Module 15.3

Nutrition Support in End-stage Renal Disease Patients on Haemodialysis (ESRD-HD)

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Learning Objectives

- To know the causes of protein-energy wasting in ESRD-HD patients;
- To learn how to evaluate nutritional status in ESRD-HD patients;
- To learn the nutritional requirements in ESRD-HD patients;
- To know the different ways of nutritional support;
- To learn the best approach to nutritional support in malnourished ESRD-HD patients.

Contents

Key Messages

- Adequate nutritional monitoring is crucial in ESRD-HD patients;
- Protein-energy wasting (PEW) jeopardizing survival is found in approximately 25% of ESRD-HD patients;
- Insufficient food intake and abnormal nutrient metabolism, mainly due to acidosis, inflammation, hormonal derangements and dialysis procedures, are considered the main causes of protein-energy wasting;
- Protein-energy wasting relevant to the patient's prognosis can be detected by a decrease in body mass index to <23, a body weight loss > 10% within 6 months, muscle loss > 10% over 6 months, serum albumin < 38 g/l and transthyretin (prealbumin) < 300 mg/l;
- Nutritional support, preferably in the form of oral nutritional supplements, is able to improve nutritional status;
- Morbidity and mortality can be reduced when an improvement of nutritional status, as assessed by a serum transthyretin increase by 30 mg/l, is obtained by nutritional support;
- In patients presenting with mild protein-energy wasting, as defined by insufficient spontaneous intake, dietary counselling, and, if necessary, oral nutritional supplements are worthwhile;
- In patients exhibiting severe protein-energy wasting, with spontaneous intakes more than 20 kcal/kg/day, dietary counselling and oral nutritional supplements should be prescribed. Intradialytic parenteral nutrition is indicated in patients non-compliant with oral supplementation. Enteral nutrition can be necessary when oral nutritional supplements or intradialytic parenteral nutrition are unable to improve nutritional status;
- In patients exhibiting severe protein-energy wasting, with spontaneous intakes less than 20 kcal/kg/day, or in stress conditions, daily nutritional support is necessary and EN should be preferred to PN.

1. Introduction

In End-Stage Renal Disease patients on haemodialysis (ESRD-HD), a progressive depletion of energy stores and protein is frequently observed (1). An expert panel has suggested the term 'protein–energy wasting' (PEW) to describe this clinical condition, also defining the criteria for the diagnosis of PEW **(Table 1)** (2). In ESRD-HD patients, the prevalence of PEW varies, according to the nutritional parameters considered, from roughly 20% to 70% of adult ESRD-HD patients. The prevalence and severity of protein-energy wasting increase with the number of years on dialysis and are more pronounced in older patients. In a European series of more than 7000 ESRD-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 (3). Similarly, in the DOPPS II Study, 20.5% of US patients had a serum albumin level less than 35 g/l (4). Given the prognostic value of serum albumin and transthyretin, it can be inferred that about 25% of patients described in these studies were severely malnourished.

Table 1
Criteria for protein-energy wasting according to the International Society for Renal Nutrition and Metabolism

Serum chemistry
• Albumin < 38 g/l (by bromocresol method, approximately 35 g/l by immunonephelometry)
• Transthyretin (prealbumin) < 300 mg/l
• Cholesterol < 100 mg /dL (26mmol/L)
Body mass
• Body mass index < 23 kg/m^2
• Unintentional body weight loss >5% over 3 months or >10% over 6 months
• Total body fat <10%
Muscle mass
• Muscle loss > 5% over 3 months or 10% over 6 months
• Reduced arm muscle area > 10% in relation to 50th percentile
• Interdialytic creatinine appearance
Dietary intake
• Spontaneous dietary protein intake < 0.80 g/kg/d for at least 2 months
• Spontaneous dietary energy intake < 25 kcal/kg/d for at least 2 months

PEW is recognized as an independent determinant of morbidity and mortality in ESRD-HD patients (for review see ref (2)). It can be estimated that yearly mortality rates in malnourished ESRD-HD patients are about 25 to 30% (5-7). Prospective studies have shown a strong association between nutritional parameters and morbidity and mortality

among ESRD-HD patients, serum albumin and transthyretin showing the strongest predictive value (7-10). Changes in serum albumin and transthyretin over a period of a few weeks provide additional prognostic information (11-13). PEW is rarely a direct cause of morbidity and mortality but rather contributes to a fatal outcome by worsening the adverse effects of cardiovascular diseases and infections which are the commonest causes of death in ESRD-HD patients (2, 14, 15). The protective effect of a high BMI on morbidity and mortality risk, which is part of the so-called reverse epidemiology, indirectly confirms the importance of nutritional factors in the outcome of ESRD-HD patients (16-18).

2. Pathophysiology of Protein-energy Wasting in ESRD-HD

The causes of PEW in haemodialysis patients are similar to those commonly found in other chronic diseases, such as chronic respiratory disease, chronic heart failure, chronic infection and cancer (19). These causes, including anorexia, physical inactivity, anaemia, inflammation, insulin resistance and hypogonadism, constitute the nutritional phenotype of these chronic diseases (20).
In ESRD-HD, although anorexia is the major cause of PEW, factors specific to the syndrome itself may contribute to the development of PEW, including acidosis, hormonal derangements, intestinal dysbiosis, chronic inflammation and dialysis procedures (**Table 2**). A decrease in physical activity also may contribute to the PEW observed in ESRD-HD patients.

Table 2
Causes and mechanisms of PEW in CKD/ESRD patients

1. Reduced protein and energy intake	a. Anorexia b. Inappropriate dietary restrictions c. Gastrointestinal diseases d. Depression e. Difficulties in food preparation f. Socio-economic difficulties
2. Hypercatabolism	a. Chronic Inflammation b. Hormonal changes
3. Metabolic acidosis	a. Increased protein breakdown b. Increased BCAA oxidation c. Insulin and IGF-1 resistance
4. Dialytic treatment	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
5. Comorbidities and life style	a. Comorbidities (diabetes, heart failure, ischemic heart disease, peripheral vascular disease) b. Sedentary lifestyle
6. Reduced physical activity	Reduced muscle trophism, reduced self-sufficiency, reduced performance

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

2.1. Reduced Nutritional Intakes

Dietary interviews show that a reduction of food intake predominates in the adverse energy balance (21-23). The main factors associated with the decrease in spontaneous nutritional intake are described in **Table 3**. Comorbidities, hospitalization, depression, low social status, dietary restrictions and multiple medical treatments appear to be predominant.

