participants were followed-up for 12 months. After adjustment for covariates, BMI <18.5 kg/m^2 was independently associated with a 3.9-fold increased mortality risk [12]. This same study also reported that LTI and BCMI were significantly lower among non-survivors, that low FTI was an independent predictor of overall mortality (HR 3.25, 95%CI 1.33-7.95; p=0.01), and that a BMI between 25.0-29.9 kg/m^2 showed a reduction of 56% in mortality risk. These findings support the results from previous studies showing that higher BMI and increased fat stores are associated with better survival in persons on dialysis (i.e. an obesity paradox); nevertheless, this survival advantage might only apply to those obese dialysis patients whose muscle mass is not depleted, as low muscle mass and strength in the setting of excess adiposity (i.e. sarcopenic obesity) is a predictor of increased mortality [13].

4. Functional markers

Handgrip strength (HGS), a measure of muscle function and strength, is a simple, reproducible and validated method of nutritional and functional assessment, as well as a risk factor for mortality in persons receiving dialysis [14, 15]. A meta-analysis of 9 prospective cohort studies conducted in both HD and PD populations has reported that low HGS was an independent predictor of increased overall mortality (HR 1.88 95%CI 1.51-2.33; p=0.001) and that each 1-kg unit increase in HGS was independently associated with a 5% reduction in the risk of death [15].

5. Nutritional scoring tools

These assessment tools use a combination of objective and/or subjective nutritional markers in order to minimize the limitations of the methods described above when used in isolation [4]. The 7-point scale Subjective Global Assessment (SGA) is the most important and validated nutritional assessment tool recommended by national and international nutrition guidelines for use in the dialysis population. The SGA consists of a comprehensive evaluation of the history of weight loss, changes in dietary intake, presence of gastrointestinal symptoms and comorbidities, functional capacity, and a physical subjective assessment of subcutaneous fat and muscle loss, and presence of oedema. According to the individual ratings of these six nutrition-related components, nutritional status is classified into well-nourished (SGA scores of 6 or 7), mild-moderate malnutrition (SGA scores of 3-5) or severe malnutrition (SGA scores of 1 or 2) [4, 5].

The independent association between malnutrition, as assessed by the 7-point scale SGA, and increased mortality was first reported by the Canada-USA Peritoneal Dialysis Study Group in 1996 [16]. Since then, several other prospective studies have confirmed that the 7-point SGA as well as other nutritional scoring tools are independent predictors of poor survival in the dialysis population [4, 11, 17-20]. Viramontes Hörner et al. [20] reported for the first time in a prospective study conducted in 150 dialysis patients that malnutrition (assessed with 7-point SGA) and increased skin autofluorescence (a marker of systemic inflammation and oxidative stress) are independently associated with a 2.3-fold and a 44% increase in the risk of all-cause mortality, respectively, despite being potentially inter-related [21].

Rodrigues et al. [11] assessed the prognostic significance of the 7-point SGA and the Malnutrition Inflammation Score (MIS) in 173 persons receiving HD. MIS is a nutritional scoring tool that includes the 6 core components of the SGA plus BMI, serum albumin and total iron binding capacity. The overall MIS score ranges from 0 to 30; the higher the score the more severe the degree of malnutrition [18]. Multivariable Cox proportional hazards models identified an SGA score $\leq$5 (HR 2.32 95%CI 1.27-4.24; p=0.01) and a MIS score >8 (HR 2.09 95%CI 1.20-3.64; p=0.01) as independent predictors of increased mortality [11]. In a cohort of 365 incident PD patients, malnutrition (SGA score $\leq$5) was independently associated with a 78% increase in the risk of all-cause mortality after adjusting for potential confounders [17].

