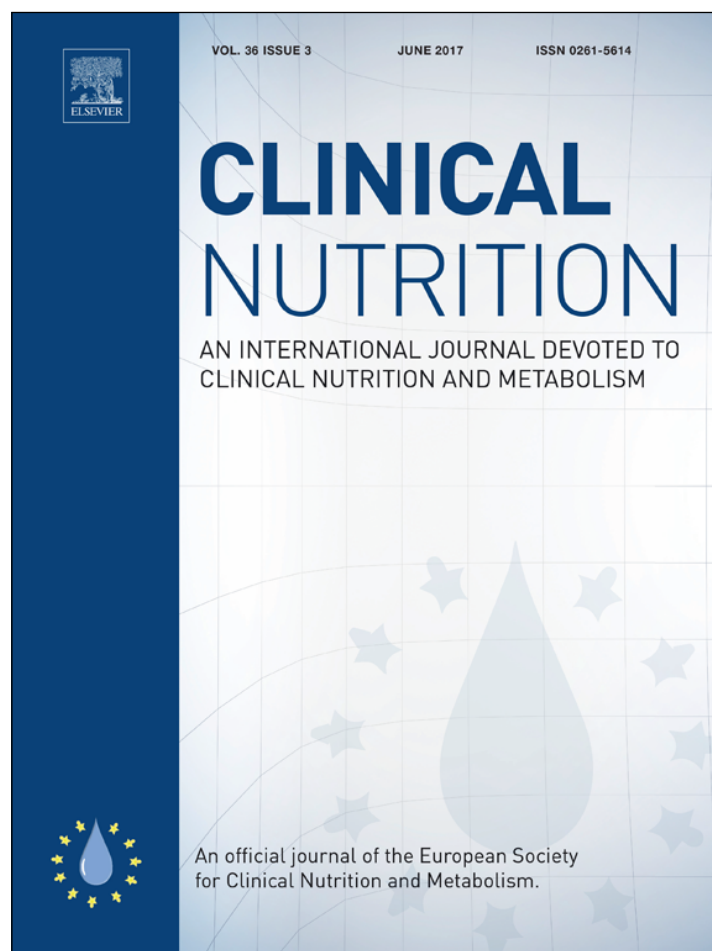


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Review

Protein-energy wasting and nutritional supplementation in patients with end-stage renal disease on hemodialysis

A. Sabatino^a, G. Regolisti^a, T. Karupaiah^b, S. Sahathevan^b, B.K. Sadu Singh^b, B.H. Khor^b, N. Salhab^c, M. Karavetian^d, A. Cupisti^e, E. Fiaccadori^{a,*}^a Acute and Chronic Renal Failure Unit, Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy^b Dietetics Program, Faculty of Health Sciences, National University of Malaysia, Kuala Lumpur, Malaysia^c Department of Nutrition and Translational Research in Metabolism, Maastricht University, Netherlands^d Department of Natural Sciences in Public Health, Zayed University, Dubai, United Arab Emirates^e Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

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SUMMARY

Background & aims: Protein-Energy Wasting (PEW) is the depletion of protein/energy stores observed in the most advanced stages of Chronic Kidney Disease (CKD). PEW is highly prevalent among patients on chronic dialysis, and is associated with adverse clinical outcomes, high morbidity/mortality rates and increased healthcare costs. This narrative review was aimed at exploring the pathophysiology of PEW in end-stage renal disease (ESRD) on hemodialysis. The main aspects of nutritional status evaluation, intervention and monitoring in this clinical setting were described, as well as the current approaches for the prevention and treatment of ESRD-related PEW.

Methods: An exhaustive literature search was performed, in order to identify the relevant studies describing the epidemiology, pathogenesis, nutritional intervention and outcome of PEW in ESRD on hemodialysis.

Results and conclusion: The pathogenesis of PEW is multifactorial. Loss of appetite, reduced intake of nutrients and altered lean body mass anabolism/catabolism play a key role. Nutritional approach to PEW should be based on a careful and periodic assessment of nutritional status and on timely dietary counseling. When protein and energy intakes are reduced, nutritional supplementation by means of specific oral formulations administered during the hemodialysis session may be the first-step intervention, and represents a valid nutritional approach to PEW prevention and treatment since it is easy, effective and safe. Omega-3 fatty acids and fibers, now included in commercially available preparations for renal patients, could lend relevant added value to macronutrient supplementation. When oral supplementation fails, intradialytic parenteral nutrition can be implemented in selected patients.

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1. Introduction

In patients with Chronic Kidney Disease (CKD), especially in those with End-Stage Renal Disease (ESRD, or CKD stage 5), a progressive depletion of protein and/or energy stores is often observed [1]. The term “Protein-Energy Wasting” (PEW) has been suggested to describe this clinical condition, which has high prevalence rates (up to 50–75% of patients with CKD stages IV–V), and

is closely associated with both increased morbidity/mortality risk and worsened quality of life [1]. Inflammation often co-exists and, together with muscle wasting, confers a specific pattern to CKD-related PEW, which distinguishes this clinical entity in respect to other forms of malnutrition [1–3].

In ESRD two important issues must be addressed to implement tailored nutritional interventions against PEW, namely: 1) a thorough understanding of the pathogenesis and 2) a timely diagnosis and a close monitoring of nutritional status [1–3]. Hence, in this narrative review we aimed firstly at exploring the pathophysiology of PEW in ESRD on hemodialysis. Subsequently, we describe the main aspects of nutritional status evaluation, intervention and monitoring in this clinical setting. Finally, we discuss the current

* Corresponding author. Unità di Fisiopatologia dell'Insufficienza Renale Acuta e Cronica, Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Parma, Via Gramsci 14, 43100, Parma, Italy.

E-mail address: enrico.fiaccadori@unipr.it (E. Fiaccadori).

approaches reported in literature, consensus and guidelines for the prevention and treatment of ESRD-related PEW.