Table 3
Causes of anorexia in ESRD-HD patients

Causes of anorexia related to chronic diseases associated with ESRD-HD
- Co-morbidities
- Frequent hospitalization
- Multiple drugs
- Depression
- Low social status
- Increased inflammatory cytokines: plasma TNF-α, Interleukin-2, leptin
Causes of anorexia related to ESRD-HD
- Uncontrolled anaemia
- Restrictive diets: fluids, phosphorus, sodium, potassium
- Dysgeusia (often associated with zinc deficiency)
- Inadequate dialysis
- Digestive symptoms, gastroparesis
- Uraemic toxins
- Altered plasma amino acids

Most ESRD-HD patients starting on haemodialysis 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 of the uraemic condition (24). When patients are started on dialysis, protein requirements increase, whereas phosphate, sodium and potassium restrictions are still recommended, along with adequate energy intake. Thus, these patients need careful dietary counselling to redefine specific dietary targets aimed at preventing PEW (24).
In ESRD-HD patients, the pathogenesis of anorexia, *per se*, is poorly understood. It has been proposed that uraemic toxins as middle molecules, chronic inflammation, altered amino-acid patterns, leptin, ghrelin, and neuropeptide Y are involved (25, 26). Abnormal plasma branched-chain amino acids (BCAA) and tryptophan transport across the blood-brain barrier may be responsible for abnormal synthesis of neuro-transmitters such as serotonin, which may in turn induce anorexia (27). Concordantly, in ESRD-HD patients, BCAA supplementation was shown to improve nutritional intakes (28).
The initiation of dialysis treatment is usually followed by an improvement in food intake. Persisting anorexia after dialysis has been started can be due to inadequate dialysis. A

total weekly dialysis time of less than 12 hours is associated with decreased protein intake, and lower serum albumin and transthyretin (3, 29). Similarly, patients with a Kt/V index (a marker of dialysis efficacy) less than 1.1 have characteristically decreased muscle mass (3, 30). Non-biocompatible membranes were also demonstrated to be responsible for less body weight gain, and lower serum albumin and IGF-1 (31).

2.2. Altered Nutrient Metabolism

2.2.1. Amino Acid and Protein Metabolism

2.2.1.1. Plasma and Muscle Amino Acids (AA)

In normal conditions, the kidneys play an important role in AA metabolism: they take up glutamine, proline, citrulline, and phenylalanine from the arterial blood, while releasing serine, tyrosine, arginine, taurine, leucine, lysine and threonine (32). In renal failure, the suppression of these exchanges participates in the plasma AA abnormalities. In ESRD-HD patients, plasma AA concentrations are characterized by a relative decrease in essential AA (EAA), with the exception of methionine and serine, and increases in citrulline and aspartate (32, 33). The net effects are such that tyrosine and histidine are considered as additional essential AA in renal failure (34).

2.2.1.2. Hepato-splanchnic Amino Acid Metabolism

In normal conditions, after a protein meal the liver retains approximately 70% of the AA delivered by the portal vein for protein synthesis (25%) and urea synthesis (45%). Of importance, the AAs released in the hepatic veins, representing about 30% of ingested AA, are characterized by an enrichment in EAA, particularly in BCAA. Ureagenesis constitutes a quantitative loss of AA but makes it possible to obtain a qualitative gain in the AA composition (35, 36).
In renal failure, following a protein meal the hepatic AA uptake is decreased and the enrichment in EAA of the AA released by the liver does not occur. These abnormalities of hepatosplanchnic AA metabolism participate in the abnormal plasma AA pattern of renal failure (36). Of interest, experimental acidosis reproduces these changes in AA handling by the splanchnic area (37).

2.2.1.3. Protein Metabolism

ESRD-HD patients characteristically have an increase in whole-body and muscle protein turnover (38, 39), together with an increase in their albumin and fibrinogen fractional synthesis rates (39). Such an increase in protein turnover accounts for the vulnerability of protein stores when protein intakes are inadequate or during inflammatory stress or acidosis. The main causes of reduced lean body mass in ESRD-HD patients are given in **Table 4.**
Acidosis was shown to be responsible for a cortisol-dependent stimulation of muscle protein degradation, through the cytosolic ATP-ubiquitin dependent proteolytic system, and for irreversible BCAA catabolism (40). Muscle proteolysis, by providing ammonium radicals for renal bicarbonate generation, is integrated into the physiological fight against metabolic acidosis. However, during renal failure, chronic acidosis is responsible for a net loss of lean body mass. Moreover, acidosis is involved in the pathogenesis of insulin resistance (41), hyperparathyroidism (42) and growth factor dysfunction (43). Diabetes is responsible for protein depletion, as reflected by decreased muscle mass, serum

albumin and transthyretin (44, 45). These effects can be at least in part reversed by bicarbonate administration (46, 47).

Table 4
Factors associated with loss of lean body mass in ESRD-HD patients

- Reduced protein-energy intakes
- Reduced physical activity
- Metabolic acidosis
- Inflammation and oxidative stress
- Hormonal derangements: insulin resistance, abnormal growth factor action, androgen deficiencies, hyperparathyroidism, decrease in 1,25-OH vitamin D synthesis, increase in catabolic hormones (cortisol, glucagon, adrenaline)
- Diabetes mellitus
- Nutrient losses during dialysis
- Dialysis–induced decrease in protein synthesis
- Dialysis induced increase in protein catabolism

The role of inflammation in increasing protein catabolism in ESRD-HD patients has been underlined (48). Systemic inflammation, related to dialysis or not, has been reported in about 50% of ESRD-HD patients **(Table 5).** Its frequency appears to be higher in severely malnourished patients (49). The influence of genetic polymorphisms on inflammatory activity now appears of key importance (49), and should be considered in the design of interventional studies (50). As an example, polymorphisms in the promotor regions of Interleukin-10, TNF-α and Interleukin-6 can each influence nutritional status and morbidity (51). Cytokine activation, the common factor of protein catabolism and atherosclerosis, is responsible for the MIA (malnutrition-inflammation-atherosclerosis) syndrome and accounts for the high prevalence of vascular complications in malnourished ESRD-HD patients (48). Evidence exists that derangements 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 (52-54).