A multicentre prospective study [18] investigated the predictive value for overall and cardiovascular mortality of three nutritional scoring tools (MIS, geriatric nutritional risk index [GNRI] and objective score of nutrition on dialysis [OSND]) in a cohort of 1,025 persons on HD. GNRI is calculated using an equation that includes serum albumin and changes in body weight. OSND consists of a combination of anthropometric measures (weight loss, BMI, triceps skinfold thickness [TSF] and mid-arm circumference [MAC]) and biochemical variables (serum albumin, transferrin and cholesterol). In multivariable analysis adjusted for potential covariates, one standard deviation increase in MIS was independently associated with 35% and 39% higher all-cause and cardiovascular mortality, respectively. OSND and GNRI were also independent predictors of increased overall and cardiovascular mortality.

The association of another nutritional scoring tool, the nutritional risk index (NRI), with all-cause, cardiovascular and infection-related mortality was investigated in a Japanese nation-wide prospective cohort study conducted in 48,349 persons receiving HD [19]. The NRI comprises BMI, serum albumin, serum creatinine and total cholesterol, and it is categorised into three nutritional risk-groups: low-risk (score 0-7), medium-risk (score 8-10) and high-risk (score 11-13). After extensive adjustments, medium-risk and high-risk groups were independently associated with a 96% and a 3.9-fold increase in the risk of overall mortality, respectively. These same nutritional-risk groups were independent predictors of higher cardiovascular and infection-related mortality. The highest HR was observed in the high-risk group for death due to infection (5.56, 95%CI 4.49-6.89).

Change in nutritional status over time has also been associated with all-cause mortality during the first year of dialysis initiation. In a multicentre prospective cohort study with a median follow-up of 30 months [22*], nutritional status of 914 persons receiving dialysis (61% HD) was assessed with 7-point SGA at baseline and at 12 months after dialysis initiation. In multivariable analysis after adjusting for covariates, those participants who were well-nourished initially but became malnourished at 12 months of starting dialysis (*n*=48) showed a 2.8-fold increase in the risk of death compared to those who stayed well-nourished throughout one year (*n*=603). Conversely, those participants who became well-nourished at 12 months (*n*=213) showed a 65% mortality risk reduction in comparison to those who stayed malnourished throughout one year (*n*=50).

Malnutrition and quality of life

Health-related quality of life (HRQoL) is another important outcome that is severely affected by the presence of malnutrition in persons receiving dialysis [1]. For instance, de Roij van Zuijdewijn et al. [23] reported in a univariable analysis that malnutrition, as assessed by SGA and MIS, was significantly associated with lower physical component score (PCS) and mental component score (MCS) of HRQoL in a sample of 489 individuals on HD. Another cross-sectional study conducted in 94 persons receiving HD observed that a lower SGA score was an independent determinant of decreased PCS; however, malnutrition was not found to be independently associated with lower MCS, possibly due to the small sample size [24]. A cross-sectional analysis based on data from 632 HD patients who took part in the PROHEMO study [25] observed that malnourished participants (MIS $\geq$6; n=268) were more likely to have lower PCS and MCS compared to those who were well-nourished (adjusted mean difference for PCS and MCS: –3.3 95%CI –1.6 to –4.9;–2.4 95%CI –0.3 to –4.4, respectively). Several other cross-sectional and prospective studies conducted in dialysis populations have confirmed that better nutritional status is associated with higher physical and mental measures of HRQoL [14, 26-28].

Malnutrition, increased hospitalisations and healthcare costs

In persons receiving dialysis, malnutrition is also associated with higher rates of hospitalisation and longer hospital stay [11, 14, 29]. In a sample of 173 participants on HD, it was observed that those identified as being malnourished according to the SGA and MIS showed 38% and 40% higher risk for hospitalisation events, respectively, after adjusting for confounders. Lower HGS and hypoalbuminaemia were also identified as independent predictors of increased hospital admissions [11]. In another study conducted in 170 persons on HD [14], Poisson regression adjusted

models identified low muscle strength, as assessed by HGS, and presence of sarcopenia (defined as low muscle mass and strength) as independent determinants of higher hospitalisation rates. Worsening of nutritional status has also been associated with increased number of hospital admissions and length of hospitalisation. In a longitudinal study (*n*=104 HD patients) [29], adjusted regression models showed that participants who had an SGA score reduction of $\geq$1 units were 2.1 and 3.7 times more likely to be admitted to hospital and to have longer hospitalisations, respectively, compared to those participants whose SGA score increased by $\geq$1 units.