2. Methods

An exhaustive review of English language literature was performed to identify all relevant articles describing the epidemiology, pathogenesis, nutritional intervention and outcome of PEW in ESRD on hemodialysis. To this purpose, we searched, PubMed, EMBASE™, CINHAL, Web of Science and Cochrane databases for relevant articles. Related search terms were used as follow: “anthropometry”, “chronic kidney disease”, “dietary fiber”, “end stage renal disease”, “exercise”, “guidelines”, “hemodialysis”, “inflammation”, “intestinal microbiota”, “intradialytic parenteral nutrition”, “intradialytic supplementation”, “malnutrition”, “nutritional status evaluation”, “omega-3 fatty acids”, “oral supplementation”, “physical activity”, “protein energy wasting”. Medical subject heading terms were used to enhance electronic searches. Additional studies of interest were identified by hand searches of bibliographies. Studies that involved patients <18 years of age, case reports, or conference proceedings were excluded. The search was last updated on March 28, 2016.

3. Pathophysiology of PEW in ESRD on hemodialysis

In renal patients, PEW is characterized by loss of protein and energy stores associated with multiple metabolic derangements, most of which are peculiar of CKD [1–3]. Several metabolic and clinical factors (Table 1) may negatively affect nutritional status and lean body mass [3,4], leading to frailty [5]. Apart from an inadequate spontaneous nutrient intake, several other factors such as metabolic acidosis, insulin resistance, chronic inflammation, intestinal dysbiosis, infection and oxidative stress are also contributive to PEW development. In addition, factors related to CKD/ESRD treatment, for example inappropriate dietary restrictions or hemodialysis procedures, may play a role [2–4]. The overall effect is

the persistence of a vicious cycle between PEW and its complications [4] (Fig. 1).

In CKD patients, inadequate nutritional intake is quite frequent and caused by taste abnormalities, loss of appetite (anorexia), uremic toxin accumulation, dysregulation of gastrointestinal homeostatic mechanisms, altered blood concentration of appetite regulators and deranged hypothalamic output (Fig. 1). The presence of frailty, poverty, advanced age and multiple acute or chronic comorbidities (diabetes, metabolic syndrome, cardiac failure, fluid overload, liver disease, infection, GI tract disturbances, etc) may also contribute to suboptimal nutrient intake in ESRD [1–4].

Moreover, most patients undergoing maintenance hemodialysis have a history of long-term dietary restrictions of several nutrients (protein, phosphorus, sodium and potassium) aimed at preventing and correcting a number of metabolic complications, also delaying the progression of the syndrome [6]. When patients are started on hemodialysis, protein requirements increase over those typical for CKD patients on conservative management with controlled protein intake (the so called “low protein diet”), whereas phosphate, sodium and potassium restrictions are still recommended, along with adequate energy intake. Thus, these patients need a careful dietary counseling to redefine specific dietary targets aimed at preventing PEW [6].

Metabolic acidosis, a common finding in the most advanced stages of CKD, is associated with increased mortality risk [7], and also plays an important role in the pathogenesis of nutritional derangements. In fact, insulin-dependent intracellular signaling is blunted, and both protein degradation and branched chain amino acid oxidation are increased, these effects being reversed by bicarbonate administration [8,9].

The presence of chronic inflammation may contribute both to an increase in nutritional needs and to anorexia through an imbalance between the orexigenic/anorexigenic mechanisms that control the energetic homeostasis of renal patients [3,4]. Evidence exists that alterations of intestinal microbiota, as well as increased permeability of the intestinal barrier, may play a pivotal role in the pathogenesis of the chronic inflammatory status of ESRD (Table 2)

Table 1
Causes and mechanisms of PEW in CKD/ESRD patients.

1. Reduced protein and energy intake	<ul style="list-style-type: none"> a. Anorexia: <ul style="list-style-type: none"> i. Dysregulation of appetite mediators ii. Amino acid stimuli in the hypothalamus iii. uremic toxins b. Inappropriate dietary restrictions c. Gastrointestinal diseases d. Depression e. Difficulties in food preparation f. Socio-economic difficulties
2. Hypercatabolism	<ul style="list-style-type: none"> a. Increase in energy expenditure: <ul style="list-style-type: none"> i. chronic inflammation ii. Increase in pro-inflammatory cytokines iii. Altered metabolism of adiponectin and resistin b. Hormonal changes: <ul style="list-style-type: none"> i. insulin resistance ii Increased glucocorticoid activity
3. Metabolic acidosis	Increased protein breakdown, increased BCAA oxidation, insulin and IGF-1 resistance
4. Reduced physical activity	Reduced muscle trophism, reduced self-sufficiency, reduced performance
5. Reduced anabolism	<ul style="list-style-type: none"> a Reduced uptake of nutrients b. Resistance to insulin, GH/IGF-1 c. Testosterone deficiency d. Reduced levels of thyroid hormones
6. Comorbidities and life style	<ul style="list-style-type: none"> a. Comorbidities (diabetes, heart failure, ischemic heart disease, peripheral vascular disease) b. Sedentary lifestyle
7. Dialytic treatment	<ul style="list-style-type: none"> a. Loss of amino acids and proteins in the dialysate b. Inflammatory processes related to dialysis c. Hypermetabolism related to dialysis d. Loss of residual renal function

CKD, chronic kidney disease; ESRD, end stage renal disease; GH, growth hormone; IGF, insulin-like growth factor.

