Nutrition support in renal disease

Module 15.3

Nutrition support in haemodialysis (HD) patients

Learning Objectives

- To know the causes of undernutrition in HD;
- To learn how to evaluate nutritional status in HD patients;
- To learn the nutritional requirements in HD patients;
- To know the different methods of nutritional support;
- To learn the best approach to nutritional support in malnourished HD patients.

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Key Messages

- Adequate nutritional monitoring is crucial in maintenance HD patients.
- It can be considered that protein energy wasting, compromising medium term survival, is found in approximately 25% of maintenance dialysis patients.
- Insufficient food intake and abnormal nutrient metabolism, mainly due to acidosis, inflammation, hormone derangements and the dialysis procedure, are considered to be the main causes of malnutrition.
- Protein energy wasting, compromising the medium-term prognosis can be detected by a decrease in body mass index < 20, a body weight loss > 10% within 6 months, serum albumin < 35 g/l and transthyretin < 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, assessed by a serum transthyretin increase by 30 mg/l, is obtained during nutritional support.

In patients presenting with mild malnutrition, defined by insufficient spontaneous intakes, dietary counseling, and, if necessary, oral nutritional supplements are worth trying.

In patients with severe malnutrition and spontaneous intakes of more than 20 kcal/day: dietary counseling and oral nutritional supplements should be prescribed; Intradialytic parenteral nutrition is indicated in patients who are non compliant with oral supplementation; Enteral nutrition may be necessary when oral nutritional supplements or intradialytic parenteral nutrition are unable to improve nutritional status.

In patients with severe malnutrition and spontaneous intakes less than 20 kcal/day, or in stress conditions, daily nutritional support is necessary with EN being preferred to PN.

1. Introduction

In haemodialysis (HD) patients, the prevalence of protein-energy wasting varies, according to considered nutritional parameters, from roughly 20% to 70% of adult HD patients. The prevalence and severity of protein-energy wasting increases with the number of years of dialysis and is more pronounced in older patients. In a European series of more than 7000 HD patients, albumin, transthyretin (prealbumin) 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 (1). Similarly, in DOPPS II Study, 20.5% of US patients had a serum albumin level less than 35 g/l (2). Given the prognostic value of serum albumin and transthyretin it can be deduced that, in these reports, about 25 % of patients were severely malnourished.

Undernutrition is recognized as an independent determinant of morbidity and mortality in HD patients. It can be estimated that yearly mortality rates in malnourished HD patients are about 25 to 30% (3-5). Prospective studies have also shown a strong association between nutritional parameters and morbidity and mortality among HD patients, with serum albumin and transthyretin showing the strongest predictive value (5-8). Changes in nutritional variables over a few weeks provide additional prognostic information (9, 10). Malnutrition is not usually a direct cause of morbidity and mortality but rather contributes to a fatal outcome by worsening the adverse effects of cardio-vascular and infection diseases which are the commonest causes of death in HD patients (11, 12). The protective effect of high BMI on morbidity and mortality risk, part of the so-called reverse epidemiology, indirectly confirms the importance of nutritional factors in the outcome of HD patients (13, 14).

2. Causes of protein-energy wasting in HD

Insufficient food intake and abnormal nutrient metabolism, mainly due to acidosis, inflammation, hormone derangements and dialysis procedures, are considered to be the main causes of malnutrition in this setting.

2.1 Reduced nutritional intakes

Dietary interviews have shown that reduced food intake is the predominant influence on energy balance. The main factors associated with impaired nutrition are given in Table 1. Comorbidities, hospitalizations, depression, low social status, dietary restrictions and multiple medical treatments appear as the predominant causes of reduced nutritional intakes.

