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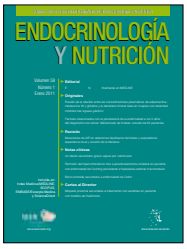

REVIEW

Efficacy of oral supplementation during dialysis in patients with chronic renal failure

Pilar Riobó Serván[a,]*, Alberto Ortiz Arduan[b]

[a]*Jefe Asociado del Servicio de Endocrinología y Nutrición, Fundación Jiménez Díaz, Madrid, Spain*
[b]*Jefe Asociado del Servicio de Nefrología, Fundación Jiménez Díaz, Madrid, Spain*

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Abstract Protein-calorie malnutrition is common in hemodialysis patients and is a powerful predictor of morbidity and mortality. Nutritional supplementation, administered orally or parenterally, especially during dialysis, may compensate for a relatively inadequate protein and energy intake and improve net protein anabolism in chronic hemodialysis patients. Intradialytic oral nutrition seems preferable to intradialytic parenteral nutrition (IDPN) due to its lower cost and the persistence of its anabolic effects after infusion is stopped, and because IDPN induces a higher increase in serum glucose and insulin levels and a greater reduction in serum ghrelin concentrations. Further larger scale randomized, controlled trials of nutritional interventions should be performed in maintenance dialysis patients to assess their efficacy in terms of quality of life, morbidity, and mortality.

PALABRAS CLAVE
Malnutrición calórico-proteica;
Morbilidad;
Mortalidad;
Suplementación nutricional;
Tratamiento nutricional;

Eficacia de la suplementación oral intradiálisis en pacientes con insuficiencia renal crónica

Resumen En los pacientes en hemodiálisis (HD) es frecuente la malnutrición calórico-proteica y además es un buen predictor de la morbilidad y mortalidad. La suplementación nutricional mediante la administración oral o parenteral especialmente en el momento de la diálisis puede compensar la ingesta inadecuada de proteínas y de energía y mejorar el anabolismo proteico neto en los pacientes en hemodiálisis crónica. Pero la vía oral parece ser preferible debido al menor coste, a que sus efectos anabólicos persisten una vez que la infusión ha cesado, y a que la nutrición parenteral intradiálisis produce una mayor elevación de las concentra-

*Corresponding author.
E-mail address: priobo@telefonica.net (P. Riobó Serván).

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Nutrición parenteral intradiálisis;
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ciones de glucemia e insulina séricas, y una mayor reducción de las concentraciones de ghrelina. Son necesarios más estudios sobre las diferentes intervenciones nutricionales en los pacientes de diálisis, para evaluar su eficacia en cuanto a calidad de vida, morbilidad y mortalidad.

Introduction

Protein-energy malnutrition (PEM) has been estimated to occur in approximately 20%-50% of patients on dialysis[1]. It may be due to different causes, including inadequate nutrient intake in diet, hypercatabolism inherent in dialysis, metabolic acidosis, chronic inflammation, and hormone changes[2]. Most patients with end-stage renal failure (ESRF) have so-called MIA syndrome (malnutrition, inflammation, anemia), consisting of low serum protein levels and lean mass loss, associated with increased levels of inflammatory markers[3]. The presence of malnutrition in dialysis patients is also known to be associated with increased overall morbidity and mortality, resulting in higher infection and hospitalization rates, longer mean hospital stay, and increased mortality[4]. And all of these occur despite current prevention and treatment methods, such as adequate dialysis dose and specific nutritional counseling. New nutritional interventions beyond the traditional prevention methods should therefore be sought.

Four nutritional factors that may be significantly related to survival have been identified: appetite, albumin, prealbumin, and body mass index. It therefore appears obvious that malnutrition prevention and treatment is of paramount importance. This is however not an easy goal to achieve because of the multifactorial origin of malnutrition.

This review will discuss the rationale for and the efficacy of nutritional supplementation such as anabolic interventions to increase body protein content in patients on dialysis with, or at risk of, malnutrition, with specific reference to recent studies in this area.