Table 5
Causes of inflammatory syndrome in ESRD-HD patients

Dialysis-independent inflammation
Renal failure *per se*
Inflammatory kidney disease
Associated inflammatory diseases
Reduced cytokine clearance
Chronic heart failure
Chronic infections (e.g. dental)
Intestinal dysbiosis
Dialysis-dependent inflammation
Cytokine and complement activation due to the use of non-biocompatible dialysis membranes
Dialysis fluid contamination
Uptake of pyrogens from the dialysis fluid
Uptake of endotoxins
Infection of the dialysis fistula

Besides the loss of glucose, amino acids and water-soluble vitamins, the haemodialysis procedure by itself may induce a decrease in plasma amino acid concentrations and a subsequent decrease in muscle protein synthesis (55). Haemodialysis is also associated with cytokine activation and an increase in protein catabolism (56).

2.2.2. Energy Metabolism

2.2.2.1. Energy Expenditure

Most studies of resting energy expenditure (REE) in ESRD-HD patients have reported REE values similar to those of controls (57-62). In three studies REE was however found to be higher than control values (63-65). Regarding the determinants of REE in this setting, it has been shown that severe hyperparathyroidism (66), elevated serum IL-6 (62) and leptin (67) are associated with increased REE. In one study conducted in ten ESRD-HD patients, REE was measured using a whole-room indirect calorimeter (63). Measurements were done continuously: for 2 hours before HD, during 4 hours of HD, for 2 hours after HD, and separately on a non-dialysis day after 12 hours of fasting. Age-, sex-, and body mass index-matched healthy volunteers were used as control subjects. ESRD-HD patients had a significantly higher REE on a non-dialysis day as compared with control subjects. REE further increased significantly during the HD procedure (63). From these studies it can be summarized that REE in ESRD-HD patients is most often similar to that of controls, but that dialysis procedures, inflammation and severe hyperparathyroidism can be responsible for increased energy expenditure.

2.2.2.2. Glucose Metabolism

Insulin resistance is a characteristic of chronic kidney disease (CKD). The mechanisms of CKD-related insulin resistance are incompletely understood. Among them, the lack of

renal breakdown of gluco-regulatory peptides (insulin, glucagon, adrenaline), and the presence of uraemic toxins have been advocated. Acidosis is also a cause of insulin resistance (41). Insulin sensitivity is negatively associated with systemic inflammation and positively with total plasma ghrelin in non-diabetic ESRD-HD patients, suggesting a potential role of ghrelin in preserving insulin sensitivity (68).
Insulin resistance in CKD mainly concerns non-oxidative glucose metabolism, i.e. its storage in the form of glycogen (58, 69). As a consequence, ESRD-HD patients characteristically have accelerated starvation metabolism: after 12 hours of starvation, fat oxidation accounts for two thirds of the non-protein contribution to REE in ESRD-HD patients as compared with only half in controls (58, 69).
Another important consideration is that (after insulin therapy) renal failure is the commonest cause of hypoglycaemia in hospitalized patients (70). Blood glucose control is impaired in CKD due to the loss of renal gluconeogenesis and a decreased ability of the liver to ensure euglycaemia in all circumstances (71, 72). Particularly, reduced clearance of antidiabetic drugs can induce hypoglycaemia. Such abnormalities can also account for the occurrence of hypoglycaemia following intradialytic hypertonic glucose administration.

2.2.2.3. Lipid Metabolism

The main abnormality of circulating lipids in ESRD-HD patients is hypertriglyceridaemia (73). It reflects a decrease in lipid particle turnover, mainly due to reduced lipoprotein lipase, hepatic lipase and lecithin-cholesterol-acyl transferase (74). As a consequence, in ESRD-HD patients, the clearance of exogenous long-chain triglycerides (LCT) is found to be decreased (75). Essential fatty acid deficiency has also been reported in ESRD-HD patients (76). It is reported that a higher dietary omega-6 to omega-3 ratio appears to be associated with worsening inflammation over time and a trend toward a higher risk of death in haemodialysis patients (77). The role of carnitine deficiency is still debated (78).
In malnourished ESRD-HD patients, prolonged intradialytic parenteral nutrition (IDPN) with LCTs from soybean oil did not alter basal plasma triglycerides, cholesterol or phospholipids (79), and induced favourable changes in lipoproteins: decrease in Lp(a) and increase in apo C-II (80). Five weeks' administration of soybean-oil or olive-oil based IDPN were reported to have no adverse effect on inflammatory and oxidative markers (81).

2.3. Reduced Rhysical Activity

ESRD-HD patients characteristically have a decrease in muscle mass, performance, endurance and oxidative capacity (82). Consistently, muscle biopsies show a decrease in oxidative muscle fibres, i.e. type 1 fibres, which are responsible for endurance exercise (83). The muscle of ESRD-HD patients is thus similar to that described in other chronic diseases such as chronic obstructive pulmonary disease (84). The cause of this chronic disease-related muscle pathology is not fully understood. However, reduced physical activity probably plays an important role.
Spontaneous physical activity has been measured using pedometers. In non-disabled ESRD-HD patients, the number of steps during daily activities was 48% of that of comparable healthy individuals. Moreover, the number of steps correlated positively with haemoglobin concentration, total body water and bioelectrical impedance-derived phase angle, and negatively with age and extracellular mass/body cell mass index (85). In a cohort of 608 ESRD-HD patients, the level of self-reported physical activity was low when

compared with age-matched healthy subjects (86). In the same study, the presence of several barriers to exercise and a non-proactive attitude by the healthcare staff impacted significantly and negatively on patients' self-reported levels of physical activity (86).
In ESRD-HD patients, weekly energy expenditure correlates positively with quality of life (87), while low physical activity is associated with higher mortality rates (88) and a decrease in bone mass (89).
Experimental and clinical data have shown that exercise is able to improve muscle energy and protein status. Exercise decreases muscle inflammation and increases oxidative capacity, the number of type 1 fibres, GLUT-4-associated glucose transport, insulin sensitivity, cell energy control, and protein balance. These effects of exercise are particularly mediated by the activation of NF−κB, PPARs δ and γ, AMP kinase, IgF-I and IGF-II (90-94).
Studies on muscle biopsies from ESRD-HD patients showed improvement in oxidative capacity after 12 weeks of exercise training (95), and transcriptional changes in genes favouring protein anabolism after 12 and 24 weeks (96). Endurance training in ESRD-HD patients was shown to improve peak oxygen consumption, peak work rate, endurance time and constant work rate (97-99). Exercise similarly improved insulin sensitivity, endothelial function, physical functioning and psychological status, leading to an improvement in quality of life (100-102). Physical activity was also shown to improve the efficacy of both intradialytic parenteral and oral nutrition in terms of muscle protein balance.

