Nutritional Requirements in Maintenance Hemodialysis

Denis Fouque

There is a high prevalence of nutritional disorders in maintenance hemodialysis patients. This fact has recently been confirmed because larger routine assessments of MHD patients body composition are now performed. Food records and dietary interviews show spontaneous low intakes of protein and energy in many patients. An increasing dialysis dose above a Kt/V (single pool) of 1.5 may not improve patients nutritional intakes. Inflammation may further impair the balance between protein synthesis and catabolism and cause anorexia. In response to these abnormalities, the management of energy, protein, vitamins, and trace elements intake will be discussed with special emphasis on calcium, phosphorus, enteral support, and parenteral nutrition.

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Index Words: Maintenance hemodialysis; nutrition

Although Dr Scribner warned physicians about the possibility of nutritional disorders shortly after he began the first renal replacement treatments in the 1960s, research on the optimal nutrient intake has been a rather neglected aspect of maintenance dialysis treatment until only a few years ago. Indeed, since the 1990s, it has become apparent that many kidney disease patients, including those undergoing maintenance dialysis treatment, presented with a mild to moderate malnutrition profile. Most cross-sectional studies have reported that 10 to 50% of patients were malnourished based on various clinical and biological parameters.

One of the major cornerstones in nutritional therapy is in fact that there is no single parameter for diagnosing protein-energy malnutrition. Thus, as compared with dialysis dose quantification, nutritional status is more difficult to assess. In addition, a number of routine nutritional indices used in other disease state conditions can not reliably be used in the context of renal disease. For example, bioimpedance measurements can be more difficult in patients with renal failure because of the peculiar hydration characteristics of such patients. Physicians are left with such tools as body weight, anthropometry, subjective global assessment, dietary interviews and food questionnaires, and for research purposes, dual energy x-ray absorptiometry.

Interpretation of serum measures of nutritional status is complicated by the influence of inflammation on many of these values. Indeed, probably the most disturbing aspect of malnutrition in renal disease is the fact that in addition to a reduced nutrient intake, there is in some patients a complex metabolic dysregulation secondary to chronic inflammation. This profile can engender resistance to anabolism, and thus chronic cachexia may develop and may be difficult to reverse.

Hemodialysis Patients Have Reduced Appetite

One of the major nutritional problems is the satiety that patients feel with a lower threshold of food intake than in healthy adults. This fact has been nicely illustrated by Wright and al, who analyzed patients food records and satiety indexes on dialysis and nondialysis days. As illus-
trated in Figure 1, patients had a similar feeling of satiety as compared with healthy volunteers but a much lower food intake, both for protein and energy. Of interest is that nutrient intakes were probably reduced only on on-dialysis days and were normal on off-dialysis days because all of the parameters reflecting appetite seemed to indicate fullness and reduced hunger only on the on-dialysis days (Fig 1). In addition, little research has been performed on the intakes on the seventh day (eg, the last day of the long interdialytic interval); it is possible that a spontaneous reduction in intake occurs because of either fears of overhydration, dyspnea, or uremic toxicity.

Very low spontaneous dietary intakes have been recently reported in the HEMO study.5 Indeed, based on dietary records from about 1,000 patients at inclusion, the mean intake was 24.1 and 21.8 kcal/kg/d and 0.98 and 0.89 g protein/kg/d for men and women, respectively.5 If this is compared with the recommended energy and protein requirements, it indicates that approximately 90% and 50% of MHD patients have insufficient intakes of energy and protein, respectively.