Causes of malnutrition in dialysis

Inadequate nutrient intake to cover current requirements is one of the main causes contributing to malnutrition in dialysis patients. This relative deficiency has multiple causes, including dialysis itself, which affects the whole protein homeostasis in skeletal muscle[5] in the whole body[6], and increased nutritional requirements in stress situations and due to intercurrent acute diseases. Other pathogenetic factors are related to uremia, intercurrent diseases, and dialysis itself (Table 1) and may lead to decreased intake, increased catabolism, and nutrient loss[7]. Anorexia, possibly related to elevated leptin levels due to a decreased renal clearance, plays a significant role in decreased intake. In addition, dietary restrictions (no salt, low potassium diet, fluid restriction) may make food less attractive. Dyspepsia caused by multiple drug administration, altered taste perception in uremia, and gastroparesis, particularly in diabetic patients, are also contributing factors, as are intercurrent diseases and hospital admissions. Uremia is associated with insulin resistance, the decreased action of insulin-like growth factor (IGF-1), and increased circulating levels of catabolic hormones such as cortisol, glucagon, and parathyroid hormone (PTH). Together, these hormone changes promote protein catabolism.

Anemia in renal failure, mainly due to a defect in renal erythropoietin production, also contributes to anorexia. Renal osteodystrophy has a deep nutritional impact and promotes secondary hyperparathyroidism. Metabolic acidosis increases the degradation of branched essential amino acids and muscle protein through activation of the branched chain keto acid dehydrogenase enzyme and the ubiquitin-proteasome proteolytic pathway respectively. Hemodialysis itself induces protein catabolism due to the bioincompatibility of certain membranes, such as cuprophan, which activate complement and cytokine production. However, the use of more biocompatible hemodialysis membranes improves nutritional status. During hemodialysis, nutrients are lost in the dialysate, including free amino acids (4-9 g/session), polypeptides (2-3 g/session), water-soluble vitamins, carnitine, and trace elements. Polypeptide losses are increased with high permeability membranes.

Diagnosis of nutritional status in renal failure

There is no single reliable nutritional parameter in patients on dialysis. Diagnosis of malnutrition should thus be based

Table 1 Causes of malnutrition in dialysis

Anorexia and low intake
Hormone changes (insulin and GH resistance)
Metabolic acidosis
Hypercatabolism
Frequent hospitalizations
Multiple drugs
Socioeconomic status of patient
Dialysis-related factors: inadequate dialysis (Kt/v < 0.8), bioincompatible membranes, loss of amino acids and proteins (carnitine), trace elements, and vitamins in dialysate
Frequent peritonitis in ambulatory peritoneal dialysis

Table 2 Interventions to treat and prevent malnutrition in dialysis

Adequate dose of dialysis
Biocompatibility of hemodialysis membranes
with peritoneal dialysis solutions with amino acids
in continuous peritoneal dialysis
Diet counseling
Nutritional supplements
Intradialytic oral nutrition
Nocturnal enteral feeding via gastrostomy
Growth factors: GHrh and IGF-1rh
Intradialytic parenteral nutrition
Total parenteral nutrition

on the use of several parameters and, most importantly, on the longitudinal follow-up of several parameters in a given patient. The normalized protein catabolic rate (nPCR) reflects protein intake under conditions of neutral nitrogen balance. Hypoalbuminemia is a late sign of malnutrition due to the long half-life of albumin and may also vary, depending on blood volume. Despite this, several studies have shown a negative correlation between plasma albumin and mortality. Retinol binding protein and prealbumin are excreted through the kidney, and their reference values are higher in dialysis patients. "Normal" values must therefore be considered "inadequately low" in this population. Moreover, prealbumin levels lower than 30 g/L suggest malnutrition in patients on hemodialysis. Total body protein content is the most physiologically relevant nutritional parameter, and is also a determinant of malnutrition. Nutritional interventions are thus aimed at achieving an improvement in malnutrition by increasing protein synthesis and/or decreasing protein catabolism in order to maximize body protein stores.

Methods for preventing and treating malnutrition in dialysis

Different approaches, summarized in Table 2, have been used to prevent malnutrition in dialysis patients. Such interventions range from diet counseling by specialized staff to the use of oral supplements adapted in their composition to the specific requirements of these patients. Clinical guidelines include other options such as the use of anabolic agents or switching to daily dialysis[8].