3. Gastrointestinal Function and the Kidney-gut Axis

Robust evidence exists that derangements of intestinal microbiota as well as increased permeability of the intestinal barrier, may play an important role in the pathogenesis of the chronic inflammatory status of ESRD-HD patients (52-54). The intestinal microbiota influence nutrition, metabolism, physiology and immune function of the host (52-54). Depending on their preferential metabolic pathway, intestinal bacteria can be classified as saccharolytic (preferential fermentation of carbohydrates) or proteolytic (preferential fermentation of protein) species. Saccharolytic species such as *Bifidobacterium* and *Lactobacillus* hydrolyze complex polysaccharides into monomeric sugars and then into short chain fatty acids (acetate, propionate, butyrate) (52-53). On the other hand, proteolytic bacterial species (for example *Clostridium* and *Bacteroides* species) produce potentially toxic substances (such as ammonium, thiols, phenols and indoles). Normally, the kidney easily excretes these "uraemic toxins" after intestinal absorption but with decreases in renal function, especially in ESRD-HD patients, they are retained (52-54). 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. In addition, the uraemic milieu of CKD-ESRD patients favours the intestinal secretion of urea which is transformed into ammonia by urease producing bacteria (103). This abnormal environment that develops during CKD/ESRD is defined as uraemic "intestinal dysbiosis". In addition, uraemia *per se* and complications related to the haemodialysis treatment (hypotension, intestinal oedema and ischaemia), are known to be responsible for depletion of the intestinal epithelial tight junction proteins, enhancing the permeability of the gut and facilitating the translocation of endotoxins, bacteria and bacterial parts to the blood stream (**Table 6**) (103). Several measures with putative impact on intestinal status have recently been tested for their influence on the generation or concentration of uraemic toxins. These include prebiotics, probiotics, synbiotics and intestinal sorbents. Recent data on this topic

suggest positive effects on uraemia and on serum levels of the protein-bound uraemic solutes that have been linked to cardiovascular events and mortality in ESRD-HD, by treating patients with prebiotics, probiotics and synbiotics (for review, see ref 52). The use of AST-120, an intestinal sorbent, was able to attenuate uraemia-induced disruption of colonic epithelial tight junction, endotoxaemia, oxidative stress and inflammation (104).

Table 6
Effects of CKD/ESRD-HD on the intestinal tract

Effects	Mechanism
1. Reduced intake of dietary fibre	Prescribed potassium and phosphorus restrictions lead to reduced consumption of fruit, vegetables and whole grain carbohydrates
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 uraemia. The reduced ratio between carbohydrate and nitrogen available in the colon increases the proliferation of proteolytic species with generation of toxic end-products such as phenols and indoles
4. Changes in the colonic microbiota	Luminal pH changes due to increased blood ammonia concentrations. Drug 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 uraemia, haemodialysis complications (hypotension, intestinal oedema and ischaemia), micro-bleeding caused by the systemic coagulation alterations typical of uraemia

4. Nutritional Assessment in ESRD-HD Patients

Given the prognostic impact of PEW, the nutritional status of ESRD-HD patients should be assessed regularly (105).

4.1. Clinical Assessment

Dietary interview should be performed twice a year in order to look for possible inadequacy of nutrient intake and to correct it. Dry body weight loss is associated with poor outcomes (106). Body mass index (BMI) should be calculated monthly. As in other chronic diseases, BMI is positively correlated with long-term survival (107). However, in addition to the assessment of BMI, body composition should be evaluated, since the presence of sarcopenic obesity, a condition in which a normal BMI may conceal low muscle mass and excess adipose tissue, is frequent (108, 109), and negatively affects long-term survival in CKD and ESRD-HD patients (110, 111).

4.2. Serum Proteins

Both serum albumin and transthyretin are influenced by non-nutritional parameters such as inflammation, liver function, hydration status, gender and age (112, 113). However, in chronically depleted patients such as those with ESRD-HD, these serum proteins also reflect protein intake and nutritional status (2, 3, 114). Serum albumin and transthyretin should be measured before an HD session. Serum albumin correlates positively with normalized protein nitrogen appearance (nPNA), lean body mass, serum cholesterol and transthyretin (3), and is recognized as an independent marker of survival (8, 10, 115).
Because serum transthyretin is linked to the metabolism of the transthyretin-retinol-binding-protein-retinol complex its serum concentration is increased in renal failure. As a consequence, serum transthyretin can only be considered as a nutritional marker in the presence of stable renal function (116, 117). In ESRD-HD patients, transthyretin is generally a reliable marker of nutritional status (8-10) and, since it has a shorter half-life than serum albumin, also the efficacy of nutritional intervention (118). A serum transthyretin of less than 300 mg/l is a strong predictor of mortality, independently from albumin (8-10, 119). In addition, an improvement in nutritional status as assessed by a serum transthyretin increase by 30 mg/l, obtained by nutritional support, correlates with reduced mortality and morbidity (118).

4.3. Urea and Creatinine-related Parameters

The normalized protein nitrogen appearance nPNA (g protein/kg/day), can be calculated from pre- and post-dialysis plasma urea and the urea dilution space (120). In stable patients the nPNA is considered to reflect protein intake (121, 122), and can be calculated by formulas using data from midweek dialysis (**Box 1**) (120). It correlates with lean body mass, serum albumin and transthyretin. Optimal values of nPNA are 1.2 to 1.4 g/kg/day. nPNA values of less than 1 g/kg/day are associated with increased hospitalization and mortality rates (7, 123, 124).
Pre-dialysis creatinine is a marker of muscle mass. Several algorithms have been developed for the estimation of lean body mass (LBM) from serum creatinine concentration or the amount of creatinine in the dialysate (125, 126). However, these equations frequently under- or overestimate LBM and should only be used in a context where no other method is available for the assessment of LBM or muscle mass; in addition, the lack of reference values allows only for intra-individual assessment of body composition over time.

Box 1
Midweek equation for the estimation of nPNA (120)

Equation 1. For patients with little or no residual urine output (24h urine output < 200ml).

nPNA = BUN/(25.8+1.15*KtV+56.4/KtV)+0.168

Where BUN is pre-haemodialysis blood urea nitrogen in mg/dL.

Equation 2. For patients with residual urine output > 200ml/24h, pre-haemodialysis BUN must be adjusted as for the following equation:

Adjusted BUN = BUN [1+(0.79+3.08/KtV)*Kr/V]
Where BUN is pre-haemodialysis blood urea nitrogen in mg/dl, Kr is residual urinary urea clearance in mL/min and V is urea distribution volume, in litres.