In HD patients, the pathogenesis of anorexia, per se, is poorly understood. Causative factors suggested include uraemic toxins as middle molecules, inflammation, altered amino-acid pattern, leptin, ghrelin, and neuropeptide Y (15). Also abnormal plasma branched-chain amino acid (BCAA) and tryptophane transport across the blood-brain barrier may be responsible for abnormal synthesis of neuro-transmitter such as serotonin which may induced anorexia (16). In support of this idea BCAA supplementation has been shown to improve nutritional intakes in patients on maintenance HD (17). The initiation of dialysis treatment is usually followed by an improvement in food intake.
Anorexia persisting after dialysis initiation can be due to inadequate dialysis. As a matter of fact, a weekly dialysis time less than 12 h is associated with decreased protein intake, and lower serum albumin and transthyretin (1, 18). Similarly, patients with a Kt/V index (marker of dialysis efficacy) less than 1.1 are characterized by decreased muscle mass. Non-biocompatible membranes were demonstrated to be responsible for reduced weight gain, and lower serum albumin and IGF-1 (19).

**Table 1 Causes of anorexia in HD patients**

<table>
<thead>
<tr>
<th>Causes of anorexia in HD patients</th>
<th>Causes of anorexia in HD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Frequent hospitalization, multiple medications</td>
<td>- Inadequate dialysis</td>
</tr>
<tr>
<td>- Co-morbidities</td>
<td>- Digestive symptoms, gastroparesis</td>
</tr>
<tr>
<td>- Uncontrolled anaemia</td>
<td>- Increased inflammatory cytokines: plasma TNF-α, Interleukin-2, leptin</td>
</tr>
<tr>
<td>- Depression</td>
<td>- Uraemic toxins</td>
</tr>
<tr>
<td>- Low social status</td>
<td>- Altered plasma amino acids</td>
</tr>
<tr>
<td>- Regimens restricted in fluids, phosphorus, sodium, potassium</td>
<td>- Taste disturbances (often associated with Zinc deficiency)</td>
</tr>
</tbody>
</table>

### 2.2 Altered nutrient metabolism

#### 2.2.1 Amino acid and protein metabolism

**2.2.1.1 Plasma and muscle amino acids**

In normal conditions, kidneys play an important role in AA metabolism: they take up glutamine, proline, citrulline, phenylalanine from the arterial blood and release serine, tyrosine, arginine, taurine, leucine, lysine and threonine (20). During renal failure, the suppression of these exchanges contributes to plasma AA abnormalities. In HD patients, plasma AA concentrations are characterized by a relative decrease in essential AA (EAA), except for methionine, and serine, and an increase in citrulline and aspartate (20). Tyrosine and histidine are considered as essential AA in renal failure (21).

**2.2.1.2. Hepato-splanchnic amino acid metabolism**

In normal conditions, after a protein meal, the liver retains approximately 70% of AA for protein synthesis (25%) and urea synthesis (45%). Importantly, 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).

During 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 also contribute to the abnormal plasma AA pattern observed during renal failure (22). It is of interest that experimental acidosis reproduces these changes in AA handling by the splanchnic area (23).

**2.2.1.3. Protein metabolism**

HD patients are characterized by an increase in whole-body and muscle protein turnover (24, 25), combined with an increase in albumin and fibrinogen fractional synthesis rates (25). Such an increase in protein turnover accounts for the vulnerability of protein stores when protein intakes are inadequate or there is inflammatory stress or acidosis. Main causes of reduced lean body mass in HD patients are given in Table 2.
Table 2 Factors leading to loss of lean body mass in HD patients

- Reduced protein-energy intakes
- Metabolic acidosis
- Inflammation and oxidative stress
- Hormone disturbances: insulin resistance, abnormal growth factor action, male hormone deficiency, hyperparathyroidism, decrease in 1-25OH vitamin D synthesis, increase in plasma catabolic hormones (cortisol, glucagon, adrenaline)
- Diabetes mellitus
- Nutrient losses during dialysis
- Reduced physical activity