In the specific case of children with chronic renal failure, these requirements cannot always be met, and consequently, home nocturnal enteral feeding has often been used. If this is expected to be required for longer than 2-3 months, percutaneous endoscopic gastrostomy should be performed[9].

Intradialytic parenteral nutrition

Recent studies suggest that nutrient supplementation by the oral or parenteral route during the dialysis process may compensate for a relatively inadequate protein and energy intake. The high flow that occurs in the dialysis fistula (IDPN)permits us to consider it almost as a central line, thus allowing for the administration of parenteral nutrition with a high osmolality. In addition, the dialysis time is used for giving the patient this type of nutrition. The classical Capelli et al study[10] showed an improved survival rate in patients treated with IDPN, associated with increased albumin levels. Chertow et al[11] conducted a retrospective study of more than 1,500 patients given IDPN. Patients receiving this nutritional support had a lower risk of death. In the Cano et al study[12] of 26 patients, administration of IDPN for three months was associated with significant increases in body weight, muscle circumference, and albumin levels. Moreover, a spontaneous increase in intake occurred in the treated group. Navarro et al[13] randomized 17 patients to a parenteral amino acid supplement (25.7 g) with HD three days a week or with no supplementation. Albumin and transferrin levels significantly increased at three months, but there were no changes in the anthropometric parameters. Studies showing that IDPN is effective for reversing catabolism associated with HD were subsequently reported[14]. The Spanish Society of Nephrology (SEN) and the Spanish Society of Parenteral and Enteral Nutrition (SENPE) have reached a consensus on the indications, contraindications, and limits of IDPN[15]. This consensus considers IDPN as a valid alternative to other types of nutritional support where these have not been effective. It does however emphasize that IDPN is a partial nutritional support measure which is only useful when combined with other oral or parenteral support because it only provides some 3,000-4,000 kilocalories weekly, which is clearly insufficient. Thus, IDPN cannot be considered as a single nutritional support (Table 3), despite the fact that its composition as regards the presence and balance of the three basic nutrients is perfect. The problems inherent to this approach are cost and the need for long-term treatment. In addition, part of the amino acids administered are dialyzed and lost in the dialysis session. Other side effects

Table 3 Recommended composition of intradialytic parenteral nutrition by dialysis session (SEN-SENPE consensus)[5]

Protein: 0.8 to 1.2 g/kg (with/without 20-30 g of glutamine)
Non-protein calories (1,000-1,200 kcal):
Carbohydrates: 150-175 g
Lipids: 40-50 g (oleic acid-rich lipid emulsions are recommended due to their high alpha-tocopherol content)
Non-protein kcal/g of N2 ratio of 100-160:1
Calorie density: 1-1.2 kcal/mL
Multivitamin solutions (water and lipid soluble vitamins)
Carnitine (1 g) in dyslipidemic patients
No electrolyte provision
Individualized phosphorus provision
Insulin (1 U per 10 to 4 g of glucose)
Infusion rate: 250 mL/h

such as nausea, hypoglycemia, and hyperlipidemia[16] and infection problems are uncommon.

A systematic review to assess the effect of IDPN on survival or quality of life found only three randomized, controlled studies, only one of which assessed the prior objectives. The authors concluded that the available scientific evidence was insufficient to show either a clear benefit or harm to survival[17]. Studies with IDPN have been criticized, with their limitations regarding experimental design, low sample size, lack of controls, lack of oral intake monitoring, recruitment of patients with no frank malnutrition, or short duration of nutritional support being given as the main reasons why no definitive conclusions could be drawn[18].

Oral supplementation and intradialytic oral nutrition

Oral nutritional supplementation (ONS) is a good anabolic nutritional intervention because it is easily available and is also more physiological. However, despite its potential benefits, a strikingly low number of studies have assessed its impact on protein metabolism in renal patients, maybe because of the difficulty in controlling oral intake, individual differences in each patient, study design problems, treatment noncompliance, and the different composition of the supplements studied.

