Clinical Nutrition (2000) **19(3)**: 197–207

doi:10.1054/clnu.2000.0130, available online at http://www.idealibrary.com on IDEAL®

CONSENSUS REPORT

Expert Working Group report on nutrition in adult patients with renal insufficiency (part 1 of 2)

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Key words: chronic renal failure; nutritional treatment; hemodialysis; peritoneal dialysis,; renal transplantation; acute renal failure

Introduction

Uraemic patients are sensitive to the effects of malnutrition and nutritional therapy, which may affect quality of life, morbidity, mortality and the rate of progression of the disease. Kidney failure is unique among clinical conditions in that nutritional therapy allows good control of several consequences of the disease and has therefore the same clinical relevance as other types of medical therapies.

The main aims of nutrition interventions can be summarized as follows: 1) minimize uraemic toxicity; 2) avoid malnutrition; and 3) delay progression of kidney disease.

Producing an overview and detailed guidelines on nutrition in renal disease is complicated by the fact that the term 'renal disease' embraces a number of clinical conditions whose common features are a decrease in glomerular filtration rate and other derangements of the kidney physiology. The following clinical conditions – 1) early and advanced renal failure in conservative treatment, 2) nephrotic syndrome, 3) haemodialysis, 4) peritoneal dialysis, 5) renal transplantation, and 6) acute renal failure deeply differ as to pathophysiology and treatment, and need to be considered as separate topics. Moreover, the distinction between early and advanced renal failure, as well as the time to start dialysis treatment are not readily defined.

The paper has therefore been divided into two parts. The first part examines the prevalence, effects and mechanisms responsible for the development of protein-energy malnutrition in uraemic patients; the tools currently available for assessing nutritional status; the possible effects of the diet on the progression of kidney disease; the nutritional problems of patients with chronic renal failure in the pre-dialytic period. The second part will examine the nutritional therapy of patients on dialysis, patients with nephrotic syndrome, patients with acute renal failure and kidney transplant patients. Each topic includes a review of the literature, a summary of conclusions, an outline of the nutritional guidelines (where possible), and suggested topics for further research.

This paper was approved by the Educational Committee of the European Society of Parenteral and Enteral Nutrition (ESPEN).

Protein-energy malnutrition (PEM) in chronically uraemic patients

Prevalence of PEM in chronic uremia

Evidence of malnutrition is common in chronic uraemic patients on conservative treatment, maintenance haemodialysis (MHD), or peritoneal dialysis (1–4). Protein-energy malnutrition (PEM) in dialysis patients may be caused partially by an inadequate nutritional management of patients in the predialytic phase. In addition, long-term dialysis treatment is frequently complicated by PEM and this complication is linked to increased morbidity and mortality during dialysis (5).

Protein-energy malnutrition usually becomes clinically evident in chronic renal failure (CRF) patients when the glomerular filtration rate (GFR) is lower than 15–10 ml/min. However, more subtle metabolic abnormalities of intermediate metabolism can be demonstrated during the early phases of renal insufficiency (1, 6, 7). In the Modification of Diet in Renal Disease (MDRD) feasibility study, 21% of patients had a weight loss after a mean of 14 months of observation (8). Recently, a 40% prevalence of PEM was

found in patients with advanced renal failure at the beginning of the MHD treatment (9). Bergström (10, 11) observed signs of PEM in 10–70% of MHD patients and in 18–51% of continuous ambulatory peritoneal dialysis (CAPD) patients. Data from a cross-sectional study in CAPD patients in Europe and North America showed moderate and severe PEM respectively in 40 and 8% of the population (12). CAPD patients were found to be more severely malnourished than MHD patients (42 vs 30%) (13). Irregularities of protein metabolism have been found in the skeletal muscle of CAPD patients, who seemed clinically well nourished (1, 14). During CAPD there may be a normalization of body energy stores (body fat) without concomitant improvement of body cell mass (15). The results obtained during the MDRD study on 840 patients followed for 26 months (16) demonstrate that the low-protein diets and the very low-protein diets used for 2–3 years are generally nutritionally adequate and safe. No patient with moderate renal insufficiency and only two patients (0.8%) with more advanced renal insufficiency reached the stop points of the follow-up for nutritional reasons.