Acidosis has been shown to be responsible for a cortisol-dependent stimulation of both muscle protein degradation, through the cytosolic ATP-ubiquitine dependent proteolytic system, and irreversible BCAA catabolism (26). 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 (27), hyperparathyroidism (28) and growth factor dysfunction (29). Diabetes is also responsible for protein malnutrition, reflected by decreased muscle mass, serum albumin and transthyretin (30). The role of a systemic inflammatory syndrome in increasing protein catabolism in HD patients has been emphasised (31, 32). Systemic inflammation related to dialysis or not, has been reported in about 50% of HD patients (Table 3). Its frequency appeared to be higher in severely malnourished patients (33). The influence of genetic polymorphism on inflammatory activity now appears to be of primary importance (34). As an example, polymorphism in the promotor region of Interleukin-10, TNF- and Interleukin-6 has been shown to be correlated with nutritional status and morbidity (35). Cytokine activation, which is considered as the common factor for both protein catabolism and atherosclerosis is responsible for the MIA (malnutrition-inflammation-atherosclerosis) syndrome which accounts for the high prevalence of vascular complications in malnourished HD patients (32).

Table 3 Causes of inflammatory syndrome in HD patients

| Dialysis-independent inflammation          | Renal failure per se. |
|                                         | Inflammatory kidney disease |
|                                         | Associated inflammatory diseases |
|                                         | Reduced cytokine clearance |
|                                         | Chronic heart failure |
|                                         | Chronic infections (dental) |

| Dialysis-dependent inflammation          | Cytokine and complement activation due to the use of non-biocompatible dialysis membrane |
|                                         | Dialysis fluid contamination |
|                                         | Uptake of pyrogen from the dialysis fluid |
|                                         | Uptake of endotoxins |
|                                         | Infection of the dialysis fistulae |

2.2.2 Energy metabolism

2.2.2.1 Energy expenditure

Most of resting energy expenditure (REE) studies performed in HD patients have reported REE values similar to that of controls (36-41). In one study REE was found to be higher than predicted (42). With regard to the determinants of REE in this setting, it has been shown that severe hyperparathyroidism (43), elevated serum IL-6 (44) and leptin (45) are associated with increased REE. In one study of ten maintenance HD patients, REE was measured using a whole-room indirect calorimeter (46). Measurements were made continuously: for 2 h before HD, during 4 h of HD, for 2

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h after HD, and separately on a non-dialysis day after 12 h of fasting. Age-, sex-, and body mass
index-matched healthy volunteers were used as control subjects. Compared with the controls, on
non-dialysis days chronic HD patients had a significantly higher REE which increased further during
the HD procedure (46). From these studies it can be concluded that, in HD patients, REE values are
similar to those of controls, but that total energy expenditure is increased by the dialysis
procedure, by inflammation and by severe hyperparathyroidism.

2.2.2.2 Glucose metabolism
Insulin resistance is characteristic of chronic kidney disease (CKD), but its mechanism is
incompletely understood. Among the possible mediating factors are uraemic toxins and the lack of
renal breakdown of gluco-regulatory peptides (insulin, glucagon, adrenaline). Acidosis is also a cause
of insulin resistance (27). More recently, insulin sensitivity has been shown to be associated
negatively with systemic inflammation and positively with total plasma ghrelin in non-diabetic
maintenance patients, suggesting a potential role of ghrelin in preserving insulin sensitivity (41).

Insulin resistance in CKD concerns non oxidative glucose metabolism, i.e. its storage in the form of
glycogen (37, 47). As a consequence, HD patients are characterized by an accelerated starvation
metabolism: after only 12-h starvation, fat oxidation accounts for 2/3 of REE in HD patients as
compared with 50% in controls (37, 47).

Another important feature is that renal failure is the second cause of hypoglycemia, the first one
being insulin therapy (48). Glucose homeostasis is impaired in CKD due to the loss of renal
gluconeogenesis and a decreased ability of the liver to ensure euglycemia in some circumstances
(49). Also reduced antidiabetic drug clearance can induce hypoglycemia. These abnormalities of
blood glucose control may account for the frequency of hypoglycemia following intradialytic
hypertonic glucose administration.

2.2.2.3 Lipid metabolism
Hypertriglyceridaemia is the main abnormality of circulating lipids in HD patients (50).
Hypertriglyceridaemia reflects a decrease in lipid particle turnover, mainly due to reduced activity
of lipoprotein lipase, hepatic lipase and lecithin-cholesterol-acyl transferase (51-53). As a
consequence, in HD patients, the clearance of exogenous long-chain triglycerides (LCT) is decreased
(54). Essential fatty acid deficiency has also been reported in HD patients (55). The role of carnitine
deficiency is still debated (56).