Increased rates of hospitalisations associated with malnutrition result in a greater use of healthcare resources and higher hospital costs. For instance, it has been reported that the average annual healthcare cost of disease-related malnutrition in England was £19.6 billion in 2011-2012. Additionally, the annual treatment cost of persons with malnutrition is three to four times higher than that of well-nourished individuals (£7,408 vs £2,155 per subject per year) due to longer, more frequent and more expensive hospital stays, as well as long-term care [30]. It has also been reported that presence of malnutrition, as assessed by different nutritional scoring tools, at hospital admission is an independent predictor of higher hospitalisation costs. For example, in a multivariable regression analysis model adjusted for patient's sociodemographic characteristics and comorbidities, severe malnutrition assessed with the Patient Generated-SGA independently predicted a 27.5% increase in hospital costs [31].

Interventions to improve nutritional status and outcomes

Although several randomised controlled clinical trials (RCT) conducted in persons receiving dialysis have reported that dietetic interventions can improve nutritional markers such as serum albumin, serum prealbumin, nPCR, energy and protein intake, BMI, body weight, TSF, MAC and SGA score [1], few studies have investigated the effectiveness of nutritional interventions in improving clinical outcomes [1, 32, 33]. In a multicentre retrospective study, 3374 HD participants with a serum albumin $\leq$3.5 g/dL who were enrolled in an 8-month pilot program providing oral nutritional supplements (ONS) showed a 69% mortality risk reduction compared to matched controls who were not participating in the ONS program [32]. A 6-month multicentre, open-label RCT conducted in malnourished (serum albumin $\leq$4.0 g/dL and BMI <24 kg/m^2) PD patients observed that the control group (n=37; dietary advice only) showed a significant reduction in PCS of HRQoL, whereas HRQoL scores remained unchanged in the intervention group (n=37; dietary advice + protein powder supplement) [33]. Several non-randomised retrospective studies have also suggested that provision of ONS may improve survival in persons receiving HD [1]. These findings emphasize the importance of conducting further well-designed prospective trials aiming at investigating the impact of interventions to improve malnutrition on clinical outcomes in dialysis populations.

Conclusions

Malnutrition is an unacceptably frequent complication in persons with ESKD receiving dialysis that continues to be associated with substantially increased all-cause, cardiovascular and infection-related mortality, decreased HRQoL, higher rates of hospitalizations and increased healthcare costs. These findings highlight the importance of prevention and early detection of malnutrition. Priority should be given

to prospective trials assessing the impact of preventing and treating malnutrition on both the clinical and economic burden of this common problem in the dialysis population.

Key Points

- Malnutrition is a highly prevalent and major complication in the dialysis population that deserves greater attention.
- Multiple methods to assess nutritional status have been identified as independent predictors of increased mortality in persons receiving dialysis.
- Presence of malnutrition severely affects health-related quality of life and increases hospital admissions and length of hospitalisations in this patient population, which results in higher hospital costs.
- Development of malnutrition and/or worsening of nutritional status is also associated with increased mortality and hospitalisations.
- Further well-designed prospective trials aiming at improving nutritional status and clinical outcomes in dialysis populations are warranted.

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Table 1. Methods of nutritional status assessment in persons receiving dialysis: pros and cons.

Method of assessment	*Strengths*	*Limitations*
Serum albumin	- Independent predictor of higher all-cause and cardiovascular mortality - Association with increased rates of hospitalisation - Easy to measure - High reproducibility - Responds well to dietetic interventions	- Systemic inflammation and metabolic acidosis decrease hepatic albumin synthesis - Hypoalbuminaemia is associated with fluid overload
Serum prealbumin	- Independent determinant of increased mortality - Correlation with several other nutritional markers including energy and protein intake, as well as body fat and muscle mass	Levels are decreased in the presence of systemic inflammation
Serum creatinine	- Surrogate marker of skeletal muscle mass and dietary protein intake - Lower creatinine associated with increased risk of death	- Affected by systemic inflammation - Concentration depends on the level of residual renal function, dialysis dose and endogenous degradation
Body mass index (BMI) and percentage of weight loss over time	- Convenient, inexpensive and easy to calculate as weight, height and time can be automatically transferred to electronic medical records - BMI and unintentional weight loss have been strongly associated with increased mortality risk	- Can be confounded by the presence of fluid overload and lacks the ability to differentiate between muscle and fat mass. - BMI does not distinguish between visceral and peripheral body fat accumulation and its interpretation can be influenced by factors such as age, sex and muscle mass