The characteristics of PEM in uraemic patients are variable, and large differences in the involvement of different body compartments have been described (17), the body fat stores and somatic and visceral proteins being most frequently compromised. More sophisticated methods are often required for early diagnosis of malnutrition. In the early phase of chronic renal failure subclinical modifications of nutritional status were found only at the cellular level (18). Measurement of body cell mass by determining total body potassium has revealed a 10% reduction in patients entering MHD (19).

Effects of PEM on morbidity and mortality

PEM in chronic renal failure is related to poor clinical outcome and to mortality (20–24), though it is difficult to distinguish a definite nutrition related cause for morbidity or mortality.

Low serum albumin in MHD patients has been found to be the strongest predictor of death risk (5, 17, 20, 25–29); albumin levels <30 g/L are associated with the worst prognosis, but levels between 30 and 35 also have a bad prognostic value (29). Other nutritional variables (anthropometry, body weight, transferrin, C-reactive protein, lymphocyte count, plasma amino acids, serum creatinine, etc.) have been related to mortality (29–32). Prealbumin plasma levels <300 mg/L have been associated with a higher mortality rate (30, 31).

The total body nitrogen (TBN) in dialysis patients is strongly correlated with mortality: in patients with low TBN (< 80% normal) the probability of death within 12 months is 4.1 times higher than in patients with TBN > 80% (33).

Besides metabolic effects and the influence on outcome, PEM itself has some negative effects on renal functions: it impairs the kidney's ability to eliminate acid and salt loads and reduces the renal plasma flow, the GFR and the urine concentrating capacity (34, 35). Proximal tubular function is impaired in PEM, as demonstrated by the increased amino acid and phosphate excretion as well as by increased tubular enzymuria (36).

Mechanisms responsible for malnutrition

The pathogenesis of PEM in patients with kidney failure is multifactorial. The principal causes are poor dietary intake, abnormal lipid and carbohydrate metabolism, amino acid imbalances, abnormal hormonal response, losses of nutrients, uraemic toxicity and catabolism. A relevant cause of malnutrition is inadequate nutrient intake. Uraemic patients, either on conservative, MHD or CAPD treatment, often develop an imbalance between intake and nutritional requirements. The low energy intake is particularly involved: despite nutritional recommendations (35 kcal/kg/day or more), a large percentage of patients eat less calories than prescribed (between 25 and 30 kcal in most studies) (1, 3, 37). Compliance to the protein prescription is also often inadequate in uraemic patients, the protein intake often being too high in predialysis patients and too low in MHD and CAPD patients. A spontaneous reduction in protein intake has been described in predialysis patients (38, 39) as their renal function decreased; for each 10 ml/min decrease in creatinine clearance, a reduction of the protein intake by 0.064 g/kg/day has been described (9). A relationship has recently been hypothesized between plasma leptin, anorexia, and body composition: leptin is related to body fat mass, and potentially to the insulin resistance often observed in CRF (40, 41).

A key role for metabolic acidosis (MA) has been clearly demonstrated in causing malnutrition: MA is a mediator of protein breakdown and amino acid oxidation (42) and proteolysis is related to its severity. Cortisol increases in MA, as well as BCKA dehydrogenase activity. Intracellular valine is directly related to blood pH. Acidosis stimulates ubiquitine mediated proteolysis and increases the m-RNA for ubiquitine and proteasome (43). MA has been shown to induce a negative nitrogen balance, to worsen nutritional status (44) and to decrease serum albumin synthesis (45). MA also impairs insulin activity and glucose utilisation, and its correction improves nitrogen and nutritional status (46).

Impaired protein metabolism and malnutrition are also related to hyperparathyroidism, insulin resistance, and growth factors deficiency (47–51).

Conclusions

Protein-energy malnutrition is frequent in uraemic patients, regardless of the treatment. It involves all the body compartments. PEM strongly affects both morbidity and mortality, and some cut-off values of prognostic significance have been indicated. The pathogenesis of PEM is multifactorial, though low nutrient intake, acidosis and increased catabolism play the strongest roles.

Evaluation of nutritional state in chronic renal failure

In the MDRD study the small, but significant decrease, of some nutritional indices, together with the decrease in pro-

tein and energy intake in all patient groups (16) strongly suggest the need for frequent nutritional monitoring in all renal patients; nutritional deficiencies should be identified before they become clinically relevant. There is no single parameter providing reliable information on the overall nutritional status (52), and nutritional assessment should evaluate body composition and function. Combined evaluations of dietary intake and compliance, as well as of anthropometric measurements, biochemical determinations, serum and cell-mediated immune responses, and assessment of body compartment status together with subjective global assessment (SGA) (53–55) or other combined nutritional indexes (56), can be utilized.