4.4. Body Composition Assessment

Bio-impedance analysis (BIA) has been validated for body composition measurements in ESRD-HD patients (127-130). Due to changes in water and ion compartments related to the HD procedure, it was initially considered that BIA should ideally be performed during an interdialytic day. However, reliable measurements have been reported when BIA is performed before dialysis, 15 minutes and two hours after dialysis (131, 132). The main information derived from BIA is total tissue fluid content, equivalent to total body water and cell mass. Recently, BIA has largely been replaced by bioelectric impedance spectroscopy (BIS) in research and clinical practice because of the recognition that it provides more accurate estimates of total body water (TBW) and intracellular water (ICW), particularly when fluid distribution may be altered (133). The advantage of BIS is that it uses a whole range of frequencies between 5 and 1000 kHz, while BIA generally uses only 1 to 4 frequencies. At lower frequencies the current passes exclusively around the cells, while in higher frequencies the current passes through the cell membranes, allowing a precise assessment of extracellular water (ECW) and intracellular water (ICW). BIS then uses equations based on a 3-compartment model to estimate lean body mass (LBM), fat mass (FM), total body water (TBW) and ICW. Nevertheless, despite a good correlation with whole body magnetic resonance imaging (MRI), precision in the single patient is low in estimating muscle mass, being highly influenced by hydration status (134), requiring standardization of the method. If repeated measurements are planned, they should be obtained between 15 and 120 minutes after the dialysis session, when patients are closer to their dry weight.
Currently, DEXA is the reference method for body composition measurement in ESRD-HD patients. Lean body mass as measured by DEXA has been shown to correlate with serum creatinine, arm muscle circumference and handgrip strength (135). DEXA was shown to be relevant to the follow-up of body composition in CKD and diabetic ESRD-HD patients (45, 136). The main limitation of DEXA is its incapacity to differentiate intra-and extra-cellular water, resulting in under- or overestimation of LBM. This limitation may be resolved by standardization of measurements in conditions closer to the dry weight. Recent consensus statements on the definition of sarcopenia, recommend the use of DEXA for the assessment of the appendicular lean soft tissue (ALST) instead of whole body LBM (137-141), which is the lean soft tissue of arms and legs and correlates better with function and mobility.

Recently, the use of ultrasound for the assessment of quadriceps skeletal muscle mass has been studied in renal patients. Ultrasound is widely available in dialysis units, safe, non-invasive and can be easily applied at the bedside. In addition, the ultrasound methodology does not require specialized staff (i.e. radiologists) and can be performed by any clinician after proper training. It allows a quantitative (by evaluating cross-sectional diameter and area) and qualitative (by evaluating muscle echogenicity) assessment of the quadriceps skeletal muscle. Available data suggest a high intra- and inter-reliability of the methodology in renal patients, even in critically ill patients (142). In addition, the assessment of quadriceps muscle mass of ESRD-HD patients was able to identify those subjects with worse nutritional status when patients were stratified by BMI and MIS score (143). The available data also suggest no need to perform measurements at a consistent time relative to the haemodialysis sessions, since no differences were found between measurements performed before and after dialysis (142, 143). More studies are still needed to validate ultrasound against DEXA or the putative gold standard techniques such as computerized tomography or magnetic resonance imaging, and to define normal ranges for muscularity to allow a uniform diagnosis of low muscle mass.

4.5. Recommendations for Nutritional Status Monitoring

The follow-up of nutritional parameters is mandatory in order to detect the malnourished ESRD-HD patients who require nutritional intervention. **Table 7** gives a summary of the follow-up guidelines for ESRD-HD patients recommended by ESPEN, US National Kidney Foundation and EBPG (105, 120, 144, 145).

Table 7
Monitoring of nutritional parameters (from 105, 120, 144, 145).

Nutritional parameter	Interval (months)
Dietary interview	6-12
BMI	1
nPNA	1
Unintentional weight-loss	3-6
Serum albumin	1-3
Serum transthyretin (prealbumin)	1-3

The unstable and high risk patient may require monitoring at shorter intervals. Severe PEW compromising the medium-term prognosis can be detected by a decrease in BMI to below 23, a weight loss of more than 10% within 6 months and the alteration of protein markers of malnutrition: serum albumin < 38 g/l, transthyretin < 300 mg/l (2).

5. Nutritional Requirements

5.1. Energy Requirements

Energy requirements generally vary between 30 and 40 kcal/kg per day and the international recommendations are summarised in **Table 8.** A number of descriptive studies have reported actual energy intakes often as low as 22-24 kcal/kg/day which thus may contribute to PEW. The recommended daily energy intakes vary according to age, gender and physical activity. The caloric supply should take into account the abnormalities of glucose metabolism and fat clearance. Fat should account for 30-40% of

energy supply. The addition of carnitine (0.5 to 1 g daily) has been proposed when plasma free carnitine is reduced.

Table 8
Recommendations for protein and energy supply in adult patients on routine haemodialysis (from 105, 120, 144, 145). ESPEN: European Society for Clinical Nutrition and Metabolism. NKF: the US National Kidney Foundation. EBPG: European best practice guidelines.

	ESPEN	NKF	EBPG
Protein intake	1.2–1.4	1.2	≥ 1.1
g/kg/day	(>50% HBV)	(>50% HBV)	
Energy intake	35	<60 y: 35	30-40
kcal/kg/day		>60 y: 30	adjusted by age, gender & activity

5.2. Protein Requirements

A meta-analysis analysed the available nitrogen balance data to establish new recommendations for the amount of protein required by healthy adults (146). The median requirement of protein for healthy adults has been estimated to be 0.65g of good quality protein/kg/day and the recommended dietary allowance (97.5th centile) is 0.83 g/kg/d. Although a neutral or positive nitrogen balance can occur in ESRD-HD patients at an intake of 1.0 g protein/kg/day (147, 148), the NKF (120), ESPEN (144, 145) and EBPG (105) propose that a higher protein intake, from 1.1 to 1.4 g/kg/day, is generally needed.
Phosphorus intake should be limited to 10-15 mg/kg/day. As phosphorus and protein are combined in nutrients with an average ratio of 10-13 mg phosphorus/g protein, most ESRD-HD patients who have an adequate protein intake will need phosphate binders to prevent an increase in serum phosphorus. The advice of a renal dietician will be helpful to choose foods low in phosphorus (149). Higher dietary phosphorus intakes and higher dietary phosphorus-to-protein ratios were reported to be associated with increased risk of death in ESRD-HD patients, even after adjustments for serum phosphorus, phosphate binders and their types, and dietary protein, energy, and potassium intakes (150).