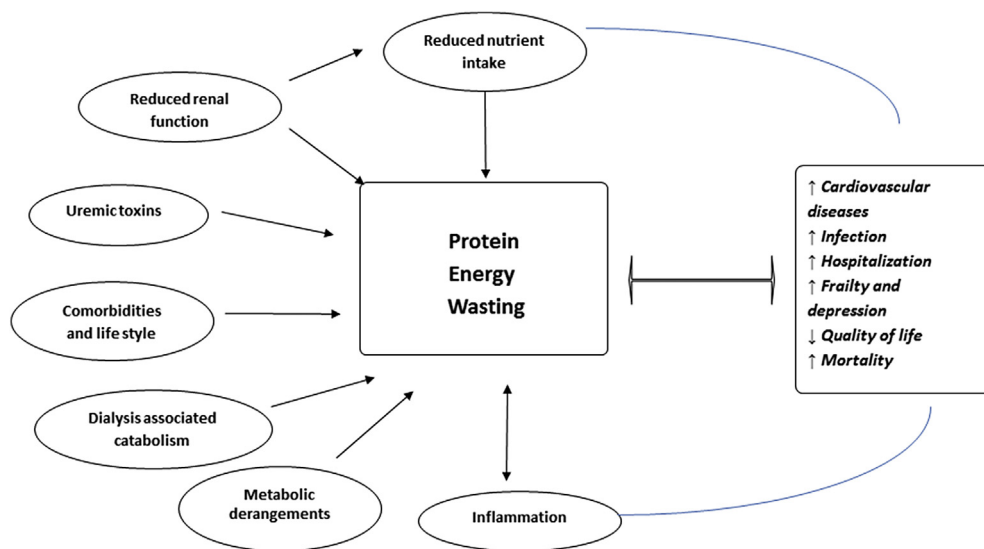


Fig. 1. Causes and consequences of Protein-Energy Wasting (PEW) in CKD/ESRD.

[10–12]. The intestinal microbiota is the set of symbiotic organisms (over 100 trillion) normally present in the gut, which influences nutrition, metabolism, physiology and immune function of the host [10–12]. Depending on their preferential metabolic pathways, intestinal bacteria can be distinguished into saccharolytic (preferential fermentation of carbohydrates) or proteolytic (preferential fermentation of proteins) species. In healthy subjects, saccharolytic species such as *Bifidobacterium* and *Lactobacillus* usually predominate. They hydrolyze complex polysaccharides into monomeric sugars, and then into short chain fatty acids such as acetate, propionate, and butyrate [10,11]. The latter are the specific fuel for the epithelial cells of the gut, and have both trophic effect on the colonic epithelium and positive immunomodulatory actions [10–12]. On the other hand, proteolytic bacterial species (for example *Clostridium* and *Bacteroides* species) produce potentially toxic substances (such as ammonium, thiols, phenols and indoles). In normal subjects, the kidney easily excretes these “uremic toxins” after intestinal absorption, but in renal failure they are retained [10–12]. Nutrient availability, in particular the ratio between carbohydrate and nitrogen substrates, is the most important regulator of bacterial metabolism, since it modulates the degree of saccharolytic vs proteolytic fermentation. The main sources of carbohydrates available in the colon are dietary fibers, while nitrogen is derived from food proteins, endogenous proteins and urea [10–12].

The peculiar “milieu interieur” of CKD may dysregulate the gastrointestinal structure and function, as well as the gut

microbiota, leading to a condition defined “intestinal dysbiosis” [10,11]. Firstly, accumulating urea within the intestinal tract is hydrolyzed by microbial urease to form large quantities of ammonia, which is also converted to ammonium hydroxide. These byproducts have been noted to disrupt the integrity of the gut epithelial barrier, thereby increasing gut permeability and promoting translocation of toxins, live bacteria and/or their structural components (e.g. lipopolysaccharide) from the gut into circulation [10]. Uremic toxins also impair the gut microbiome milieu, which shifts towards the growth of bacterial strains with urease, uricase and indole and p-cresol-forming enzymes [11]. Fermentation of the amino acids tyrosine and tryptophan by intestinal microbiota generates p-cresol and indole, respectively which are further metabolized to generate p-cresyl sulfate and indoxyl sulfate [10,11] (Fig. 2) (Table 3).

4. Assessment of nutritional status in CKD/ESRD on hemodialysis

The available recommendations for the assessment of nutritional status in CKD/ESRD patients are toward an integrated approach combining the evaluation of body mass and anthropometric parameters, and biochemistry and dietary intake assessment [1,2,13,14]. The International Society of Renal Nutrition and Metabolism (ISRNM) recommends that the diagnosis of PEW be established by the presence of at least one criterion in three out of four categories of nutritional variables [1] (Table 4).

Table 2
Factors contributing to chronic inflammation in ESRD.

Factors	Mechanism
Decreased renal function	Decreased clearance of cytokines Accumulation of uremic toxins
Dialysis-related factors	Bio-incompatibility of membranes Backfiltration/Endotoxins Intradialytic protein catabolism Vascular access
Co-morbidities	Chronic infections Diabetes mellitus Atherosclerosis Congestive heart failure
Intestinal dysbiosis	Increased production of uremic toxins by proteolytic bacteria Disruption/increased permeability of the intestinal barrier

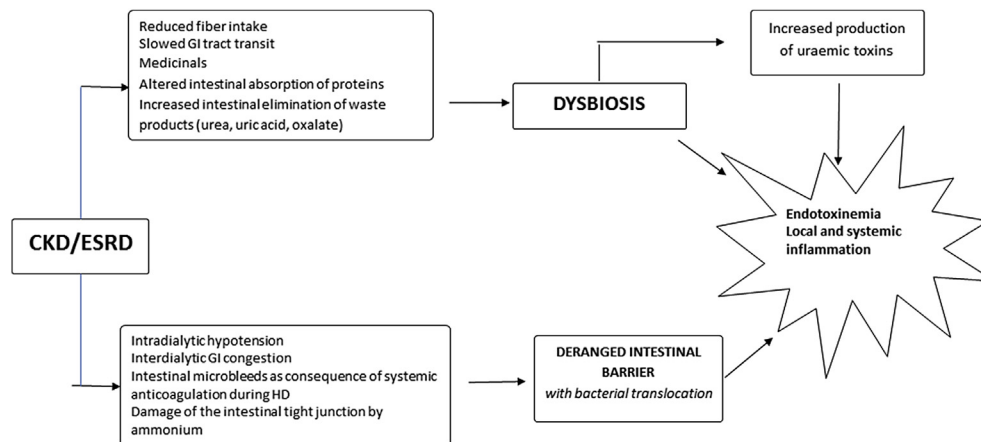


Fig. 2. Intestinal microbiota in CKD/ESRD. CKD/ESRD, chronic kidney disease/end stage renal disease; GI gastrointestinal; HD, hemodialysis.