1. Assessment of dietary intake and dietary compliance: this is of crucial importance in all uraemic patients. Evaluation by a skilled dietician (by means of dietary interviews and three days recalls, or food diaries) is recommended (37, 57), since there is no other way of determining total energy intake and distribution of energy sources (lipids or carbohydrates). On the contrary, objective methods for measuring protein and phosphorus intake are well established. Urea nitrogen appearance, 'protein catabolic rate', urinary urea excretion and blood urea levels are directly related to protein intake in stable uraemic patients. Phosphaturia is also related to dietary intake of phosphorus (P), but the correlation is less close, depending on P absorption, use of oral P binders, Vitamin D status and hyperparathyroidism (58).
2. Anthropometry: these measurements may be influenced by a number of factors unrelated to nutrition.

   Body weight and body mass index. Severe biases hamper their validity as nutritional indices, i.e. a) lack of national or regional standards; b) dependence on the total body water content. However, knowledge of body weight and its time-related modifications are of great clinical value.

   Skinfold thickness and arm muscle circumference. In the absence of oedema or significant changes of body water, skinfold thickness is related to total body fat (59). Reproducible information is best given by measurements from multiple locations. Arm muscle circumference or area, corrected for age and sex are reliable indices of total body proteins and lean body mass, though the results are influenced by overhydration. Appropriate reference values are required for elderly patients, because of the age-related changes in body composition.
3. Plasma protein concentrations: they are indices of protein synthesis, mainly by the liver. Serum albumin has been recently identified as a prognostic index (5, 17, 20, 25–29) in chronic uremia. However, serum albumin concentration is also influenced by extracorporeal losses, fluid retention, vascular permeability and hypercatabolism ('negative acute phase protein'). In CAPD patients particularly, low serum albumin may be related to non nutritional causes (60): however, its nutritional value is accepted. Serum transferrin: due to its short half-life time (9 days), this protein is a sensitive marker of PEM. However, iron status, infections and inflammation influence its levels independently of nutritional status. Short half-life protein (retinol-binding protein, prealbumin, ribonuclease) serum concentrations are closely associated with the level of renal function because of their reduced filtration and their diminished tubular metabolism (61); on the contrary, monitoring the variations of prealbumin is helpful in stable uraemic patients in dialysis treatment (25, 26, 30, 31). Furthermore determination of C-reactive protein (32), cholinesterase, fibronectin and IGF-1 (62) can also aid in assessing nutritional status.
4. Subjective global nutritional assessment: SGA has been proposed as a simple, inexpensive and easy-to-apply method using variables derived from history and physical examination (53). This method has been recently validated in uraemic patients (54, 55).
5. Other biochemical determinations Plasma creatinine is roughly related to muscle mass. The value of creatinine/height index is, however, diminished in stable uraemic patients partly as a result of tubular and gut excretion. Low serum cholesterol levels may reflect energy balance. Urinary 3-methylhistidine correlates with muscle mass and protein catabolic rate, but its usefulness in uremia is limited because of reduced renal excretion rates.
6. Amino acids: plasma fasting amino acid concentrations show characteristic abnormalities in patients with renal failure that may be dependent on uremia itself and/or on nutritional abnormalities and deficiencies. Some of these changes at plasma and tissue levels are peculiar to the uraemic condition, and can be partially corrected by modified amino acid formulas (63, 64), while others are unspecifically related to PEM.
7. Nitrogen balance (NB) studies: if properly performed, they can be very accurate and precise, but they do not give any information on the mechanisms of nitrogen depletion or gain, and they reflect only the NB during the study period. In addition, it must be pointed out that, in malnourished populations like uraemic patients, NB can be achieved with less protein or at the expenses of a reduced body protein pool and may therefore not be a criterion for nutritional adequacy (65). Moreover, NB is also sensitive to the amount of other nutrients (e.g. energy) (66).
8. Immune function: the immune system is often adversely affected in renal failure (67, 68) but the relative importance of toxicity, drugs, malnutrition, or other deficiencies is unknown. Levels of C3, C3a, C1q may be reduced in uraemic patients, and the total lymphocyte count is often low. Neutrophiles metabolism and function are also impaired. Higher levels of proinflammatory cytokines are related to a higher mortality risk, while T-cell number and function are associated to better prognosis (69).
9. Body composition measurements: these may represent a 'gold standard' for evaluating nutritional status. The increasing complexity of available technologies allows greater accuracy in measuring body composition. Body

impedance analysis (BIA) for total body water, intracellular water and lean body mass (70, 71) is widely used, but the results should be interpreted with caution in patients with body water changes. Better results have been obtained with DEXA, especially if serial measurements are required (72). More sophisticated instruments to determine total body potassium or nitrogen content as well as other macro or microelements (neutron activation analysis) might be more useful for scientific studies of body composition and for the evaluation of the efficacy of nutritional interventions, but they are not available for clinical use.