5.3. Mineral and Micronutrient Requirements

Due to dialysis-induced losses, water-soluble vitamins should be supplied: folic acid (1mg/day), pyridoxine (10–20 mg/day) and vitamin C (30–60mg /day) (105, 120, 144, 145). Vitamin D should be given according to serum calcium, phosphorus and parathyroid hormone levels. Infection, surgery, and a large quantity of glucose infusion may increase the need for thiamine. The common dietary intake of 0.5–1.5 mg/day can be supplemented with a daily oral dose of 1–5 mg of thiamine hydrochloride (149). Vitamin E may be prescribed to patients at high cardiovascular risk at the daily dose of 800 IU of alpha-tocopherol (151).
Routine HD does not induce significant trace-element losses. However, in depleted patients, zinc (15 mg/day) and selenium (50–70 µg/day) supplementation may be useful. Mineral requirements are summarised in **Table 9.**

Table 9
Mineral requirements of patients on ESRD-HD

Phosphate, mg/d	800-1000
Potassium, mg/g	2000-2500
Sodium, g/d	1.8-2.5
Fluid, ml	1000 + urine volume
Requirements may differ in acute conditions	

6. Methods for Nutritional Support

Nutritional support in ESRD-HD patients includes nutritional counselling regarding spontaneous intake, oral supplementation, intradialytic parenteral nutrition (IDPN) and enteral nutrition. Nutritional support should be assessed in terms of metabolic efficacy, nutritional gain and outcome benefit. The ability of both oral supplementation and IDPN to improve protein metabolism during dialysis has been clearly demonstrated. In a crossover study, non-diabetic non-malnourished ESRD-HD patients were studied on two interdialytic days and during two separate dialysis sessions, with and without test meals (protein 46.2 g, carbohydrate 63 g, fat 75 g) (152). Whole body protein metabolism was studied by primed constant infusion of L-(1-^{13}C) valine. Both during interdialytic days and dialysis sessions, oral supplementation changed a negative whole body protein balance to a positive protein balance. Similarly, in non-malnourished ESRD-HD patients, a study of whole body and forearm protein metabolism during a constant infusion of L-(1-^{13}C) leucine and L-(ring-$^{2}H_5$) phenylalanine showed that IDPN could reduce protein catabolism and improve protein synthesis both in the whole body and the forearm area (153).
The recommended management of ESRD-HD patients has been addressed in several consensus papers (1, 105, 144, 145). It includes counselling by a dietician, oral nutritional supplements, IDPN and enteral nutrition via tube feeding. Regarding the strategy of nutritional support, it must be underlined that both oral supplementation and IDPN can only provide the equivalent of 7 to 10 kcal/kg/day and 0.3 to 0.4 g protein/kg/day. Therefore oral supplementation and IDPN only make it possible to reach the recommended levels of protein and energy intakes when spontaneous oral intakes are already at least 0.8 g protein and 20 kcal/kg/day (155).

6.1. Dietician Counselling

Dietetic counselling, the first step in nutritional support, has been reported to improve nutritional status (156). Early and regular dietary counselling is the first and most cost-effective intervention aimed at preventing and treating PEW in ESRD (157). The beginning of haemodialysis is accompanied by changes in nutritional needs as compared with previous restricted regimens (24, 154). On these grounds, an early and individualized intervention by the healthcare team is needed to prevent erroneous eating habits (for example reduced protein intake) that could lead to PEW (158). These data argue for the need of regular (twice yearly) dietician intervention in dialysis patients in order to quantify and adjust spontaneous intakes and to adapt oral supplementation.

6.2. Oral Nutritional Supplements

Oral nutritional supplementation (ONS) represents the first step of nutritional intervention when dietary counselling alone fails. Various ONS have been tested in ESRD-

HD patients including isolated administration of amino acids, protein or glucose polymers, or associated protein and energy supplies, providing 200-600 kcal and 8 to 25g of protein daily. A systematic review with meta-analysis addressing protein-calorie oral and enteral supplements showed an increase in serum albumin by 2.3 g/l (95% confidence interval, 0.37-4.18) in ESRD-HD patients (159). Six controlled studies conducted in malnourished ESRD-HD patients reported a positive effect of oral supplementation on nutritional parameters (28, 160-164). Interestingly, an improvement of Karnofsky scale (118, 164) and spontaneous feeding during oral supplementation was also reported (28).
Three premises should be considered in the optimal timing of ONS consumption: 1) to make a nutritional supplementation and not a nutritional substitution; 2) to shorten the length of overnight starvation by a late evening ONS; 3) to reduce the dialysis-induced negative protein balance. Taking into account this rationale, the following timing for ONS may be proposed: one hour after breakfast, one hour after lunch, late in the evening (eg 9:00, 14:00, 22:00), and during the first hour of each dialysis procedure. Renal specific supplements may afford some advantages compared to standard commercial preparations, since they have higher caloric density (1.5-2 kcal/ml) and increased protein content (75-81 g/l), with reduced content of potassium, sodium and phosphorus in terms of phosphorus/protein ratio (mg P/g of protein).

6.3. Intradialytic Parenteral Nutrition (IDPN)

IDPN is typically cyclic (three times weekly) PN given through the venous line of the dialysis circuit. It has been recommended by the ISRNM consensus as the last resource to supplement spontaneous nutrient intake in ESRD patients on haemodialysis diagnosed with PEW, or at risk of PEW, when compliance with ONS is low, or when it is not tolerated (158). The following technical rules have been proposed in order to ensure its good tolerance (165): a) Do not start IDPN if serum triglycerides > 300 mg/dl (about 3 mmol/l); b) serum glucose levels should be maintained between 110-180 mg/dl, if serum glucose > 180 mg/dl add subcutaneous insulin as rapid action analogues, however do not give insulin after the 3rd hour of dialysis; c) IDPN should be infused at a constant rate during 4-hour dialysis sessions; d) IDPN delivery should be progressively increased from 8 ml/kg/dialysis session (representing 500 ml in a 60kg patient) during the first week, to a maximum of 16 ml/kg/IDPN, without exceeding 1000 ml/HD session; e) IDPN should be associated with controlled ultrafiltration, volume per volume; d) sodium losses due to ultrafiltration should be compensated (equivalent of 75 mmol Na^+ per litre of IDPN solution (5).
As reported above, ESRD-HD patients are characterized by numerous abnormalities of nutrient metabolism concerning both amino acid and energy metabolism. HD sessions are responsible for a decrease in total plasma amino acids that has been shown to alter protein synthesis (55). It has been shown that the intradialytic infusion of amino acids prevents this decrease in plasma amino acid concentrations and the subsequent decrease in protein synthesis (55, 153).
Both glucose and lipid metabolism are altered in ESRD-HD patients. On one hand, the use of hypertonic glucose is limited by glucose intolerance and the risk of post-dialysis hypoglycaemic accidents. On the other hand, despite the fact that exogenous lipid clearance is reduced, fat represents the preferential fuel in ESRD-HD patients during the post-absorptive phase (58). Other arguments in favour of providing fat emulsions in association with glucose during IDPN are: a) the essential fatty acid deficiency reported in ESRD-HD patients (76); b) the higher energy/volume ratio of fat emulsions and their