Table 3
Effects of CKD/ESRD on the intestinal tract.

Effects	Mechanism
1. Reduced intake of dietary fibers	Prescribed potassium restrictions leads to a reduced consume of fruits and vegetables
2. Prolonged colonic transit times (constipation)	Multifactorial: dialysis modality, lifestyle, inactivity, phosphate binders, dietary restrictions, low fluid intake, primary renal disease and comorbidities (diabetes, heart failure, malnutrition, cerebrovascular disease)
3. Increased amounts of protein available for proteolytic bacterial species	Protein assimilation is impaired in uremia. The reduced ratio between carbohydrate and nitrogen available in the colon increase the proliferation of proteolytic species with generation of toxic end-products such as phenols and indoles
4. Changes on the colonic microbiota	Luminal pH changes due to increased blood ammonia concentrations. Drugs therapy (antibiotics, phosphate binders, antimetabolites etc.)
5. Preferential growth of pathogenic bacteria	Use of antibiotics and oral iron supplementation.
6. Loss of the intestinal epithelial barrier function of the intestine	Depletion of the intestinal epithelial tight junction proteins caused by uremia, hemodialysis complications (hypotension, intestinal edema and ischemia), micro-bleeding caused by the systemic coagulation alterations typical of uremia

Generally, indicators of PEW correlate with increased mortality, decreased appetite and low protein intake [1,3]. The following discussion is directed to highlighting key points that should be considered in the choice of criteria to identify PEW in a CKD/ESRD patient, along with their limitations.

a) Biochemical markers

Amongst the biochemical markers available for the diagnosis of PEW in CKD/ESRD patients, low serum albumin is a strong predictor of mortality [2,14]. However, it cannot be regarded exclusively as a marker of nutritional status, as it is largely influenced by non-nutritional factors (e.g., inflammation), hydration status and changes in synthesis, degradation, and body distribution of this protein [1,13,14]. Other useful nutritional markers are prealbumin and cholesterol serum levels [2,13,14].

b) Body mass index

The body mass index [BMI = weight (kg)/height² (m²)] is the most commonly used parameter for nutritional assessment

[1–3]. Body mass index cannot distinguish muscle from fat mass, and is affected by hydration status. Nevertheless, BMI values <25 kg/m² predict poor outcome in patients undergoing chronic hemodialysis, as they are closely associated with increased mortality risk [1–3]. The ISRNM has suggested that the lower threshold for BMI values should be increased to 23 kg/m² [1], which is considerably higher than that recommended by the World Health Organization (18.5 kg/m²) for the general population.

In general, as part of the dietary history, any recent unintentional weight loss, appetite change, gastrointestinal symptom and the presence of chewing or swallowing problems should be carefully investigated. Dynamics of weight loss are of outstanding importance: unintentional weight loss (>5% in 3–6 months) and/or a reduction of any degree in the body weight over a short period of time strongly suggests a high risk for PEW [1–3]. Therefore, physical examination and close monitoring by nephrologists and dieticians, specifically aimed at identifying nutritional deficits, would become an important component of nutritional status assessment.

Table 4
Criteria for the diagnosis of PEW [1].

a) Reduced levels of biochemical markers of nutritional status such as prealbumin, albumin (<3.8 g/dl) and cholesterol
b) Reduced body mass: BMI < 23 kg/m ² or unintentional weight loss of >5% in 3 months or 10% in 6 months, reduced fat mass < 10%;
c) Reduced muscle mass: reduction of muscle mass by 5% in 3 months or 10% in 6 months reduced arm muscle area by 10% as compared to the 50 th percentile of the reference population;
d) Inadequate nutritional intake: spontaneous intake of protein and calories of <0.8 g/kg/day and <25 kcal/kg/day respectively for at least 2 months

PEW can be diagnosed when at least one criterion in three out of four categories is present.

c) Muscle mass

Loss of muscle mass has been proposed as a useful parameter for nutritional assessment, as it may help to discriminate between PEW and non-PEW patients [1]. The assessment of skeletal muscle mass (the main component of lean body mass, LBM) may provide the most reliable information for PEW diagnosis and monitoring [1]. Currently available gold standard imaging methods such as computed tomography (CT) scan, magnetic resonance imaging (MRI) or dual energy X-ray absorptiometry (DEXA) are expensive and/or not suitable for serial routine use. Anthropometric or biochemical methods have poor accuracy and produce scarcely reproducible data for quantitative assessment [15]. Anthropometry mainly consists in triceps skinfold thickness and arm circumference measurements, whilst biochemical methods for muscle mass evaluation are based on serum creatinine and creatinine kinetics [16]. Creatinine is a breakdown product from normal muscle metabolism and its production is dependent on muscle mass and consumption of foods high in creatine or creatinine. For the principle of creatinine kinetics in the steady state, creatinine production is equal to the sum of creatinine excretion and metabolic degradation. Creatinine production is, in turn, proportional to the lean body mass of the patient [16]. Therefore, a relatively low level of pre-hemodialysis serum creatinine may reflect decreased skeletal muscle mass or poor dietary protein intake.