In malnourished maintenance HD patients, prolonged intradialytic parenteral nutrition (IDPN) with
LCTs from soybean oil did not alter basal plasma triglycerides, cholesterol and phospholipids (57)
and induced quite favorable changes in lipoproteins with a decrease in Lp(a) and increase in apo C-II
(58). Five weeks administration of soybean-oil as well as olive-oil based IDPN was reported to have
no adverse effect on inflammatory and oxidative markers (59).

3. Nutritional assessment in maintenance HD patients

Given the prognostic impact of protein energy wasting, the nutritional status of HD patient should
be regularly assessed. The term ‘protein-energy wasting’ in acute and chronic kidney disease has
been recently proposed by an expert panel for loss of body protein mass and fuel reserves. Protein-
energy wasting should be diagnosed if three characteristics are present (low serum levels of
albumin, transthyretin, or cholesterol), reduced body mass (low or reduced body or fat mass or
weight loss with reduced intake of protein and energy), and reduced muscle mass (muscle wasting
or sarcopenia, reduced mid-arm muscle circumference) (60).

3.1 Clinical assessment
Dietary interview should be performed twice a year in order to look for possible nutrient intake
inadequacy and to correct it. Dry body weight loss is associated with a poor outcome (61). Body
mass index (BMI) should be calculated monthly. As in other chronic diseases, BMI has been shown to
be positively correlated with long-term survival (62).
3.2 Serum proteins
Both serum albumin and transthyretin are influenced by non-nutritional parameters such as inflammation, liver function, hydration status, gender and age (63, 64). However, in chronically depleted patients such as those undergoing HD, these serum proteins also reflect protein intake and nutritional status (1, 60, 65). Serum albumin and transthyretin should be measured before an HD session. Serum albumin is correlated with normalized protein nitrogen appearance (nPNA), lean body mass, serum cholesterol and transthyretin (1), and is recognized as an independent marker of survival (5, 8, 66).

Because serum transthyretin is linked to the transthyretin-Retinol-binding-protein-retinol complex metabolism, its serum concentration is increased during renal failure. As a consequence, serum transthyretin can only be considered as a nutritional markers in the presence of stable renal function (67, 68). In maintenance HD patients, transthyretin is a reliable marker of both nutritional status (6-8) and the efficacy of nutritional intervention (69). Serum transthyretin less than 300 mg/l strongly predicts mortality risk, independently of albumin (6-8, 70).

3.3 Urea and creatinin-related parameters
Predialysis plasma urea reflects nutritional status. In stable patients, nPNA (g protein/kg/day), calculated from pre- and post dialysis plasma urea and urea dilution space is considered to reflect of protein intake (71, 72). nPNA, which should be calculated from midweek dialysis data (73), is correlated with lean body mass, serum albumin and transthyretin. Optimal values of nPNA are 1.2 to 1.4 g/kg/day. nPNA values less than 1 g/kg/day are associated with increased hospitalization and mortality rates (5, 74, 75). Predialysis creatinine is a marker of muscle mass. Creatinine kinetic studies offer reliable tools for muscle mass measurement (5, 66, 76).

3.4 Body composition assessment
Bio-impedance analysis (BIA) has been validated for body composition measurements in maintenance HD patients (77-79). 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. Recent studies suggest that reliable measurements can be obtained when BIA is performed two hours after dialysis (80). Body composition follow-up, using BIA or Dual-energy X-ray absorptiometry (DEXA) should be performed in constant hydration conditions.

DEXA is the reference method for body composition measurement. This method was shown to be of interest for the follow-up of body composition in CKD and diabetic maintenance HD patients (81, 82). The main limitation of DEXA is its inability to differentiate intra- and extra-cellular water. This limitation may be resolved by the association of DEXA with multi-frequency BIA which makes it possible to measure body cell mass.