iso-osmolarity which make their intravenous infusion well-tolerated; c) the lack of effect of fat emulsions on dialysis efficiency (81, 118).
IDPN provides up to 800-1200 kcal three times weekly, in the form of glucose and fat emulsions, and 30 to 60 g of protein, as amino acids. IDPN improves energy and protein balance as well as albumin synthesis rates (153, 166). Despite the lack of studies demonstrating any positive effect of IDPN on mortality, in more than thirty studies, including five prospective, randomized, controlled trials, IDPN has been shown to improve nutritional parameters (for reviews, see 144, 145)(167, 168).
IDPN should not be used as a long-lasting therapy. ONS should be continued or restarted, and IDPN should be discontinued based on the following criteria: stable serum albumin > 38 g/l for 3 months, clinical examination of improved nutritional status, increases in protein and energy oral intake to > 1.0 g/kg/day and to >30 kcal/kg/day respectively (118).

6.4. Enteral Nutrition

When PEW is associated with spontaneous intakes less than 0.8 g protein and 20 kcal/kg/day, daily nutritional support is needed to ensure recommended nutritional intakes. In these patients, enteral nutrition should be preferred to parenteral nutrition (144). Only a few studies have addressed the use of enteral nutrition in dialysis patients. Enteral nutrition is most often used when oral supplementation and/or IDPN are not able to satisfy nutritional requirements, as in conditions such as severe anorexia, swallowing troubles secondary to neurological or head and neck disease, the peri-operative period, and stress. In these clinical conditions enteral nutrition may need to consist of total enteral nutrition, providing all required macro- and micronutrients. Enteral nutrition has been shown to be safe and able to ensure the total nutritional needs of dialysis patients (169). Because the duration of enteral nutrition usually exceeds one month in ESRD, a gastrostomy is generally needed, mostly in the form of a percutaneous endoscopic gastrostomy (PEG) although this may be relatively contraindicated in a patient who has extensive intra-abdominal adhesions or fibrosis from complications of earlier chronic peritoneal dialysis.

7. Strategy for Nutritional Support

Based on the information presented above, **Fig. 1** illustrates a decision tree for the management of PEW according to nutritional assessment in the ESRD-HD patient:

- In patients presenting with mild malnutrition as defined by insufficient spontaneous intake, dietary counselling, and, if necessary, ONS should be prescribed.
- In patients exhibiting severe malnutrition, with spontaneous intakes of at least 20 kcal/kg/day: dietary counselling and ONS should be prescribed; IDPN is indicated in patients non-compliant with ONS; EN can be necessary when ONS or IDPN are unable to improve nutritional status.
- In patients exhibiting severe malnutrition, with spontaneous intakes less than 20 kcal/kg/day, or in stress conditions: both ONS and IDPN are unable to provide satisfactory nutritional supply and are not recommended; daily nutritional support is necessary and EN should be preferred to PN; central venous PN is indicated when EN is impossible or insufficient.

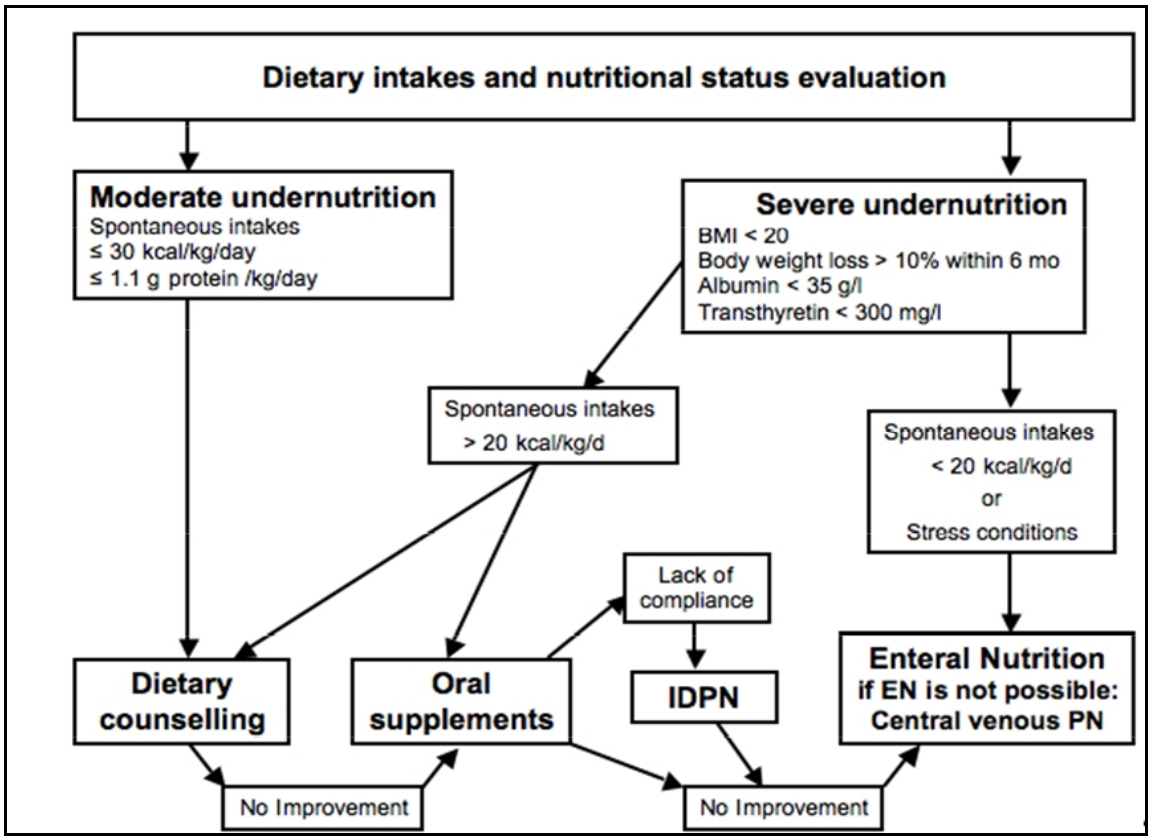

Fig. 1. Algorithm for the management of protein-energy wasting in ESRD-HD patients (145).