Bioelectrical impedance analysis (BIA) is a bedside technique that exploits the different electrical properties of tissues and body fluids during the application of an alternating low intensity electric current; the values of resistance and reactance allow an estimation of total body water and total body cell mass, particularly useful when serial measurements are performed [17]. The applied current may be single frequency or multi-frequency, and in both cases it is possible to gain information about body composition. Diagnostic accuracy for estimating total body water is similar between the two BIA methods, whereas conflicting results have been obtained with regard to the extracellular water quantification [18]. In fact, multi-frequency BIA was shown to track effectively a decrease in lean body mass and an increase in fat mass in the first 2 years from hemodialysis initiation, and BIA parameters were significantly correlated with mortality in patients with ESRD [19].

Hand grip strength (HGS) muscle test has also been proposed as an easy and non-invasive method for the evaluation of nutritional/functional status [20,21]. Basically, HGS measures the upper body muscle strength, and has a good correlation with 'gold standard' lean body mass measurements such as DEXA [20]. However, studies reporting on the use of HGS to assess presence of PEW in dialysis population are limited [20].

d) Assessment of nutritional intake

Assessment of dietary history and appetite is critical to evaluate the adequacy of nutrient intake. As a matter of fact, anorexia and reduced intake of protein (<0.8 g/kg/day) and/or calories (<25 kcal/kg/day) are closely associated with increased risk of PEW [1–3,21]. The application of tools for periodic appetite assessment and food diaries also allows early intervention when the dietary intake of protein and energy is significantly lower than recommended (<1.0 g/kg/day and <30 kcal/kg/day, respectively) [1–3,13,14]. Dietary intake studies on ESRD patients on hemodialysis indicated that the average reported calorie intake is 22.7–29.8 kcal/kg/day [22], and that underreporting is frequent [23]. On the other hand, calculation of the protein catabolic rate is a useful method for quantifying the protein intake accurately, provided that patients are clinically and metabolically stable [13,14]. Protein catabolic rate can be calculated based on a 24-h urinary collection in CKD on

conservative nutritional treatment, or by urea kinetic methods in ESRD patients on hemodialysis [2,13,14]. A regular assessment of nutritional status should be performed at least every 6 months in patients who are well nourished and under 50 years of age, but more frequently in patients at high risk for PEW.

e) Multidimensional scoring tools for nutritional status assessment in ESRD on hemodialysis

The Subjective Global Assessment (SGA) is a simple nutritional scoring tool deemed as appropriate for the assessment of nutritional status in CKD/ESRD [2,13,14]. The original SGA only included medical history and physical examination as components for assessment. The Malnutrition Inflammation Score (MIS), which is a modification of SGA, was specifically proposed for patients on hemodialysis [25], and converts the SGA to a semi-quantitative score by adding laboratory parameters (serum albumin and total iron binding capacity) and BMI. In ESRD patients on hemodialysis, higher MIS scores are associated with increased morbidity and mortality [24].

5. Nutritional approach to PEW in ESRD on hemodialysis

a) Targets for nutritional support in ESRD on hemodialysis

Current guidelines and expert consensus recommend at least 1.1 g of protein/kg of ideal body weight per day for stable hemodialysis patients [1,2,13,14]. Higher protein intakes are suggested compared to the minimum recommended for the healthy population (0.8/kg/day), since hemodialysis may lead to protein and amino acid losses. An energy intake of 35 kcal/kg ideal body weight per day, adjusting for age and the level of physical activity is usually indicated [1,2,13,14], even though dietary energy requirements, when measured, could be lower [25]. Literature data suggest that the average protein consumption in ESRD patients is usually low (less than 1.0 g/kg/day in ~50% of subjects) and is associated with reduced energy intake [27]. Thus, nutritional intervention should start early, when spontaneous energy intake is <30 kcal/kg/day and protein intake <1.0 g/kg/day [1,2,13,14].

The treatment of conditions known to increase catabolism is of primary importance to prevent the development of PEW in patients with CKD/ESRD on hemodialysis [1]. Figure 3 illustrates a proposed algorithm for nutritional intervention.

b) Nutritional counseling

An early and regular dietary counseling still represents a relevant component aimed at preventing and treating PEW in ESRD. The beginning of hemodialysis requires a thorough change in the information given to the patient, aimed at increasing dietary protein intake as compared with previous restricted regimens [2,6]. On these grounds, an early and individualized intervention by the healthcare team is needed to prevent erroneous eating habits that could lead to PEW [27]. Therefore, the aims of nutritional counseling in ESRD patients on dialysis are as follows:

- 1) Providing correct dietary information, tailored according to the dialysis modality;
- 2) Re-assessing patients' eating habits;
- 3) Identifying any deficiency in energy and protein intake;
- 4) Helping patients at high nutritional risk (with energy and protein intakes <30 kcal/kg/day and <1.0 g/kg/day respectively) to increase their food intake;
- 5) Providing information to avoid excess of phosphate, potassium or sodium intake