**Which Dose/Frequency of Dialysis Induces Nutritional Improvement?**

Although insufficient dialysis is associated with a low protein nitrogen appearance (PNA, also known as protein catabolic rate), does an increase in dialysis dose above current standards improve nutritional intake and/or status? In the recently published HEMO randomized clinical trial, during standard thrice weekly hemodialysis, neither an increased dialysis dose of a Kt/V (equilibrated) of 1.53 as compared with 1.16 nor the use of more biocompatible membranes reduced the patients' mortality,6 improved serum albumin levels or increased nutrient intake. Another recent cross-sectional study from Kalantar-Za-deh et al7 reported that nPNA increased as Kt/V (single pool) rose from 1.2 to 1.5; however, no further increase in nPNA was observed as Kt/V rose further, above 1.5 (Fig 2).7 Thus, increasing dialysis dose may not be sufficient to improve the nutritional status of malnourished MHD patients already receiving an adequate dialysis dose (eg, equal or superior to a Kt/V of about 1.25-1.5).

Another important parameter is the dialysis frequency. Recent programs of more frequent dialysis, either short daily or long nocturnal, have all shown a substantial increase in nutrient intakes, with reduced interdialytic weight gain, better hemodynamic stability, and general well-being.5,9 In these studies, anthropometric as well as biological measures (ie, serum albumin, prealbumin, cholesterol) rapidly improved when the patients’ treatment was changed, in a non-randomized fashion, from standard thrice weekly to 6 weekly sessions. Thus, there are unidentified factors related to dialysis frequency.

**Figure 1.** The appetite profile of maintenance hemodialysis patients based on subjective indexes and food reports, according to the dialysis schedule. D, dialysis day; ID, nondialysis day; Con, healthy volunteers. *P < .05 versus controls.

<table>
<thead>
<tr>
<th>Score</th>
<th>MHD</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Protein (g/kg/d)</td>
<td>0.96±0.3*</td>
<td>1.15±0.3</td>
</tr>
<tr>
<td>Energy (kcal/kg/d)</td>
<td>26.5±8.6*</td>
<td>30.4±9.9</td>
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and not dialysis dose per se, which appear to improve nutritional status in MHD patients.

Is Inflammation Associated With Weight Loss?

There is ample evidence that inflammation directly causes catabolism. In addition, inflammation may induce anorexia. Indeed, investigational studies have shown that infusion of inflammatory cytokines (tumor necrosis factor and interleukin [IL]-1) into hamsters resulted in a dramatic reduction in food intake. Kaizu et al. reported that in 45 MHD patients followed for 3 years, body weight and serum albumin declined in those who presented with a serum IL-6 level greater than 10 pg/mL as compared with those who had an IL-6 lower than 10 pg/mL. Kaizu et al. reported that in 45 MHD patients followed for 3 years, body weight and serum albumin declined in those who presented with a serum IL-6 level greater than 10 pg/mL as compared with those who had an IL-6 lower than 10 pg/mL. In a recent prospective study in 83 MHD patients, Kalantar-Zadeh and colleagues showed that serum C-reactive protein (CRP) and a malnutrition-inflammation score was positively associated with 1-year mortality and hospitalization rates and negatively related to lean body mass. In a subsequent extended study in 331 MHD patients, the MIS and serum CRP and tumor necrosis factor α were negatively correlated with the patient’s appetite. Thus, there is growing evidence that inflammation is associated with poor nutritional intake in maintenance dialysis patients.

Hemodialysis Patients Often Cannot Ingest Their Nutritional Requirements

Apart from a spontaneous reduction in nutrient intake as a result of anorexia, we have reported that the nutrient intake of patients is insufficient when they are hospitalized for whatever reason. Patients are compelled to fast for examinations or procedures, or in response to disease-induced anorexia or impaired gastrointestinal function. Many older patients have dental problems, which may impair nutrient intake during their hospital stay. During a 1-week survey in a renal ward, we have estimated that maintenance hemodialysis patients will approximately miss 20% of their lunches and dinners, resulting in a 3,000 kcal weekly debt.

What Are the Energy and Protein Requirements for MHD Patients?