3.5 Recommendations for monitoring nutritional status
The follow-up of nutritional parameters is mandatory in order to detect malnutrition requiring nutritional intervention. Table 4 gives a summary of guidelines for HD patient nutritional follow-up according to the ESPEN, US National Kidney Foundation and EBPG (73, 83, 84). The unstable and nutritionally at risk patient may require monitoring at shorter intervals. Severe malnutrition, compromising the medium term prognosis, can be diagnosed by a decrease in BMI below 20, a body weight loss of more than 10% within 6 months and an alteration in the protein markers of malnutrition with a serum albumin < 35 g/l, transthyretin < 300 mg/l (69).

<table>
<thead>
<tr>
<th>Nutritional parameters</th>
<th>Intervals (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary interview</td>
<td>6 - 12</td>
</tr>
<tr>
<td>BMI</td>
<td>1</td>
</tr>
<tr>
<td>nPNA</td>
<td>1</td>
</tr>
<tr>
<td>Midweek predialysis creatinine</td>
<td>1</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>1 - 3</td>
</tr>
<tr>
<td>Serum transthyretin (prealbumin)</td>
<td>1 - 3</td>
</tr>
</tbody>
</table>
4. Nutritional requirements

4.1 Energy requirements
Energy requirements are given in Table 5 (85). A number of descriptive studies have reported energy intake to be frequently as low as 22-24 kcal/kg/day, contributing to malnutrition by depleting body adipose stores and by favouring negative nitrogen balance. The recommended daily energy intake varies from 30 to 40 kcal/kg/day according to age, gender and physical activity. The energy supply should take into account abnormalities of glucose metabolism and fat clearance. Fat should account for 30 to 40% of energy supply. When plasma free carnitine is reduced, the addition of carnitine (0.5 to 1 g daily) has been proposed.

Table 5 Recommendations for protein and energy supply in adult patients on routine haemodialysis (73, 83, 84). ESPEN: European Society of Parenteral and Enteral Nutrition. NKF: National Kidney Foundation. EDTA: European Dialysis transplantation association

<table>
<thead>
<tr>
<th></th>
<th>ESPEN</th>
<th>NKF</th>
<th>EDTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein intake, g/kg/day</td>
<td>1.2-1.4 (&gt; 50 % HBV)</td>
<td>1.2 (&gt; 50 % HBV)</td>
<td>≥ 1.1</td>
</tr>
<tr>
<td>Energy intake, kcal/kg/day</td>
<td>35</td>
<td>&lt; 60 y. 35</td>
<td>30-40, adjusted to age, gender and activity</td>
</tr>
</tbody>
</table>

4.2 Protein requirements
A meta-analysis addressed nitrogen balance studies that estimated basal or maintenance requirements or tested of the adequacy of specific nitrogen intakes in healthy adults (86). Assuming an adequate energy intake, the median requirement for protein in healthy adults has been estimated to be 0.65 g good-quality protein/kg/day and the recommended dietary allowance (97.5th percentile) to be 0.83 g (86). Although a neutral or positive nitrogen balance can be achieved in HD patients at an intake of 0.9-1.0 g protein/kg/day (87, 88), it has been proposed by the NKF (73), ESPEN (83), and EDTA (84) that a higher protein intake, from 1.1 to 1.4 g/kg/day, is needed in HD patients. Phosphorus intake should be limited to 10-15 mg/kg/day. As phosphorus and protein are combined in nutrients with a ratio of 10-13 mg phosphorus/g protein, most HD patients who have an adequate protein intake will need phosphate binders to prevent an increase in serum phosphorus. A renal dietician is helpful in choosing nutrients low in phosphorus (89). Different AA formulae have been proposed according to the essentiality of tyrosine and histidine, to the abnormalities of plasma amino acids, and to the clearance of amino acid solutions. However, because there is no substantial clinical data to support these specific amino acid formulae, standard amino acid formulae are commonly used.