While the anabolic effects of IDPN have been clearly shown, they appear to be limited to its administration period, with no persistence of anabolism once infusion has been stopped. IDPN is also costly, and alternative approaches to nutritional support in these patients have been sought due to its potential side effects. A systematic review by Stratton et al[19] including 18 studies, five of which were randomized and controlled, concluded that enteral nutritional support to HD patients by both oral and tube feeding increased total energy intake, of both protein and energy, and increased serum albumin levels by 0.23 g/dL with no side effects in plasma electrolytes (potassium and phosphorus), and so could improve prognosis.

The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines[20] state that oral supplements are the preferred way for refeeding patients on HD.

Based on our clinical practice, such supplements should be tried in any patient with a poor general condition at risk for malnutrition, and an attempt should be made to adapt them to the patient's diet. These supplements should be especially designed for patients with renal failure: this requires a high energy density (2 kcal/mL) to limit water supply, a high protein content, restricted potassium, sodium and phosphorus content, absence of aluminum, and enrichment in vitamin D and folic acid. In some patients with a minimum food intake, treatment with low sodium supplements not especially designed for renal failure may be attempted, keeping in mind that volume should be limited and serum potassium levels should closely be monitored because of the risk of hyperkalemia. It appears that administration of nutritional supplements during dialysis, so-called intradialytic oral nutrition (IDON), may be advantageous because it is associated with improved compliance and it is at this time that catabolism is increased.

More than 10 years ago, Kuhlmann et al[21] randomized 8 malnourished HD patients to receive, in addition to their standard diet, oral nutritional supplements in order to increase their intake by 25% or 10% for three months. Significantly increased serum albumin levels were seen in the supplemented group. Cockram et al[22] compared the safety and tolerability of three different formulas used as the only nutritional source in 79 HD patients with a normal nutritional status. During the first study week, gastrointestinal symptoms, urea kinetics, and biochemical data were assessed while patients were on their standard diet. The same data were collected during the final two weeks while participants were taking 35 kcal/kg current weight/day by the oral route from three different nutritional formulas, a standard and two specific formulas. All three groups had achieved a mean energy and protein intake of approximately 35 kcal/kg/day and 1.25 g protein/kg/day by the last 10 study days. No changes in gastrointestinal symptoms, stool frequency, or urea kinetics were found during intake of enteral nutrition products as compared to baseline. However, no improvement in serum phosphorus levels and calcium-phosphorus product was achieved with specific formulas as compared to the standard product. In the Sharma et al study[23], non-diabetic patients on HD with a body mass index less than 20 kg/m^2 and serum albumin less than 4.0 g/dL were randomized to a control group which was subject to adequate monitoring including intake recording and nutritional counseling for the prescribed diet (protein intake of 1.2 g/kg/day and energy intake of 35-40 kcal/kg/d) or to two other treatment groups which additionally received a nutritional supplement after dialysis providing 500 kcal and 15 g of protein (a home-made and a dialysis-specific supplement) for 30 days. All these groups experienced improvements in dry weight and body mass index, but the supplemented groups showed a significant increase in albumin levels and performance status, as assessed on the 10-point Karnofsky scale (from 8.0 to 8.4, as compared to a change from 8.1 to 8.0 in the control group).

In France, Fouque et al[24] assigned 86 HD patients to standard treatment or ONS for three months. No statistically significant changes were found in dietary intake or albumin or prealbumin levels. However, patients in the supplemented group did not show electrolyte changes and impairment of nutritional status was prevented in them, as assessed by Subjective Global Assessment. They also experienced an improvement in their quality of life.

Other non-randomized studies have also assessed the role of IDON. Thus, Cuppari et al studied 10 HD patients before and after three months of oral supplementation and found significant increases in weight (+1.5 kg; 3%) and fat mass, but not in muscle mass[25]. Beutler et al[26] assigned 11 HD patients to nutritional supplementation and diet counseling, while only diet counseling was given to other patients. Serum albumin levels significantly improved at 4 months from 3.2 ± 0.8 to 3.32 ± 0.8 mg/dL in the supplemented group, but remained unchanged in the control group.