Many studies have reported energy intakes as low as 22 to 24 kcal/kg BW/d in MHD patients. There is no metabolic or disease-related reason for not giving a
standard energy intake to stable adult maintenance dialysis patients. Indeed, based on resting energy expenditure measurements, metabolic needs are similar to those of normal adults (eg, 35 kcal/kg BW/d). Energy balance studies confirmed that positive nitrogen balance can be reached in sedentary individuals about 60 years of age or older with daily energy supplies greater than 30 kcal/kg.\textsuperscript{15}

The dialysis procedure itself increases protein needs above the level of 0.6 g protein/kg BW/day that is normally required to reach neutral nitrogen balance in pre–end-stage renal disease adults. Based on nitrogen balance studies, a minimum of 1.2 g protein/kg BW/d should be given to ensure neutral protein balance in MHD patients. Half of this intake should be of high biological protein (ie, from animal origin, meat, fish, or dairy products).\textsuperscript{16}

These intakes may not be easily met for the following reasons. Patients are frequently anorectic during the last weeks or months preceding the beginning of dialysis. In addition, the dramatic life change may have psychological impacts that prevent them from behavior modifications, including dietary changes. This observation is of special interest because any delay in increasing protein and energy intakes will induce a loss of energy stores and protein mass. Patients may then need months to recover from this acute stress. Based on these observations, a nutritional care plan should be set up no later than 1 to 2 weeks after the start of dialysis and implemented at regular intervals.\textsuperscript{17}

As indicated earlier, attention should be focused on energy intake as well as protein intake. In maintenance dialysis patients, for unexplained reasons, energy intake appears to be more greatly reduced than protein intake. It has been reported during the HEMO study that 78% of the patients had energy intakes lower than 28 kcal/kg BW/d, a value considered to be insufficient itself, whereas only 59% of patients had a protein intake lower than 1.0 g/kg BW/d. Energy intake is particularly difficult to monitor, since, whereas protein intake is indirectly assessed by the regular use of protein nitrogen appearance (PNA), energy intake is generally assessed by dietary diaries and interviews. This reinforces the importance of providing MD patients with surveys of dietetic intakes at regular intervals.

**Should Supplements Be Prescribed to Increase Nutrient Intake?**

When diet interviews, food diaries, or normalized PNA indicate that intakes do not meet the recommended daily intake, oral nutrient supplements are often proposed. Overall, there is a common belief that these supplements are not well accepted, and their administration is associated with poor compliance. Furthermore, they are costly and not always covered by health insurances. However, most of the short-term studies report benefits from energy and/or protein or amino acid supplements.\textsuperscript{18-25} In a cross-sectional analysis of 3 university hospitals that treated over 100 MHD patients, almost 50% of the patients received oral supplements.\textsuperscript{26} The energy and protein intake obtained through these supplements provided each week between 1,500 to 2,200 kcal and 110 to 160 g protein. Only 25% of the supplements were withdrawn because of the patients’ personal initiative.

Recently, Veeneman and colleagues\textsuperscript{27} administered a liquid meal to 8 MHD patients that was composed of yogurt, protein, and cream containing a total of 1,100 kcal and 45 g protein split into equal portions that were taken every 30 minutes over a 4-hour dialysis session.\textsuperscript{27} Intake of this oral supplement was associated with a reversal of the net protein loss and negative protein balance. This effect was mainly attributed to the fact that plasma amino acids were maintained in the “fed”
range (ie, higher than during the postabsorptive state), whereas a regular dialysis session induces a sharp drop in plasma amino acids, which is believed to blunt protein synthesis.27 Thus, despite the taste, financial costs, and lassitude, this approach, best superintended by the renal dietitian, should be considered for moderately malnourished MHD patients.

Is Parenteral Administration Indicated in MD Patients?