IDPN: intradialytic parenteral nutrition. Therapeutic decisions should be adapted according to nutritional monitoring.

8. Perspectives to Improve Nutritional Management

Ensuring nutritional intake at the level of nutritional requirements, as defined by available recommendations, is the usual goal of nutritional support. However, several concepts have evolved in the last few years concerning the treatment of malnutrition in dialysis patients. They include different treatments aimed at improving appetite, to decrease protein breakdown and/or to promote protein synthesis.

8.1. Optimizing Nutrition Support

8.1.1. Essential Amino Acids

In order to improve protein nutrition, another concept for nutritional support has been developed which consists of the provision of nutrients with a specific ability to promote protein synthesis. This concept was the basis for the use of essential amino acid supplements. Indeed some essential amino acids directly activate protein synthesis (170). In elderly ESRD-HD patients, branched-chain amino acid supplements have been shown to improve both nutrient intake and nutritional status (28). The effects on protein accretion of essential amino acids (171) and leucine (172) reported in the elderly, now require confirmation in controlled trials in dialysis patients. Protein synthesis could also be improved by the nature of protein delivery either in terms of timing or composition of

protein supply (173). Hence, the modulation of protein and amino acid supply may be a way to counteract altered protein synthesis in ESRD-HD patients.

8.1.2. Fibre

According to the NHANES III data, the CKD population has a lower fibre intake than that recommended for the healthy population (15.4 g/day versus 25-30 g/day respectively) (174). Recent data suggest that supplementation with dietary fibre could positively influence the intestinal environment and help to treat intestinal dysbiosis, leading to reduced concentrations of plasma protein-bound uraemic toxins, urea and creatinine (54, 175). Considering the available data, it is recommended that ESRD-HD patients achieve daily dietary fibre intakes similar to those recommended for the healthy population (25 g/day). Increasing dietary fibre intake poses a possible risk from the concomitant increase in potassium and phosphorus intake. However, timely counselling by renal dietitians and nephrologists could allow an increased fibre intake from a choice of low potassium fruits and vegetables, and possibly fibre supplements without added phosphorus.

8.1.3. Omega-3 fatty Acids

Recent studies in healthy elderly patients demonstrated that ω-3 PUFAs seems to exert a positive effect in the muscles, stimulating protein synthesis and counteracting anabolic resistance and sarcopenia (176). Few data are currently available regarding the effects of ω-3 PUFAs on nutritional status in ESRD-HD patients. Recent data suggests improvement of nutritional and metabolic parameters (177), especially regarding inflammatory markers such as IL-6, TNF-α, C-reactive protein and IL-10 (178). Randomized clinical trials are needed to confirm the putative positive effects of ω-3 PUFA supplementation on the nutritional and inflammatory status of ESRD-HD patients.

8.2. Anti-inflammatory Drugs

The administration of pentoxifylline together with amino acids was reported to reduce whole body protein catabolism evaluated during labelled leucine infusion and to increase serum albumin (180-182), suggesting that the reduction of protein catabolism may be another prospect in the treatment of malnutrition in dialysis patients. Etanercept (an antagonist of TNF-α), administered for 44 weeks, led to an increase in serum albumin and transthyretin (183). The administration of IL-1 antagonists in patients on dialysis presenting chronic inflammation showed a significant improvement of CRP and IL-6, although large-scale studies are needed to understand the effects on nutritional status (1).

8.3. Exercise Training

Exercise also appears to be an efficient means to improve protein status. As shown above, exercise was reported to promote muscle energy and protein anabolism in dialysis patients. There is ample evidence that exercise can improve fitness (VO_2 peak), physical functioning, and some cardiovascular risk factors in the dialysis population (102). Although the association of endurance and resistance training seems to be confirmed, there have been few comparative studies, and there is no consensus regarding the most beneficial regimen or the one most acceptable to large numbers of patients (for review,

see 102). Patients should be checked for possible cardiovascular contraindications before initiating exercise training.

8.4. Anabolic Hormones

In a controlled, randomized, double blind study, the administration of nandrolone decanoate was associated with an increase in muscle mass, as assessed by pre-dialysis creatinine and DEXA, and an improvement in muscle performance (184). The European Best Practice Guidelines for nutrition in dialysis state that: "In cases of severe malnutrition resistant to optimal nutritional intervention, a course of androgens should be considered in ESRD-HD patients for three to 6 months (Evidence level II); Patients should be monitored at regular intervals for side effects (hirsutism, voice change, priapism, alteration in plasma lipids, liver tests and prostatic markers) (Evidence level II); Patients with a known prostate cancer should not receive androgens (Evidence level II) (105)".
Similarly, anabolic effects have been obtained in pilot studies with recombinant growth hormone and insulin-like growth factor-1 in adult dialysis patients (185, 186). However, more data are needed before a firm recommendation for their use in clinical practice (187).

8.5. Daily Dialysis

Maintaining an adequate dialysis dose is a necessary element to preserve the nutritional status of ESRD patients. However, increasing the frequency of dialysis to daily, despite allowing for a liberalization of alimentation, does not seem to improve the nutritional status of malnourished ESRD-HD patients (1). Daily dialysis reduces the extracellular body water but is unable to positively modify the nutritional status of ESRD-HD patients (188). In another study, overnight dialysis was found to be able to increase protein intake, without, however, demonstrating any positive effects on body composition within a year (189).

9. Summary

Protein-energy wasting is found in approximately 25% of ESRD-HD patients and has a major impact on survival.
Present data show that: 1) nutritional support, preferably in the form of ONS, is able to improve nutritional status; 2) morbidity and mortality can be reduced when improvement of nutritional status, as assessed by a transthyretin increase of 30 mg/l, is obtained during nutritional support. Early administration of nutritional support and rational timing of ONS consumption may improve the efficacy of nutritional support.

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