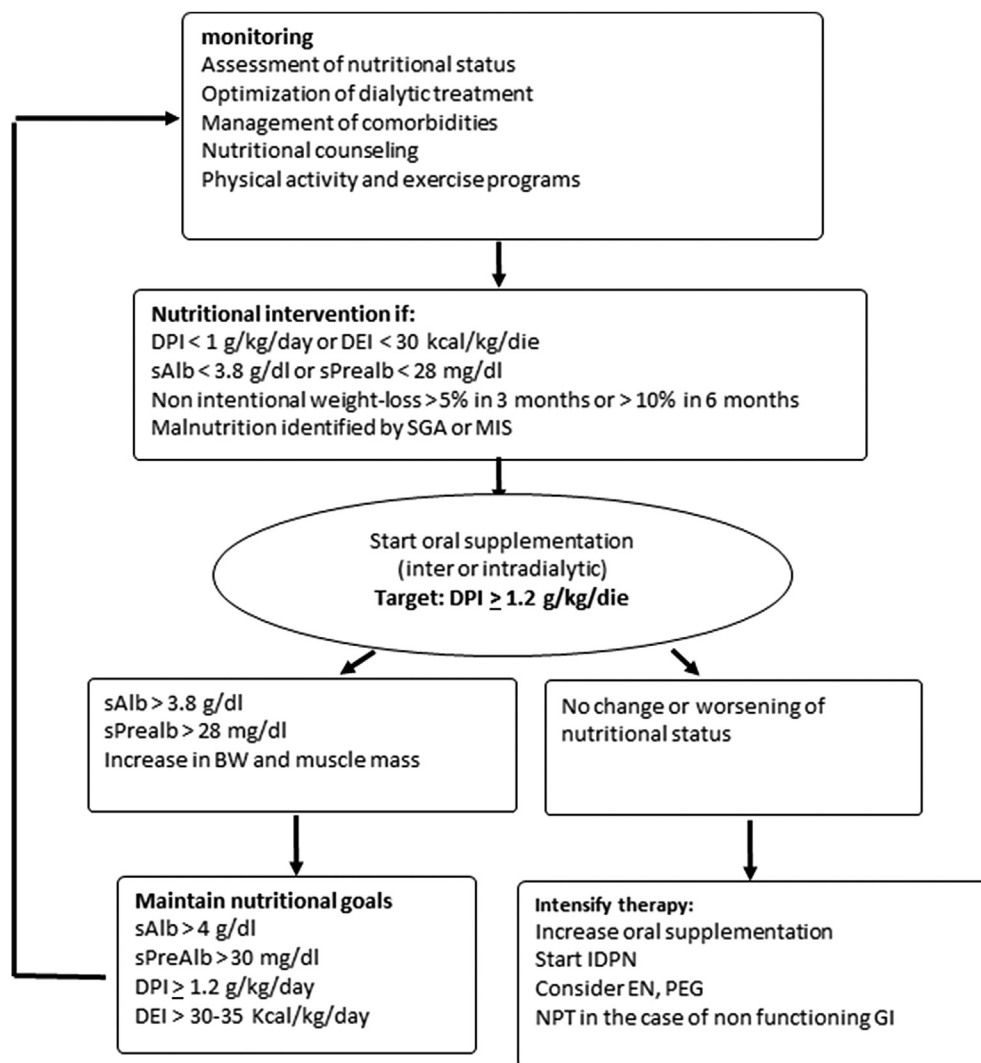


Fig. 3. Algorithm for nutritional support in PEW.

6) Avoiding periods of unnecessary fasting (interference with meals because of dialysis schedule, dietary inadequacy during acute illness and hospitalization, etc).

Special attention is to be reserved to phosphorus intake, that includes total consumption from both organic and inorganic food sources. Organic phosphate is abundantly available in animal and vegetarian proteins, while inorganic phosphate is mainly found in processed food, since it is used as preservative. Due to the linear relationship between protein and phosphorus content of a mixed diet, the recommendation of a high protein diet is unfortunately linked to a high phosphorus diet. Animal-based phosphorus is more readily absorbed (around 60%) by the human gastrointestinal tract compared to plant phosphorus (20–40%), because humans lack of phytase [27]. In contrast, inorganic phosphorus found in processed foods such as cheese and carbonated beverages is almost completely absorbed by the gut. Phosphate to protein ratio can be used to guide patients in food choices to ensure phosphate restriction does not compromise protein intake. Furthermore, the nutritional counseling of patients on hemodialysis should favor an increased protein intake of plant origin, avoiding processed foods [28].

c) Oral nutritional support

When dietary counseling is not sufficient to achieve the planned nutritional requirements, oral nutritional supplementation (ONS) is recommended as the first step of nutritional support for ESRD patients [2,13,14]. ONS can add up to 10 kcal/kg and 0.3–0.4 g of protein/kg daily over the spontaneous intake, favoring the achievement of nutritional targets. Intradialytic intake of protein-rich food or oral supplements (snacks or light meals) appears to be effective in mitigating the catabolism associated with hemodialysis procedure and in increasing total protein intake. Many of the feared negative effects related to intradialytic feeding (hypotension, gastrointestinal symptoms, reduced dialysis efficiency, risk of aspiration and risk of contamination) are not commonly observed, and can be avoided by careful selection of patients based on the evaluation of the clinical condition and individual characteristics [26]. Intradialytic hypotension, due to splanchnic vasodilation during and after the ingestion of ONS is quite infrequent in clinically stable patients without risk factors [26].

An alternative to intradialytic meals is represented by the provision of specific, commercially available oral formulations. In a recent observational study that enrolled patients on hemodialysis

with low serum albumin, intradialytic oral supplementation led to a greater intake of protein, calories and improved survival rates [29]. Renal specific supplements have high energy density (1.8–2 kcal/ml), thus reducing the risk of fluid overload (Table 5).

In addition to positive effects on nutritional status, serum albumin, inflammation, physical functioning, mortality and hospitalization rates [29–31], metabolic studies have shown that oral protein intake during a dialysis session antagonizes catabolism induced by hemodialysis *per se*, with a positive effect that is prolonged even in the subsequent hours [32].