4.3. 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) (73, 83, 84). Vitamin D should be given according to serum calcium, phosphorus and parathyroid hormone levels. Due to abnormal metabolism and dialysis-induced losses, supplements of water-soluble vitamins have been recommended. Infection, surgery, and a large quantity of glucose infusion may increase the need for thiamine. The usual dietary intake of 0.5-1.5 mg/day can be supplemented with a daily oral dose of 1-5 mg of thiamin hydrochloride (89). Vitamin E may be prescribed to high cardio-vascular risk patients at a daily dose of 800 IU of alpha-tocopherol (90).

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 given in Table 6.
Table 6 Mineral requirements of patients on HD and CAPD

<table>
<thead>
<tr>
<th></th>
<th>Phosphate, mg/d*</th>
<th>Potassium, mg/g</th>
<th>Sodium, g/d</th>
<th>Fluid, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>800 - 1000*</td>
<td>2000 - 2500*</td>
<td>1.8 - 2.5*</td>
<td>1000 + urine volume</td>
</tr>
</tbody>
</table>

* Individual requirements may differ in acute conditions

5. Methods of nutritional support

Methods of nutritional support in HD patients include nutritional counseling, oral supplementation, IDPN and enteral nutrition. The value of nutritional support has to 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 was recently demonstrated. In a crossover study, non-diabetic non-malnourished 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) (91). Whole body protein metabolism was studied by primed constant infusion of L-(1-13C) valine. During both interdialytic days and dialysis sessions, oral supplementation changed the negative whole body protein balance to a positive one. Similarly, in non-malnourished HD patients, the study of whole body and forearm protein metabolism during a constant infusion of L-(1-13C) leucine and L-(ring-2H5) phenylalanine showed that IDPN can reduce protein catabolism and improve protein synthesis in both the whole body and the forearm (92).

5.1 Dietician counseling

This first step in nutritional support, has been reported to improve nutritional status (93). These data argue the need for regular (twice yearly) dietician intervention in dialysis patients in order to quantify and adjust spontaneous intakes and to adjust oral supplementation.

5.2 Oral nutritional supplements

Various oral nutritional supplements (ONS) have been tested in HD patients: isolated administration of amino acids, protein or glucose polymers, and preparations combining protein and energy to provide 200-600 kcal and 8 to 25g protein. A systematic review with meta-analysis addressing protein-calorie oral and enteral supplements showed an increased in serum albumin by 2.3 g/l (95% confidence interval, 0.37-4.18) in maintenance HD patients (94). Six controlled studies reported a positive effect of oral supplementation on nutritional parameters (17, 95-99). Interestingly, an improvement in Karnofsky scale (69, 99) and spontaneous food intake was reported during oral supplementation (17).

Two rationales can be considered in relation to the optimal timing of ONS consumption: 1/ to avoid any reduction of normal food intake really making it a nutritional supplement and not a nutritional substitution; 2/ to shorten the length of overnight starvation by late evening ONS. Taking into account these rationales, the following time schedule for consuming ONS is proposed: one hour after breakfast, one hour after midday dinner and late in the evening (9:00, 14:00, 22:00).

5.3 Intradialytic parenteral nutrition

IDPN is a cyclic PN given three times weekly through the venous line of the dialysis cannula. The following technical rules have been proposed in order to ensure its good tolerance (59): a) IDPN should be infused at constant rate during 4-hour dialysis sessions; b) IDPN delivery should be progressively increased from 8 ml/kg/IDPN (representing 500 ml in a 60-kg patient) during the first week, to a maximum of 16 ml/kg/IDPN without exceeding 1000 ml/HD; c) IDPN should be associated with a controlled ultrafiltration, volume per volume; d) 75 mmol Na should be added per liter of IDPN solution in order to compensate Na losses due to ultrafiltration (3).