In the Patel et al study[27], 17 HD patients with a low protein catabolic rate and a protein intake less than 1.2 g/kg body weight received dietary supplements for two months. Protein catabolic rate and protein intake improved at 2 and

6 months as compared to baseline, but no changes were seen in nutritional status.

Wilson et al[28] showed that nutritional repletion occurred more rapidly and was maintained for a longer time in HD patients with mild hypoalbuminemia receiving diet counseling together with nutritional supplementation as compared to those given diet counseling only.

In the Caglar et al study[29], IDON improved various nutritional parameters, including albumin and prealbumin levels, as well as scores in Subjective Global Assessment, in patients with PEM.

Kalantar-Zadeh et al conducted a controlled study of HD patients with hypoalbuminemia given IDON consisting of a Nepro can and an Oxepa can (Abbott Labs.) for 4 weeks; IDON was associated with a significant increase in serum albumin levels[30].

A review of both oral and parenteral intradialytic nutrition by Bossola et al[31] identified 34 studies published in the MEDLINE and PubMed databases, both randomized and comparative, non-randomized trials, including studies where patients acted as their own controls (3,223 patients). Seventeen studies used oral supplements (778 patients), and the other 17 studies used IDPN (2,475 patients). Oral supplements were shown to improve albumin and other nutritional parameters, but there were no adequate data about long-term mortality. On the other hand, IDPN improved albumin and body weight, but did not affect survival in the only study conducted with an adequate population sample.

In a series of metabolic studies, Pupim et al[32] attempted to assess whether IDON or IDPN could compensate for protein loss in skeletal muscle and the whole body which occurred as a consequence of HD, that is, if they were able to achieve net protein anabolism. For this, these authors studied protein metabolism (synthesis and catabolism) by dilution and enrichment of phenylalanine across the forearm in 8 HD patients for three different HD sessions, one with IDON, another with IDPN, and a third control session where no nutritional supplement was administered. IDON was administered with a protein content and a volume similar to the nutritional content of IDPN. Specifically, two cans of a specialized complete formula with restricted fluid and electrolytes (NEPRO, Abbott Laboratories) were administered, 5 spoonfuls of powder protein (PROMOD, Abbott Laboratories)being added. IDON provided a total of 474 mL and 1,090 kcal, including 57 g of amino acids, 48 g of lipids, and 109 g of carbohydrates. IDPN provided amino acids at a 15% concentration, dextrose at a 50% concentration, and lipids at a 20% concentration, globally providing 525 mL and 188 kcal/h, including 59 g of amino acids, 26 g of lipids, and 197 g of carbohydrates. Nutritional supplementation administered by both the oral or intravenous routes was shown to improve anabolism and to be able to compensate for the catabolic effects of HD. It should be noted that these elevations occurred despite a potential increase in amino acid losses in dialysate.

It appears possible that increased plasma amino acid concentrations are one of the factors which promote a positive protein balance[33]. However, muscle protein stores do not only depend on nutrient intake. Insulin also plays a significant role in the control of nutrient deposits. Specifically, circulating insulin influences carbohydrate homeostasis, increasing glucose transport at muscle cell level, but also glucose utilization, and regulates protein metabolism by stimulating amino acid transport, promoting muscle and whole body protein synthesis and inhibiting proteolysis. These effects are amplified when there is a concomitant increase in the availability of amino acids and insulin, as occurs when IDPN or IDON is administered, resulting in a decreased proteolysis and an increased protein synthesis. Moreover, insulin appears to play a critical role in the metabolic response associated with IDPN because, once infusion is stopped, insulin concentration returns to baseline values simultaneously with a reversion of the net protein balance. With IPON, however, insulin concentrations remain high during the period subsequent to HD. Net protein balance in skeletal muscle also remains high. It may therefore be concluded that IDON achieves a clear benefit as compared to IDPN in terms of muscle protein homeostasis because it is able to reverse the elevated net protein catabolism maintained in the post-dialysis period.