When oral supplementation is used for treating PEW, selection of ONS is as important as the patient's compliance towards a specific product, as both factors will determine the success of this approach. Therefore, one should consider carefully the acceptability of such products in terms of appearance, smell and taste before prescribing it. ONS products with different flavors and type of preparation (energy or protein bars that are low in potassium and phosphorus, protein powders that can be added into puddings, fruit juice or shake) may further increase compliance towards supplementation, as they hinder taste fatigue and product monotony throughout the period of supplementation. In addition, frequent interaction with the dietician during the supplementation period may further increase patients' adherence and effectiveness.

d) Intradialytic Parenteral Nutrition

Intradialytic parenteral nutrition (IDPN) has been suggested by the ISRN as an intensive treatment option to address PEW [1]. In IDPN a mixture of amino acids, glucose and lipid emulsions is administered through the extracorporeal circulation during each dialysis session. Thus, by definition, IDPN suffers from a major time-limitation, due to hemodialysis frequency and duration (usually 4 h thrice weekly). It is suggested that a safe IDPN in each hemodialysis session should involve the administration of not more than 1 L of fluids, 1000 kcal and 50 g of amino acids in a 75 kg patient [33]. Therefore, the potential of IDPN to cope with protein and energy targets in patients on hemodialysis mainly depends on the actual difference between these targets and the spontaneous intakes. It has been calculated that the maximum intake of nutrients obtained with IDPN is about 3000 kcal and 150 g of amino acids, i.e., 5 kcal/kg/day and 0.25 g/kg/day of amino acids in a 70 kg patient. In as much as this accounts for not more than 25% of the ideal daily nutrient intake, IDPN is recommended only for patients with spontaneous intakes of at least 20 kcal/kg/day and 0.8–0.9 g/kg/day of proteins [13,33]. In some patients, electrolyte-free all-in-one admixtures (i.e. with no sodium, potassium, and phosphorus) could be more indicated.

IDPN cannot be considered as a long-term nutritional approach. Thus, it should be discontinued and the resumption of oral supplementation should be attempted as soon as improvements are

observed. Improvements in nutritional status parameters during IDPN should be evaluated after at least 3–6 months of treatment [34]. Discontinuing IDPN is based on a combination of three of the following criteria: stable serum albumin >3.8 mg/dl for 3 months, improvement in SGA score to A (well-nourished) or B (moderately malnourished), clinical examination of improved nutritional status, increase in protein and energy oral intake to >1.0 g/kg/day and to >30 kcal/kg/day, complications or intolerance related to IDPN [33]. If the combination of oral feeding or EN with IDPN does not achieve the nutritional needs of the patient, or if the gastrointestinal tract is not functioning, then total parenteral nutrition (TPN) should be considered.

Available data on the effects of IDPN on hard outcomes are scarce and conflicting. In fact, while there is convincing evidence about IDPN safety and its positive effects on metabolic parameters, nitrogen balance and nutritional status of patients with ESRD on hemodialysis, the data on the relationship between IDPN and decreased need for hospitalization and mortality are still inconclusive [2,6,33–35].

Some practical aspects regarding IDPN safety should be taken into account (Table 6). Although clinically significant increases in serum triglycerides (TG) have not been demonstrated during IDPN [33], it is not recommended that IDPN be started when baseline TG levels are greater than 300 mg/dl (about 3 mmol/L), or that nutrient administration be continued when TG are greater than 400 mg/dl (about 4 mmol/L). Serum glucose goals during hemodialysis should be maintained between 110 and 180 mg/dL. In the case of insulin need, the use of subcutaneous short acting insulin analogs should be preferred to avoid post-dialytic hypoglycemia. The ultrafiltration rate must be adjusted to remove the extra fluid provided by IDPN [33].

e) Enteral nutrition (EN) and total parenteral nutrition (TPN)

In patients with severe PEW, spontaneous intakes less than 20 kcal/day, stress conditions and/or in case of major swallowing difficulties, both ONS and IDPN are generally unable to provide satisfactory nutritional provision and are therefore not recommended. Complete daily nutritional support is necessary, and enteral nutrition (EN) should be always preferred to parenteral nutrition [13], when possible.

Enteral nutrition is less expensive as compared with PN, has a low rate of metabolic or septic complications and exerts trophic effects on the gastrointestinal tract. It can be delivered via nasogastric or naso-jejunal tubes (the latter in patients with gastroparesis and unresponsive to prokinetic agents), or via percutaneous-endoscopic gastrostomy (PEG) [14]. When EN is contraindicated due to severe dysfunction of the gastrointestinal tract (peritonitis, ischemia, and intestinal obstruction), the only chance is TPN [13].

Table 5

Comparison between average macro- and micronutrient content of standard enteral nutritional supplements vs nutritional supplements specific for dialysis patients.

	Standard supplements	Renal supplements
Energy (kcal/ml)	1	1.8–2
Protein (g/100 ml)	4	7.5–8.0 ^a
Carbohydrates (g/100 ml)	12.3	15–20
Lipids (g/100 ml)	3.9	10
Omega-3	Yes	Yes
Fiber (g/100 ml)	No	Yes
K (mg/100 ml)	150	106
Na (mg/100 ml)	100	70
P (mg/100 ml)	72	72

^a 3.0–4.0 g/100 ml in the case of supplements for CKD patients on low-protein nutritional therapy.

6. Special nutrients for nutritional supplementation in ESRD

a) Fiber: Despite growing evidence on the favorable effects of dietary fiber intake in CKD/ESRD patients, the optimal amount of fiber intake for this population is not yet defined [36]. However, according to the NHANES III data, the CKD population has a lower fiber intake than that recommended for the healthy population (15.4 g/day versus 25–30 g/day respectively) [37]. Dietary fiber supplementation may reduce plasma levels of some protein-bound uremic toxins typically derived from the gut, such as indoxyl-sulfate and *p*-cresyl-sulfate, that have been linked to poor outcomes in CKD/ESRD patients [10–12]. However, it remains to be fully clarified if the effect of fibers on

Table 6
Practical aspects of IDPN [33].