Intradialytic parenteral nutrition (IDPN) has been proposed during the course of the dialysis session. Indeed, the venous line can be used without the need for extra puncture or a central line, and nutrient administration can be repeated 3 times a week. For example, a mixture of lipids (50 g), hypertonic glucose (125 g), and amino acids (40 g) is generally proposed in a one-liter format every dialysis session, with the corresponding adaptation in ultrafiltration.28 One gram of sodium chloride may be added every hour to avoid hyponatremia. IDPN administration has been associated with a strong improvement in protein anabolism when it is measured during the dialysis session.29 However, there are limitations to this treatment. First, the duration of infusion should not be shorter than 4 hours when lipids are administered to not exceed the rate of plasma triglyceride clearance and avoid the development of hypertriglyceridemia and possibly the attendant nausea or malaise. Second, if a high intake of carbohydrates is provided, hyperglycemia may occur during the infusion; this can be followed by hyperinsulinemia and possibly hypoglycemia at the end of the dialysis, particularly if the infusion is terminated before dialysis is completed. Third, over the long-term, chronic dyslipidemia may become more abnormal after starting IDPN. Another major concern is the efficacy of this nutritional intervention; indeed, there are no good quality prospective randomized controlled clinical trials that have evaluated the potential value of IDPN.28,30-33 The total amount of nutrients administered with each administered IDPN treatment are limited to about 800 to 1,000 kcal per session 3 times per week, which corresponds to a maximum of 3,000 kcal weekly. Thus, if a patient’s spontaneous intake is too low (eg, less than 20 kcal/kg/d) or his nutritional status is severely impaired, IDPN may not provide sufficient nutrients to rectify the malnutrition.

Vitamins and Trace Elements (Table 1)

Abnormal renal metabolism, insufficient intake, and/or intestinal absorption and dialysis losses may cause vitamins and trace elements deficiencies. The most frequently altered vitamins are water soluble and also vitamin D.

Vitamin B6 (pyridoxine) is often reduced in plasma and red cells of patients undergoing maintenance dialysis if patients do not take vitamin B6 supplements.34,35 Vitamin B6 supplements have been reported to improve immune function. Pyridoxine is also involved in homocysteine metabolism. However, it is unclear whether pyridoxine supplements per se are able to decrease plasma homocysteine levels because most studies examined the effects of a combined administration of pyridoxine and folate. A daily supplement of 10 mg of pyridoxine hydrochloride is recommended and results in normalization of the transamination activation index.35 Higher doses such as 1 to 5 g per day have been associated with severe neuropathy in individuals without renal failure. Thus, when progressive neuropathy occurs (an infrequent symp-
Table 1. Recommended Nutrient Intakes for Maintenance Hemodialysis Patients

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Requirement</th>
</tr>
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<tbody>
<tr>
<td><strong>Protein</strong></td>
<td>1.2 g/kg/d (50% of high biological value)</td>
</tr>
<tr>
<td><strong>Energy</strong></td>
<td>35 kcal/kg/d</td>
</tr>
<tr>
<td><strong>Fat (percent of total energy intake)</strong></td>
<td>30-40</td>
</tr>
<tr>
<td><strong>Polyunsaturated/saturated fatty acid ratio</strong></td>
<td>1.0:1.2</td>
</tr>
<tr>
<td><strong>Carbohydrate</strong></td>
<td>Rest of nonprotein calories</td>
</tr>
<tr>
<td><strong>Total fiber intake</strong></td>
<td>20-30 g/d</td>
</tr>
<tr>
<td><strong>Minerals</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>1,000-1,500 mg/d</td>
</tr>
<tr>
<td>Potassium</td>
<td>40-70 mEq/d</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>8-17 mg/kg/d</td>
</tr>
<tr>
<td>Calcium</td>
<td>1500 mg/d†</td>
</tr>
<tr>
<td>Magnesium</td>
<td>200-300 mg/d</td>
</tr>
<tr>
<td>Iron</td>
<td>&gt;10-18 mg/d</td>
</tr>
<tr>
<td>Zinc</td>
<td>15 mg/d</td>
</tr>
<tr>
<td>Water</td>
<td>750-1,500 mL according to diuresis</td>
</tr>
<tr>
<td><strong>Vitamins (supplements to diet)</strong></td>
<td></td>
</tr>
<tr>
<td>Riboflavin</td>
<td>1.8 mg/d</td>
</tr>
<tr>
<td>Thiamin</td>
<td>1.5 mg/d</td>
</tr>
<tr>
<td>Niacin</td>
<td>20 mg/d</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>Pyridoxine HCL</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>3 µg/d</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>75-90 mg/d</td>
</tr>
<tr>
<td>Folic acid</td>
<td>1 mg/d</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>No addition</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Depending on parathyroid hormone and bone status</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>15 IU/d</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>None</td>
</tr>
</tbody>
</table>