Conclusions

No single method is available for the diagnosis of PEM. Standardization of methods, and 'alarm' limits of single markers of malnutrition for supportive nutritional intervention or initiation of dialysis need further confirmation.

A two-tier methodology for assessing nutritional status can be proposed:

(a) A simpler level for clinical purposes will include the following items:

Dietary history, estimation of protein intake (from urea nitrogen appearance, protein catabolic rate, etc.)

Anthropometry: body weight (BMI, ideal BW, relative BW, usual BW, dry BW), skinfold thickness (multiple locations), arm muscle circumferences, fat and muscle areas.

Visceral proteins: albumin, transferrin; prealbumin is useful in dialysis patients with stable renal function.

Biochemical indices: Serum creatinine, urea, potassium, phosphate and cholesterol. Urinary urea, creatinine and phosphate excretion.

Lymphocyte count, complement protein concentration.

Subjective Global Nutritional Assessment.

(b) A more complex level, for scientific work, will include the following items:

Nitrogen balance studies, if properly designed, are among the most precise methods for investigating N equilibrium.

BIA gives easy and reproducible measurements of total water, and indirectly of lean body mass: therefore the results should be interpreted with caution in patients with renal failure. DEXA gives measurements of bone and tissue composition.

Neutron activation analysis gives the most reliable measurement of subtle modifications of body composition.

The best insights into metabolic irregularities at the intracellular level can be gained by directly approaching single tissues (e.g. muscle biopsy), by NMR studies, or by isotope studies: metabolism of protein, amino acid and other substrates (synthesis, degradation, oxidation, turnover) can be investigated at whole body or organ tissue level.

Effects of nutritional therapy on the progression of renal insufficiency

Non-diabetic CRF patients

It has not yet been definitively established whether protein (and phosphorus) restriction in CRF patients during conservative treatment is able to slow down the progression of renal failure to end stage uremia. The reasons are multiple: heterogeneous populations, different kidney diseases, low dietary compliance, difficulties in measuring progression and nutritional adequacy, different end-points, co-existence of other factors responsible for progression, different diet composition (quality of protein, type of energy supply, etc). Some exhaustive meta-analyses, the largest and best designed MDRD study (73–76), as well as other well-conducted studies (77) 'suggest' or 'show' that dietary protein restriction significantly delays the progression of renal disease. A 28% reduction of GFR slope was found in low protein diet (LPD) treated patients with early renal failure (GFR 39 ± 9 ml/min/1.73 m^2) compared to patients on normal protein diets. Unfortunately, during the first 4 months of treatment, the LPD induced a decrease in GFR 'likely caused by haemodynamic adjustments rather than renal structural injury', but 'large enough to confound the results of the trials' (78). For these reasons 'a definitive conclusion of a beneficial effect of the diet intervention based solely on MDRD study A' is still precluded (79).

Some authors (80, 81) demonstrated that, if the nephropathy is progressive, a low protein intake should be prescribed before the progression reaches a 'non-return' point (approximately creatinine 170 μmol/L). However, it is not known whether patients with GFR >60 mL/min and progressive renal failure benefit from protein restriction in terms of slowing the progression of renal damage.

In more advanced renal failure (GFR 18 ± 3ml/min/1.73m^2) treated with very low-protein diet supplemented with ketoanalogues (KA) plus essential amino acids, a reduction of 0.2 g/kg/day in protein intake was associated with a slowing of the GRF decline of approximately 30% (76). On the contrary, the KA and amino acid supplements did not show an independent effect on GFR decay (82).