Formula	Use the most concentrated all-in-one total admixtures for parenteral nutrition Use the electrolytes- free formulas in case of severe hyperkalemia (>6 mmol/l) and hyperphosphatemia (>5.5 mg/dl)
Metabolic parameters	Do not start IDPN with lipids If triglycerides levels >300 mg/dl Serum glucose should be maintained between 110 and 180 mg/dl. Use subcutaneous insulin administered as rapid action analogs 15 min after the start of dialysis (0.1 UI/kg as first step) if necessary.
Administration	Infuse IDPN in the venous drip chamber by a parenteral pump Wait to start IDPN until dialysis machine pressure and patient parameters are stable (nearly 15 min after the beginning of dialysis) Increase IDPN volume weekly for the first 3 weeks to achieve regimen rates
Dialysis procedures	Adjust the ultrafiltration rate as per patient need to remove IDPN fluids
Nutrient intake	Calculate the maximum macronutrient amount given by IDPN per dialysis (4 h) as energy 15 kcal/kg/dialysis and amino acids: 0.8–1 g/kg/dialysis

uremic toxins really translates into clinical advantages on hard outcomes, particularly on mortality [37].

A recent systematic review and meta-analysis on the effects of fiber supplementation on standard clinical markers of uremia (blood urea nitrogen and serum creatinine) has shown that dietary fiber supplementation may reduce serum concentrations of urea and creatinine [36], highlighting the potential benefits of increasing fiber intake in this population. Considering the available data, it is recommended that CKD/ESRD patients achieve dietary fiber intakes as high as those recommended for the healthy population (25 g/day). Regarding the feasibility of increasing dietary fiber intake in this clinical setting, a possible risk is an increased potassium intake and hyperkalemia. However, timely counseling by renal dieticians and nephrologists would guide patients to increase fiber intake by choosing low potassium fruits and vegetables.

b) Omega-3 fatty acids: Omega-3 polyunsaturated fatty acids (ω -3 PUFAs) are essential fatty acids known for their protective role against cardiovascular diseases and anti-inflammatory effects [38,39].

Recent studies in healthy elderly patients suggest that ω -3 PUFAs stimulate muscle protein synthesis, counteracting the anabolic resistance and sarcopenia [40]. Patients on maintenance hemodialysis have lower levels of serum ω -3 PUFAs and a reduced intake of fish in comparison to the general population [39]. Few data are currently available regarding the effects of ω -3 PUFAs on nutritional status in CKD/ESRD. In 110 hemodialysis patients the SGA score and other metabolic parameters improved after 12 weeks of ω -3 PUFAs and ω -3 PUFAs + vitamin E supplementation [41]. Similarly, a 4-month administration of ω -3 PUFAs to ESRD patients on hemodialysis improved some inflammatory markers such as IL-6, TNF- α , C-reactive protein and IL-10, with no effect on markers of nutritional status as albumin, prealbumin, transferrin, body weight [42]. In a recent meta-analysis on fish oil supplementation in hemodialysis, C-reactive protein was the only inflammatory marker significantly reduced [43]. Randomized clinical trials are needed to confirm the putative positive effects of ω -3 PUFAs supplementation on nutritional and inflammatory status of CKD/ESRD patients.

7. The influence of life-style: physical activity and exercise

Physical functioning (defined as the ability to perform activities of daily living) and exercise capacity are seriously reduced in patients with CKD, particularly in patients with ESRD on hemodialysis, when compared to healthy individuals [44–46]. A sedentary lifestyle is considered a modifiable risk factor for the development of PEW among ESRD patients and, apart from the consequent skeletal muscle hypotrophy and loss of strength, it may cause further increase in the cardiovascular risk [45,46]. Increase of

physical activity and exercise is able to reduce symptoms of depression, increasing feeling of well-being, appetite and energy supply [46]. When performed during the hemodialysis session in association with oral or parenteral nutrition, exercise may increase amino acid and protein uptake by muscle, attenuating dialysis-associated catabolism [47]. A customized exercise program based on patient's capabilities represents a therapeutic intervention that, along with the nutritional intervention, may blunt muscle loss in patients with ESRD, also enhancing the anabolic effects of nutritional supplementation [46]. However, few data are currently available to support possible direct positive effects of exercise on muscle mass or function and mortality.

8. Hemodialysis related factors

An adequate hemodialysis dose delivery is needed to preserve nutritional status of ESRD patients. However, the increase of hemodialysis frequency to daily treatments is not associated with any further improvement in nutritional status [1]. As a matter of fact, daily hemodialysis was able to reduce the extracellular body water without positively modifying nutritional variables in ESRD patients [48]. Moreover, although overnight hemodialysis was associated with increased protein intake, no positive effects on body composition were observed after one year [49].

9. Management of comorbidities

Patients with CKD/ESRD often have many comorbidities that negatively impact on nutritional status. In particular, diabetic patients have a higher incidence of PEW than non-diabetics, probably because of the negative role played by insulin resistance on protein muscle metabolism [8]. Therefore, adequate management of diabetes and insulin resistance is important in the prevention of PEW in hemodialysis patients [1]. Patients with CKD also often suffer from disorders of the gastrointestinal tract, such as nausea, vomiting, diabetic gastroparesis and pancreatic insufficiency, and the management of these complications is critical in maintaining an optimum nutrient intake [1]. Other factors associated with PEW are represented by uncontrolled secondary hyperparathyroidism, cardiac cachexia, depression and/or cognitive disorders [1–3,50].

10. Conclusion

Patients undergoing maintenance hemodialysis are at high risk for developing PEW. Thus, regular and careful assessment of nutritional status is warranted, with the purpose of establishing an early diagnosis of PEW. This condition is frequently observed in the ESRD population, and is associated with increased mortality risk. Different nutritional approaches are currently available to prevent and treat PEW, and they should be carefully individualized. Intradialytic nutritional administration, both by the oral and the parenteral routes, is safe and should be encouraged.

Conflict of Interest

The authors have no conflicts to declare.

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