*Calculations are made on the basis of a standard body (SBW) weight taken from the NHANES 1983 tables. If the patient’s body weight is lower than 90% or greater than 120% of IBW, a corrected BW should be used (see K/DOQI†). †If calcium-based phosphate binders are administered, the daily amount of calcium element (from diet + supplement) should not be greater than 2,000 mg.

Vitamin E (tocopherol) has strong antioxidant properties. A recent randomized controlled trial (SPACE study) has addressed the potential benefit of a high-dose vitamin E supplement in MHD patients at high cardiovascular risk. After 2 years of a daily supplement of 800 IU of alpha-tocopherol, there was a statistically significant 50% decrease in a cardiovascular composite index as compared with the placebo group. Although serum levels of vitamins or lipid fractions were not mea-
sured, it may be worth considering treating high cardiovascular risk dialysis patients with vitamin E. However, some studies in individuals without advanced CRF show no benefit to giving vitamin E supplements.37,38

Thiamin (vitamin B1) deficiency has been rarely described in dialysis patients and may mimic such neurologic symptoms as confusion or encephalopathy. Surgical intervention, infection, and a large quantity of glucose administration may increase the need for thiamin. A routine dietary thiamin intake of 0.5 to 1.5 mg/d can be supplemented with 1.5 mg of thiamin hydrochloride per day.

In MHD patients not taking folic acid supplements, folate may be reduced in serum and red blood cells of dialysis patients. Before the erythropoietin era, abnormal red cell precursors in blood often decreased with folic acid supplements. On the long-term, secondary to possibly decreased absorption from intestinal mucosa, medications that compete with or antagonize folate, and dialysate losses of folate, it is recommended that 1 mg of folic acid be given daily. It is unclear whether larger amounts of folate should be given when EPO treatment is started. Whether folate supplements should be prescribed to reduce elevated plasma homocysteine levels and improve cardiovascular morbidity and mortality is still an unanswered question. Five to 10 mg of folic acid have been shown to reduce plasma homocysteine levels by about two thirds, although these doses do not restore plasma homocysteine to normal levels. A dose-ranging study in MHD patients showed that 30 to 60 mg of folic acid daily administered was no more effective at decreasing plasma homocysteine than 15 mg per day.39 Side effects such as headache or nausea have been reported, and divergent results have been published in nonrenal patients.40 Thus, more robust evidence is still awaited to ascertain the value of administering larger amounts of folate to MHD patients.

Trace elements needs are not well defined in hemodialysis. Because the kidney has a major role in trace element clearance, it is possible that in CRF patients, accumulation of some trace elements occur.41 Also, because trace elements are strongly bound to serum proteins, small quantities of trace elements contained in the dialysate may be taken up against a concentration gradient.