Other nutritional and non nutritionally related factors are involved in the control of the progression of nephropathy:

- hypertension: its role is well established (75, 76, 83);
- proteinuria: it has been defined as an independent risk factor for progression (83);
- type of nephropathy (84, 85): the decline of GFR is faster in patients with polycystic kidney disease and chronic glomerulonephritis;
- hyperlipoproteinaemia (86, 87): combination of hypertension and hyperlipaemia may have a very negative prognostic relevance;
- calcium and phosphorus metabolism (88): the role of dietary phosphorus could be independent from that of proteins (89–92). The positive effects of phosphorus

dietary control on renal insufficiency might be mediated by calcium metabolism (93);
- intake of vegetable vs animal proteins (94–96)

Diabetic nephropathy

According to many experimental studies a low protein diet is effective in reducing albuminuria and in slowing progression of renal insufficiency in diabetic nephropathy. In patients, a low protein diet (0.6 g/kg/day) seems to be able, in comparison with a normal protein diet, to slow the worsening of renal failure by 75% (97).

In diabetic patients with more severe renal damage (heavy proteinuria, more advanced renal failure) the results were less striking (98). A positive effect was also described in diabetic patients with severe nephropathy given 0.3g/kg/day of vegetable proteins supplemented by 100 mg/kg/day of essential amino acid (EAA) + (KA) (99). However, a recent meta-analysis (73) concluded that there is 'a strong indication, but not conclusive proof, that the low protein diet is beneficial' in patients with insulin-dependent diabetes mellitus. Glycaemic control is paramount to the progression of diabetic nephropathy (100); the nutritional management of diabetic patients in early renal insufficiency must include tight control of glucose homeostasis.

Conclusions

Some evidence suggests that protein restriction may have beneficial effects on the decline of renal function. Many other factors responsible for progression are likely to be important. A predominant role is attributed to proteinuria, to the type of nephropathy, to hyperlipidaemia, to hypertension, and smoking. A role for an early restriction of dietary protein in diabetic nephropaty has been suggested. The nutritional management must include a tight glycemic control.

Need for further research:
1. To determine the relative importance, if any, of each progression factor.
2. To identify additive effect of ACE inhibitors and low protein diets.
3. To identify the optimal level of GFR to start protein-phosphorus restriction.
4. To determine the possible influence of genetic factors on the positive effects of low protein diets in slowing down the decline of GFR.

Nutritional therapy in patients with chronic renal failure: predialysis period

Rationale and goals

In chronic uremia the accumulation of urea and of other nitrogen waste products and uraemic toxins are diminished by lowering protein intake. Metabolic acidosis, hyperparathyroidism, osteodystrophy, hyperkalaemia, neuropathy as well as symptoms like fatigue, anorexia, and itching, are better controlled if the protein intake is low. This was the main, if not the only aim of nutritional treatment of uraemic patients in the sixties. However, it soon became evident that severe PEM could be accelerated by those restrictive diets. In the seventies a large body of evidence was collected on the minimal protein requirements and the quality of proteins for uraemic patients, as well as on their recommended energy intake, in order to avoid the occurrence of PEM. In the 1980s, large randomized controlled trials and meta-analyses were performed to confirm the initial uncontrolled studies on the slowing effect of low protein-low phosphorus diet on the rate of deterioration of renal function. As we have previously stated, a definitive conclusion on this topic is still lacking.

Nutritional therapy

Proteins

1. Conventional low-protein diet (LPD)

An amount of 0.55–0.6 g protein/kg body weight/day is the minimum protein requirement for patients with CRF (101–103). This intake equals the minimum requirements of healthy individuals (104), though the recommended intake in normal individuals has been increased by two standard deviations to meet the requirements of all the population (105). This means that all CRF patients treated with 0.55–0.6 g/kg/day should be carefully monitored and their nutritional status assessed regularly. This amount of protein can maintain a neutral nitrogen balance and body composition, if the clinical conditions are stable and the patients' compliance optimal (106). With this protein intake, serum urea levels can be easily maintained at the recommended level of 25–30 mmol/L. Provision of sufficient energy is of paramount importance for maintenance of protein equilibrium.

The amount of nutrient intake for CRF patients must be calculated per kg of ideal body weight (IBW). An adjusted weight for obese or underweight patients has been recently proposed (107). Two-thirds of dietary proteins must be of high biological value (HBV) to ensure adequate intake of essential amino acids, and animal proteins are necessary for this purpose. With this amount of protein, the dietary phosphorus intake can also easily be reduced to 600–700 mg/day. Meticulous treatment of acidosis and fluid and electrolyte disturbances is required.