The FINE study[34] is the study with the largest patient sample, and was also conducted with an excellent methodology. FINE investigators randomized 186 HD patients with PEM to receive for one year IDPN and oral supplementation or oral supplementation alone. Oral supplements provided 500 kcal/day and 25 g/day of protein. Supplementation was intended to achieve an intake that met the recommendations of 30-35 kcal/kg/day and 1.2 g/kg/day respectively. The primary objective and two-year mortality were similar in both groups (39% in the control group and 43% in the IDPN group), which suggests that oral supplementation is as effective as IDPN when oral intake is possible. Increased prealbumin levels in both groups were associated with decreases in two-year mortality and hospitalization rates, thus providing the first evidence of a direct relationship between response to nutritional treatment and improved prognosis. Thus, despite the negative result in the primary study objective, there are several important observations which give reasons for optimism. First, the nutritional supplementation route, oral versus combined oral and parenteral, has no impact on survival provided an adequate amount of protein and calories is given, and has no effect either regarding the improvement of nutritional parameters.

Second, the results show that nutritional support improves nutritional markers in HD patients with PEM if the nutritional requirements recommended by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative-KDOQI[35] are met (more than 1.2 g/kg/day and more than 30 kcal/kg/day respectively). It should be noted that serum albumin improvement in FINE (~2 g/L) was similar to that reported in most other reported studies concerning the efficacy of nutritional support[19]. These data also support the suitability of KDOQI recommendations for calorie and protein intake. Finally, the results suggest that nutritional interventions improve survival in patients on HD. This study has been criticized because of the lack of a control group with no supplementation. However, it does not currently seem ethical to deprive participating patients of nutritional support. A comparison of the two-year mortality rate in the study (42%) with that recorded in the

European registry, adjusted to one of the inclusion criteria of the FINE study (albumin levels less than 35 g/L; 49%), showed a 15% improvement in mortality, which represents a higher survival benefit than with any other treatment proposed for HD patients. Finally, these results imply that some routinely used parameters, such as serum prealbumin levels, may be used as markers not only of nutritional status, but also of the probability of hospitalization and survival.

A significant aspect in oral nutritional supplementation is compliance with the administered formulas. Most studies, as well as our personal experience,have reported a high non-compliance rate, 25% on average but up to 49% in some studies. This occurred despite the fact that patients were participating in a research study with strict monitoring by specialized staff.

Compliance rates in FINE were 60% and 75% in the oral supplementation and IDPN groups respectively. However, despite this poor compliance all patients achieved the goal of protein and calorie intakes higher than 1.2 g/kg/day and 30 kcal/kg/day respectively, and albumin and prealbumin levels were also increased.

As regards the underlying hormone changes, IDPN has been shown to induce higher glucose and insulin levels and also a greater suppression of levels of ghrelin, the orexigenic hormone par excellence, which does not appear to be advisable in malnourished patients[36]. In addition, the incretin system, and specifically GLP-1, does not appear to play a significant role in the regulation of carbohydrate metabolism during intradialytic nutrition[37].

The effect of exercise was also tested in a long-term study (6 months) to assess whether it could improve the results of IDON[38]. Thirty-two patients on HD with a mean age of 43 ± 13 years were randomized to IDON alone or combined with resistance exercise, performed before the session. IDON consisted of two cans of a lactose-free complete formula (Nepro, Abbott Laboratories) during dialysis sessions. Each can contained 236 mL and 480 kcal (66.8 kcal of protein, 211.2 kcal of carbohydrates, and 204.3 kcal of fat). After the 6-month intervention period, no changes were seen in either group regarding lean mass or body weight. However, body weight and muscle strength increased at the end of the study period in all patients. Thus, although this study showed no additional benefits when long-term exercise was added, it did show an increase in weight and muscle strength as compared to baseline with IDON.

In conclusion, malnutrition in dialysis is common and multifactorial. Intradialytic nutrition is an excellent strategy for preventing and treating nutritional changes in the HD population. Both intradialytic oral supplementation and parenteral nutrition may be used to provide a high amount of nutrients in a short time period to malnourished patients on dialysis, but oral supplementation should be the procedure of choice in malnourished patients. Prospective, controlled studies are needed on the effects of the different forms of nutritional support on nutritional status and morbidity and mortality in patients on dialysis.

Conflict of interest

The authors state that they have no conflict of interest.

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