Iron management has become a priority through anemia control. Iron is now routinely prescribed before and during the start of erythropoietin treatment because erythropoietin may rapidly deplete iron stores by enhancing erythropoiesis. Current guidelines suggest that iron should be given to maintain serum ferritin in the range of 200 to 500 μg/L and hypochromic red cells lower than 2.5% (equivalent to a transferrin saturation ratio [TSAT] of 30%-40%). Ferrous sulfate, 300 mg, may be given orally 3 times per day, taken one half hour after meals to reduce gastric discomfort. Some patients may develop nausea, constipation, anorexia, or abdominal pain. These patients may better tolerate ferrous fumarate, gluconate, or lactate. Because iron is poorly absorbed through the intestinal tract, iron may better be administered intravenously (eg, once weekly). There is some concern about the oxidative burst in polymorphonuclear leukocytes that follows the administration of high doses of intravenous iron that may induce an inflammatory response.42,43 More investigation is needed to clarify this point.

Zinc deficiency may occur in chronic renal failure and is reported to be associated with anorexia, diarrhea, and skin abnormalities. Dysgeusia and impotency have been improved by administration of zinc supplements in some but not all studies.44-48 A recent randomized study in MHD patients reported that a daily supplement of 2.2 mg
of zinc sulfate corrected serum zinc levels to normal levels and was associated with an increase in nPNA.49

Serum selenium levels have been reported to be reduced in MHD patients.50-52 Patients with a selenium deficiency may present with muscle pain and weakness, and more importantly, cardiomyopathy that may progress to intractable cardiac failure.53 Because selenium has strong antioxidant properties and might be involved in the prevention of cardiovascular symptoms and cancer, a trial of selenium supplements should be recommended in case of low serum selenium values. In short-term administration studies on MHD patients, selenate seems more efficiently absorbed than selenite.54

How to Monitor Calcium and Phosphorus Intakes?

If phosphorus intake is severely limited, protein intake will also decrease. Indeed, the ratio of dietary phosphorus/protein is roughly constant and ranges from about 10 to 13 mg phosphorus/g protein. Based on an optimal protein intake for MD patients, the daily amount of ingested phosphate will be approximately 1,000 mg. Although about 40% to 80% of ingested phosphorus is absorbed, a regular hemodialysis session can only clear 600 to 1,000 mg phosphorus, and most of this occurs during the first 2 hours of a dialysis treatment. Phosphorus clearance also decreases somewhat when the hematocrit is increased by EPO treatment. Thus, patients with adequate protein intake will eventually need oral phosphate binders to prevent a rise in serum phosphorus and concomitant increase in parathormone levels.

Whereas the optimal calcium intake may be more easily attained, the question of whether high intakes of calcium-based phosphate binders should be given to MD patients has been challenged by the recent study of Goodman et al55 showing rapidly progressing vascular calcification in young adults undergoing maintenance dialysis who received high doses of calcium based phosphate binders. The forthcoming K-DOQI guidelines on bone disease recommend that the total calcium intake be less than or equal to 2,000 mg daily (including the calcium contained in food). Thus, intake of calcium-containing phosphate binders should provide no more than about 1,500 mg of calcium per day. Noncalcium phosphate binders, such as sevelamer hydrochloride, may be useful in selected patients, alone or combined with calcium phosphate binders or noncalcium-containing phosphate binders.56,57

Effort should be made to increase phosphorus clearance and binding rather than solely limiting its intake, which may induce a limitation in protein intake. Short duration daily dialysis has been shown to increase weekly phosphorus clearance and decrease serum phosphorus by about 15% from 6.8 to 5.8 mg/dL (P < .05), despite a 40% increase in phosphorus intake from 980 to 1,330 mg/d and an important reduction in phosphate binders.8 Thus, new dialysis programs may help to reconcile intakes and clearances in uncontrolled hyperphosphatemic patients.

Alternate Strategies

Although beyond the scope of this article, recent studies have addressed the effects of anabolic compounds (eg, recombinant growth hormone and insulin-like growth factor-1, androgens) or new dialysis strategies such as more frequent dialysis.58 Promising results have been reported and suggest that some combination of nutritional support and pharmaceutical therapy may be used in the future to restore or improve nutritional status in malnourished MD patients.
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