As reported above, HD patients are characterized by numerous abnormalities of both amino acid and energy metabolism. HD sessions are responsible for a decrease in total plasma amino acid concentration which alters protein synthesis (100). The intradialytic infusion of amino acids prevents the decrease in plasma amino acid concentration and the subsequent decrease in protein synthesis (92).
Both glucose and lipid metabolism are altered in HD patients. On the one hand, the use of hypertonic glucose is limited by insulin resistance, glucose intolerance and the risk of post-dialysis hypoglycemic accidents (101). On the other hand, despite the fact that exogenous lipid clearance is reduced, fat is the preferred fuel in HD patients during the post absorptive phase (37). Other arguments for providing fat emulsions in addition to glucose during PN in HD patients are: a) the essential fatty acid deficiency reported in HD patients (55); b) the high energy/volume ratio of fat emulsions and their iso-osmolarity which make them well-tolerated in peripheral vein feeding; c) the lack of effect of fat emulsions on dialysis efficacy (59, 69).

IDPN provides up to 800-1200 kcal three times weekly, in the form of glucose and fat emulsion and 30 to 60 g of protein, improving energy and protein balance as well as albumin synthesis rates (92, 102). In more than thirty studies, including five prospective, randomized, controlled trials, IDPN was shown to improve nutritional parameters (57, 59, 103, 104, 105).

5.4 Oral supplements or Intradialytic parenteral nutrition: criteria of choice

Regarding the strategy of nutritional support, it must be emphasised that both oral supplementation and IDPN can only provide the equivalent of 7 to 8 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 more than 0.8 g protein and 20 kcal/kg/day.

Data presented above argue for a metabolic and nutritional efficacy of both ONS and IDPN and question the usefulness of IDPN. Other key questions remained to be answered: 1) what are the effects of nutritional support on patient morbidity and mortality? 2) are nutritional marker changes obtained during nutritional support predictors of improved patient survival? These questions were addressed in the French Intradialytic Nutrition Evaluation Study (FINES) (69). One hundred and eighty six malnourished HD patients were randomly assigned to receive IDPN or not during a one-year period, and were then followed up for two years, including the year of treatment. The two groups also received ONS. In both groups, independently of serum C-reactive protein, body mass index, the serum albumin and transthyretin increased after the initiation of nutritional support. This improvement in nutritional markers persisted for six months after the treatment period. Mortality rates (23.1 and 41.8 % after one and two years) did not differ between the two groups, showing that the addition of IDPN to oral supplementation did not improve survival. Using a multivariate Cox model analysis, the early response to nutritional support, as assessed by the increase in serum transthyretin concentrations by more than 30 mg/l within three months, independently predicted a 54-percent decrease in the two-year mortality (odds ratio, 0.464; 95 percent confidence interval, 0.273 to 0.787). Multivariate regression analysis also showed that the nutritional improvement was associated with a reduction in the hospitalization rate and an improvement in Karnofsky score. In diabetic patients, the increase in serum transthyretin was not associated with any improvement in survival. This observation is consistent with previous data showing that survival of diabetic patients on maintenance HD was independent of nutritional status as assessed by BMI, serum albumin and transthyretin (30).

These data showed the efficacy of nutritional support in terms of both nutritional and outcome endpoints. Because the addition of IDPN to oral supplementation did not improve either the nutritional parameters or the outcome, IDPN should be reserved for undernourished maintenance HD patients who do not tolerate ONS or are poorly compliant with it.

5.4 Tube feeding

When malnutrition is associated with spontaneous intakes of 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 (85). Only few studies have addressed the use of enteral tube feeding in dialysis patients. This method is most often used when oral supplementation and/or IDPN are not able to satisfy nutritional requirements in conditions such as severe anorexia, impaired swallowing due to neurological or head and neck diseases, perioperative periods and stress. In these situations enteral nutrition should be total, providing all the required macro and micronutrients. It has been shown to be safe and to able to
ensure the total nutritional needs of dialysis patients (106). Because the duration of enteral tube feeding often exceeds one month, a percutaneous endoscopic gastrostomy is usually needed.

6. Strategy for nutritional support

Data from FINES give rise to three main conclusions (69): 1) the addition of IDPN to oral supplements has no advantage in terms of mortality, morbidity and nutritional status; 2) oral supplements, given alone or in association with IDPN, induce a dramatic and sustained improvement in nutritional status, which is independent of inflammatory status; 3) the improvement in nutritional status during nutritional therapy, as assessed by an increase in serum transthyretin of more than 30 mg/l, is an independent predictor of survival.