2. Very low-protein supplemented diet (VLPD)

In more advanced CRF, when the LPD is not sufficient to control the uraemic toxicity, a VLPD (~0.3 g/kg/day) supplemented with EAA or a mixture of EAA and KA can be prescribed. This diet has some potential advantages (90, 91, 108–112): 1) it controls the levels of urea and uraemic toxicity; 2) it helps to control the hyperparathyroidism and improves osteodystrophy; 3) it ameliorates insulin sensitivity and Na^+K^+ pump activity; 4) it might improve compliance, by increasing the variety of foods; and 5) it allows neutral nitrogen balance and a good nutritional status, pro-

vided that an adequate energy intake is maintained. Because the dietary proteins are supplemented with KA and/or EAA their biological value is less important, and more vegetable proteins can be allowed. With respect to the Rose formula, the formula of supplements of EAA was modified, according to the intracellular amino acid pattern findings (113), by changing the proportions of branched chain amino acids (more valine than leucine), increasing threonine content, adding histidine and tyrosine and reducing the relative amounts of isoleucine, lysine, methionine and phenylalanine (114).

Alternatively to EAA, keto or hydroxy analogues of leucine, isoleucine, valine, methionine and phenylalanine plus tyrosine, threonine, lysine and histidine can be supplemented to VLPD as calcium salts. This supplementation has been reported to result in a better control of urea production and nitrogen balance, of hyperparathyroidism, acidosis and glucose metabolism (115–118). After 1–2 months of adjustment, most of these patients 'acknowledge feeling a clear-cut amelioration of their state of health', and, if well monitored in the predialysis period, they enter dialysis without malnutrition (111) and have an improved survival during the first 2 years of dialysis (112).

The adaptive mechanisms of normal individuals to a reduced dietary protein intake are preserved in the short and in the long term in uraemic patients both on LPD (0.6 g/kg/day) and on supplemented VLPD (0.28 g/kg/day + KA) (119–121). Both EAA and KA are probably useful only in combination with VLPD, but have no detectable nutritional benefit with diets providing more than 0.6 g/kg/day of proteins.

As a general rule, the protein intake should be reduced in parallel with the worsening of renal function: an optimal level of 25–30 mmol/L of urea and normal levels of phosphatemia might be the targets to modulate the protein intake. Below 0.6–0.5 g/kg/day, essential amino acids and ketoacids must be supplemented to maintain nitrogen balance; the residual renal function and the patients' compliance must be monitored to avoid long-term nutritional complications, and to start alternative substitutive therapy.

Energy

A crucial role in the nutritional adequacy of LPD and VLPD in CRF patients on conservative treatment is linked to the appropriate energy intake. Indeed, also in physiological conditions the optimal use of minimal quantities of protein requires an adequate energy supply (104). It was clearly demonstrated that in the range of 15–45 kcal/kg/day, higher energy intakes are associated with better nitrogen balance in predialysis patients on LPD (0.6 g/kg/day), with body weight gain and improved body composition (66). On the other hand, the energy requirements of CRF are not reduced (122), and might be higher during LPD (7), in association with improved insulin sensitivity and glucose metabolism (48). For these reasons the low energy intake often described in CRF patients (3, 16, 37) is probably one of the main reasons for abnormal body composition and malnutrition. The energy needs of these patients are similar to those of normal populations; 35 kcal/kg IBW/day or more (7) are recommended with adaptation to individual needs in case of severe underweight or overweight/obesity (107).

Recommendations for the general population are also valid for patients with CRF: 30% or less of energy as fat with saturated fats < 10% of total calories, cholesterol < 300 mg/day, and simple sugars < 10% is a reasonable goal for all uraemic patients. If an overt dyslipidaemia is present, further modifications are recommended, but because of the need for appropriate energy intake, the dietary treatment of uraemic dyslipidaemia can be difficult (123).

As a general rule, successful dietary treatment requires close cooperation between a trained physician and a skilled dietician. It also requires thorough education of the patients and their families. It is important to recognize the limitations of the dietary treatment, which are the development of nutritional deficiencies or the occurrence of severe uraemic symptoms that require dialysis.

Phosphorus

Reduced intake of phosphorus can be achieved by stricty limiting phosphorus-rich foods of animal origin (e.g. dairy products, egg yolks, meat). Vegetable foods can also be chosen according to their phosphorus content (124). By following these recommendations a phosphorus intake between 5 and 10 mg/kg/day can be achieved.