Anthropometric measurements • Mid-arm circumference • Skinfold thicknesses – body fat percentage • Mid-arm muscle circumference (MAMC)	• Simple and cost-effective for assessing nutritional status and for indirectly estimating total body fat and muscle mass • Association with higher all-cause mortality • MAMC is a surrogate marker of muscle mass	Interpretation of anthropometric assessment might be affected by: • Lack of anthropometric reference standards for the dialysis population • High inter- and intra-observer variability • Variable hydration status
Bioelectrical impedance analysis (BIA)	• Quick, safe, convenient and easy to perform technique that directly measures and, therefore, differentiates between total body water (i.e. extra- and intracellular water), total body fat mass and lean body mass (i.e. muscle mass) • Estimation of phase angle, a measure of nutritional health of muscle cell membranes and total cell integrity, which is associated with poor quality of life and is an independent predictor of malnutrition, muscle weakness, hospitalisation and mortality • Low fat and muscle tissue index are also independent determinants of increased mortality	• Need of expert and trained staff who can manage and interpret data appropriately • Fluid overload influences BIA measurement, leading to inaccurate estimations of muscle and fat mass; however, in order to improve the accuracy of the method, it has been suggested that all BIA measurements should be performed post haemodialysis or with the peritoneum drained of dialysis fluid
Dietary intake • 24-hour dietary recalls • 3 or 7 day-food diaries • Normalised protein catabolic rate (nPCR)	• 24-hour dietary recalls: convenient and quick; involve a face to face or telephone interview conducted by an experienced dietitian who collects precise and comprehensive information regarding food and drink intake during a 24-hour period	• 24-hour dietary recalls rely on interviewee's memory, their cooperation and communication to provide accurate information, their estimation of portion sizes

	• Food diaries: record data for a longer period of time and supplementary relevant diet information can be obtained once the food diary has been recorded and returned to the dietitian • nPCR, a measure of total body nitrogen balance, is a valid and clinically useful method of assessment of dietary protein intake • Low energy and protein intake (<1.0 g/kg/day in HD and <0.73 g/kg/day in PD) estimated by either 24-hour dietary recalls, food diaries or nPCR are associated with increased overall mortality	and their understanding of the questions • Risk of incomplete or inaccurate description of food/drink intake and lack of compliance with the instructions for completing food diaries • nPCR might overestimate or underestimate protein intake under catabolic or anabolic conditions, respectively; nPCR depends on daily protein intake and it can therefore change rapidly from day to day
Handgrip strength (HGS)	• Simple, non-invasive, quick, reliable and validated method of nutritional and functional assessment • Lower in persons with malnutrition and positively associated with serum albumin, serum creatinine and lean body mass as assessed by BIA and anthropometry • Systemic inflammation does not affect HGS • Independent predictor of all-cause mortality and hospitalisation • Association with worse quality of life	• Lack of reference values in the dialysis population • Inconsistency regarding position and time of measurement, as well as choice of arm
7-point scale Subjective Global Assessment (SGA)	• Valid, comprehensive and reliable nutritional scoring tool • Recommended by national and international nutrition guidelines in the dialysis population • Association with several nutritional markers such as serum albumin, BIA-phase angle, MAMC, fat percentage and nPCR	• Accuracy to assess nutritional status relies on the dietitian's experience and training to interpret the data collected

- Independent predictor of increased overall, cardiovascular and infection-related mortality, as well as decreased quality of life
- Independent determinant of frequent hospitalisations, increased length of hospital stay and higher hospital costs