FINES helped to clarify the management of malnutrition in dialysis by demonstrating prospectively that nutritional support can improve both nutritional status and outcome. Figure 1 shows a decision tree for the management of malnutrition according to nutritional assessment:

- In HD patients presenting with mild malnutrition as defined by inadequate spontaneous food intake, dietary counseling, and, if necessary, ONS should be prescribed.
- In patients with severe malnutrition, i.e. with spontaneous intakes more than 20 kcal/day: dietary counseling and ONS should be prescribed; IDPN is indicated in patients non compliant with ONS; EN by tube may be necessary when nutritional status fails to improve with ONS or IDPN alone.
- In patients with severe malnutrition, i.e. with spontaneous intakes less than 20 kcal/day, or stress conditions: ONS and IDPN are unable to provide satisfactory nutritional supply and are not recommended; daily nutritional support is necessary using EN in preference to PN; central venous PN is indicated when EN is impossible or insufficient.

![Decisional algorithm for the management of undernutrition in HD patients. IDPN: intradialytic parenteral nutrition. Therapeutic decisions should be adapted according to nutritional monitoring (107).](image-url)
7. Perspectives to improve nutritional management

While the mainstay of treatment of malnutrition in patients undergoing dialysis remains nutritional support, ensuring that intake from all sources meets nutritional requirements in full, other adjunctive treatments developed in recent years have included specific measures to improve appetite, to decrease protein breakdown and/or to promote protein synthesis. Daily dialysis, which is suitable for selected patients, has removed the necessity for over-restrictive diets and has allowed some liberalization of food intake leading to improved nutritional status (108). Another approach has been to use nutrients able to promote protein synthesis e.g. essential amino acids, some of which have been shown to be able to activate directly the eucaryotic initiation factor 2B, which initiates protein synthesis (109). In elderly patients on HD, branched-chain amino acid supplements have been shown to improve both nutrient intakes and nutritional status (17). Similarly, the effects on protein accretion of essential amino acids (110) and leucine (111), reported in elderly people, need to be studied in a controlled fashion in dialysis patients (110, 112). Protein synthesis was also reported to be improved by optimizing the timing or composition of protein intake (112). These modulations of protein and amino acid intake may be a useful way to counteract altered protein synthesis in maintenance HD patients. The administration of pentoxifylline in combination with amino acids has been reported to reduce whole body protein catabolism during labeled leucine infusion (113), suggesting that it may be possible to improve protein balance in dialysis patients by pharmacological as well as nutritional means. Similarly, recent data has shown that statins are able to reduce inflammation and increase serum albumin levels (114). Exercise is also an important factor in maintaining or improving muscle mass, and has been reported to promote muscle anabolism in dialysis patients (115, 116). Exercise has also been shown to improve IDPN effects on both forearm muscle essential amino acid uptake and net muscle protein accretion, as well as inducing an increase in albumin synthesis rates (117, 118). Anabolic hormones have also been used. In a randomized controlled 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 (119). Similarly, anabolic effects have been obtained in pilot studies with recombinant growth hormone and insulin-like growth factor-1 in adult dialysis patients (120, 121).

These data suggest that a multimodal management, combining nutritional support (including additional essential amino acids), exercise and an anabolic hormone may be the optimal treatment for protein energy wasting during dialysis. Such a multimodal approach to malnutrition in chronic diseases has led to encouraging results in chronic obstructive pulmonary disease patients (122) and should be evaluated in HD patients.

8. Summary

Protein energy wasting, compromising middle term survival, is found in approximately 25% of maintenance dialysis patients.

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 an improvement in nutritional status, as assessed by a transthyretin increase by 30 mg/l, is obtained during nutritional support.

Early nutritional intervention and a rationalized timing of ONS consumption may improve the efficacy of nutritional support.

Future developments in the treatment of protein energy wasting during dialysis may be: the development of ONS formulae specifically for HD patients; multimodal therapy combining nutritional support, exercise and an anabolic hormone; the use of daily dialysis in selected patients.

References


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