Vitamins

(a) *Water soluble vitamins.* In the long term, LPD or VLPD present a risk of water-soluble vitamin deficiency. Low levels of riboflavin, of thiamine and even greater deficiency of pyridoxine were found (125). Supplements of 5 mg/day of pyridoxine in predialysis patients and 10 mg/day in MHD and CAPD patients are recommended. Cyanocobalamine (B12) and folic acid levels are normal in CRF, and supplements are not required (126). Ascorbic acid is often low in CRF patients in conservative or dialytic treatment (127) and a supplement of 30–50 mg has been suggested in uraemic patients. Amounts higher than 60 mg are not recommended because of the risk of secondary oxalosis (128).

As a general rule, patients treated with LPD and supplemented VLPD must systematically be supplemented with water soluble vitamins. Patients treated with long term vegetarian diets are also at risk of developing water-soluble vitamin deficiency.

(b) *Fat soluble vitamins.* The plasma levels of vitamin A are frequently high in CRF (129). Supplements of fat soluble vitamins A, E and K are not recommended. Deficiency of vitamin D active metabolite progressively develops with the lowering of GFR, and symptoms of hyperparathyroidism and osteodystrophy appear. Therefore long term oral supplements of low doses of 1–25 $(OH)_2$ D_3 are recommended. The initial doses of 0.25 µg/day or every second day may prevent the development of secondary hyperparathyroidism (130). To

control hypocalcaemia the dose of 1–25 $(OH)_2$ D_3 can be increased. Calcium plasma levels must be closely monitored to avoid hypercalcemia (131), especially in the case of calcium carbonate supplementation.

Minerals

Calcium. Low-protein, low-phosphorus diets are, as a rule, low in calcium because of a low intake of dairy products. Vegetarian diets are even more at risk of calcium deficiency, because of the poor calcium bioavailability in vegetable foods. Calcium supplementation, to reach a total calcium intake of 1.5–2.0 g/day, is recommended: it is helpful in the amelioration and prevention of secondary hyperparathyroidism and its metabolic and clinical consequences (102, 131).

Iron. In predialysis patients, iron deficiency is rare but supplementation might be necessary in patients on VLPD supplemented with KA and/or EAA and in patients on long-term vegetarian diets. During erythropoietin therapy, iron supplements are necessary to obtain better erythropoiesis.

Trace elements. If the dietary intake is suboptimal, there is a risk of developing trace element deficiency. However, routine supplementation with trace elements is not recommended (126). Zinc deficiency can worsen some uraemic symptoms, such as ageusia, impaired olfactory acuity, anorexia, delayed wound healing, sexual dysfunction, and impaired neutrophil leukotaxis (132). Zinc deficiency can be caused by decreased intestinal absorption, deranged tubular transport and/or urinary loss in patients with heavy proteinuria or diminished carrier proteins (133). Selenium: its action is associated with the activity of glutathione peroxidase that protects cells against oxidative damage. Low selenium levels have been found in CRF patients with or without cardiovascular complications (134). Both zinc and selenium deficiency may be due to chronically low protein intake or to diminished levels of plasma carrier protein. Copper: hypercupraemia occurs in CRF, but no clinical symptoms of uremia have been attributed to high copper levels. Aluminium toxicity (main manifestations: dialysis-related dementia and osteomalacia) has been described in uremia. The main sources of aluminium in predialysis CRF patients are aluminium containing phosphate binders.

Recommendations for nutritional treatment of CRF on conservative treatment

Protein

(a) Nephropathy without renal insufficiency (GFR > 70 ml/min). Normal protein intake, as suggested for the general population (0.8–1.0 g/kg/day)

(b) Early to moderate renal failure (GFR 25–70 ml/min).

LPD: 0.5–0.6 g/kg IBW/day (2/3 of HBV) is the minimum protein requirement, but there is not general agreement on the level of GFR below which dietary protein intake should be reduced, nor on the quantity of proteins to be prescribed; 600–700 mg phosphorus/day.

(c) Advanced renal failure: (GFR <25ml/min)

LPD: 0.5–0.6 g/kg IBW/day (2/3 of HBV) (minimum protein requirement); 600–700 mg phosphorus/day.

In selected patients, with lower GFR (10–20 ml/min), with the highest compliance to energy intake, and under strict nutritional monitoring, an alternative to the maintenance dialysis treatment can be tried, by prescribing VLPD: 0.28 g/kg of IBW/day + EAA supplements or KA and EAA supplements. These supplements are not available world-wide.

Energy

Most active patients, with body weight in the range ±10% IBW, need 35 kcal/kg/day. Overweight (>120% of the standards) or malnourished patients might need adjustment of daily energy intake. Normal percent distribution between lipid and carbohydrate (30% and 55–60% respectively) is suggested, with emphasis on fibre, complex carbohydrates and unsaturated fatty acids. If hypertriglyceridaemia is present, avoid simple sugars and ethanol. If hypercholesterolaemia is present, dietary cholesterol <300 mg/day, saturated fatty acid <10%, monounsaturated fatty acid >10% are suggested.

In malnourished patients, if anorexia inhibits a higher energy intake, supplements with a low protein to energy ratio can be given: commercial products are available, with casein as a source of protein, and a nitrogen/energy ratio of 1/318–427.

Conclusions

1. It is of the utmost importance to monitor closely the nutritional status and the nutrient intake to avoid malnutrition. Closely supervised low protein diets can provide a safe and cheap treatment for the early stages of uremia in renal failure. Protein restriction is indicated in more advanced renal failure. If the nutritional status is threatened and supportive measures are ineffective, and uraemic syndrome develops, dialysis should be contemplated without delay;
2. An adequate energy intake is often difficult to achieve and to maintain;
3. There is no agreement on the level of GFR below which dietary protein intake should be reduced. Some authors suggest starting protein restriction early, but not modifying the prescription with the worsening of renal failure that can lead to difficult compliance of the patients. The expected beneficial effects of low protein diets have to be balanced with the fact that malnutrition in patients entering dialysis is a major cause of death during the 3 months following dialysis initiation. There are many variables affecting the choices of each nephrological group regarding the best time to initiate protein restriction and the extent to which it should be restricted. These include: 1) dietary habits in different countries; 2) the nutritional status of the individual patient; 3) the rate of progression of the disease; 4) the presence or the severity of acidosis, hyperparathyroidism, and the other disorders caused by

Table 1 Recommendations for nutritional treatment of adult patients with renal insufficiency

Chronic renal failure on conservative treatment	Non-protein energy, kcal/kg/day*	Protein, g/kg/day
GFR >70 ml/min	≥35	0.8–1.0
Early to moderate renal failure (GFR 25–70 ml/min)	≥35	0.55–0.6 (2/3 of HBV) (minimum protein requirement)**
Advanced renal failure (GFR <25 ml/min)	≥35	0.55–0.6 (2/3 of HBV) (minimum protein requirement)** or, in compliant patients and under strict monitoring 0.28 + EAA or KA and EAA supplements (see text)

GFR: glomerular filtration rate; HBV: high biological value; EAA: essential amino acids; KA: Ketoanalogues. *Adapted to individual needs in case of underweight or obesity. **There is no agreement on the level of GFR below which dietary protein intake should be reduced. The quantity of proteins to be prescribed in early to moderate renal failure is also controversial and varies from 0.5 to 0.8 g/Kg/day.

uraemic syndrome; 5) the patient's desire to delay initiation of dialytic treatment; 6) the possibility of carrying out a careful and effective nutritional follow-up; 7) the availability of amino acid or ketoanalogue supplements; and 8) the economic background.

The quantity of proteins to be prescribed in early to moderate renal failure is also controversial and varies from 0.55 to 0.8 g/Kg/day.

Suggestions for future research

1. Safety and efficacy of the vegetarian diet in the long term in CRF.
2. In depth studies on the beneficial effects of low protein diets on diabetic nephropathy.
3. Clinical, metabolic and renal effects of low protein diets in type II diabetes mellitus.
4. The effects of treatment with protein-reduced diet in the predialytic phase on subsequent morbidity and mortality during dialysis.
5. When to start phosphorus restriction in order to prevent hyperparathyroidism.

Acknowledgments

The authors wish to thank Prof. A. Alvestrand, Ms M. Vennegoor, Ms E. Sikkes for useful discussion, comments or suggestions during the preparation of the report, and the ESPEN Educational Committee, and in particular Dr. M. Barnett, Dr. M. Camilo and Dr. R. Meier, for their helping comments and editing. They wish also to express their appreciation to Itala Brancaleone for revision of the manuscript.

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Submission date: 21 February 2000 *Accepted:* 28 March 2000