Kidney International, Vol. 58, Suppl. 76 (2000), pp. S-133–S-139

Nutritional aspects in hemodialysis

MAURICE LAVILLE and DENIS FOUQUE

Department of Nephrology, Claude-Bernard University, Edouard-Herriot Hospital, Lyon, France

Nutritional aspects in hemodialysis. The results of cross sectional studies throughout the world indicate that maintenance hemodialysis patients are at risk of malnutrition. Longitudinal studies show that malnutrition is associated with a reduced life expectancy mainly because of cardiovascular and infectious complications. Several factors are responsible for malnutrition of hemodialysis patients. Protein-energy intake is often reduced because of inappropriate dietary restrictions, anorexia, and taste alterations, promoting malnutrition in most patients entering dialysis. Intercurrent illnesses and frequent hospitalizations add to meal disturbances. A state of persistent catabolism may result from acidosis, resistance to anabolic factors such as growth hormone, insulin, and insulin-like growth factor-1, as well as a chronic inflammatory state caused by dialysis membrane and fluid bioincompatibility. In addition, losses of nutrients, including glucose, amino acids, proteins, and vitamins, occur during the dialysis treatment. Careful monitoring of dietary intakes is mandatory even in predialysis patients. In hemodialysis patients, the dose of dialysis should be adapted to correct acidosis and to relieve anorexia caused by accumulation of uremic toxins and hyperleptinemia. When malnutrition is established, active therapeutic interventions should take place, including intradialytic parenteral nutrition if oral supplementation has failed to improve nutritional status. Anabolism has been observed during the administration of recombinant growth hormone and insulin-like growth factor-1. Emerging therapeutic strategies against malnutrition may also involve a short period of daily dialysis.

End-stage renal disease (ESRD) patients treated by maintenance hemodialysis (MHD) are at risk of malnutrition, as shown by several cross sectional studies in the United States, Japan, and Europe. In fact, virtually every study examining the nutritional status of hemodialysis patients indicates that such patients frequently manifest protein calorie malnutrition [1]. The clinical evidence for malnutrition includes decreased relative body weight, skinfold thickness, arm muscle circumference, and low growth rates in children (Table 1). Body composition measurements using total body nitrogen, bioelectrical impedance measurements, and dual-energy x-ray absorptiometry (DEXA) also reveal a high incidence of protein calorie malnutrition. Serum levels of albumin and prealbumin are strongly correlated with body composition and dialysis outcomes and represent suitable surrogates to follow-up closely the nutritional status of the patients [2]. According to threshold values of 35 g/L for albumin and 300 mg/L for prealbumin, recent data from France on more than 7000 hemodialyzed patients indicated that 20 or 36%, respectively, of them suffered from malnutrition despite satisfying dialysis adequacy (mean Kt/V 1.36 ± 0.36). In this study, the mean normalized protein nitrogen appearance (nPNA) was 1.13 ± 0.32 g/kg/day; however, 35% of patients had a nPNA below 1 g/kg/day [3].

Key words: malnutrition, diet and dialysis, growth factors, uremia.

CONSEQUENCES OF MALNUTRITION ON DIALYSIS OUTCOMES

While reported annual mortality rates range from 23.6% in the United States in 1993 [4], to 10.7% in Europe [5], and to 9.5% in Japan in 1994 [6], a common factor of increased death risk in these populations is malnutrition [7]. Serum albumin below 35 g/L [2, 8–10] and serum prealbumin below 300 mg/L (abstract; Chiappini et al, *Nephrol Dial Transplant* 5:699, 1990) [2, 11–13] have been shown to be independent predictors of increased morbidity and mortality.

An early report from 98 nondiabetic hemodialysis patients followed for 12 months showed an inverse relationship between the protein nitrogen appearance and the frequency of hospitalizations and mortality rate [14]. In 1990, Lowrie and Lew showed that in over 12,000 MHD patients followed for 12 months, of various predialysis serum chemistries, the serum albumin exhibited the most striking odds ratio for survival [15]. The multicenter Canadian Hemodialysis Morbidity Study reported a direct correlation between the serum albumin level and the morbidity and mortality risk in 486 hemodialysis patients [16]. Two other recent studies also confirm that a low serum albumin concentration is a strong predictor of high death rates [17, 18].

A follow-up from the large French multicenter study on a representative subset of more than 1600 patients reported a survival of 90 and 78% at one and two years,

Table 1. Nutritional parameters in chronic hemodialysis patients

Clinical	Biological
Body weight	Serum urea/creatinine
Skinfold thickness	nPNA
Arm muscle circumference	Serum albumin
Subjective Global Assessment	Serum prealbumin
Growth rate (children)	Transferrin
Cholesterol	
IGF-1	
Total body nitrogen	
Bioelectrical impedance	
Dual energy x-ray absorptiometry	

Table 2. Factors of malnutrition in chronic hemodialysis patients

Previous malnutrition
Reduced protein-energy intakes
Inadequate diet counseling
Anorexia
Taste disturbances
Digestive side-effects of drugs
Frequent hospitalizations
Primary/intercurrent illnesses
Reduced dietary intakes
Catabolic state
Chronic inflammation
Endocrine and metabolic disorders
Acidosis
Anemia
Uremic toxins
Hyperparathyroidism
Hyperleptinemia
Growth hormone and IGF-1 resistance
Dialysis-related events
Inadequate Kt/V
Bioincompatible membranes
Chronic inflammation
Endotoxin back-filtration
Amino acid and protein losses
Vitamin losses

respectively, and confirmed a significant influence of serum levels of albumin and prealbumin on survival (abstract; Combe et al, *J Am Soc Nephrol* 10:239A, 1999) [3].

It should be emphasized that these findings do not indicate that improving nutritional status by increasing nutritional intake or other maneuvers will reduce morbidity or mortality. Malnutrition by itself is rarely reported as a cause of death in ESRD patients. In fact, malnutrition itself may be detrimental on outcomes of infectious and cardiovascular complications. It is also possible that the same illnesses that engender malnutrition will independently cause the high morbidity and mortality, therefore reducing the pathogenetic weight of malnutrition per se.

FACTORS OF MALNUTRITION IN HEMODIALYSIS PATIENTS

A high prevalence of protein calorie malnutrition is observed in patients commencing hemodialysis (Table 2) [19]. Those hemodialysis patients who are malnourished at the onset of dialysis therapy are likely to stay malnourished one to two years later. Conversely, those individuals who are well nourished at the onset of maintenance dialysis therapy are likely to remain well nourished.

Malnutrition can result from several factors that can be found in different combinations in selected patients, and it involves reduced dietary intakes, metabolic disorders, and inadequate dialysis [20] in terms of dose [21, 22] or membrane biocompatibility [23, 24].

DIETARY NUTRIENT INTAKE

There are many possible causes for protein calorie malnutrition in patients receiving maintenance dialysis therapy. These patients are chronically exposed to the risk of inadequate diet counseling or self-designed restrictions, and repeated hospitalizations (abstract; Young et al, *J Am Soc Nephrol* 10:259A, 1999) [25], which disturb dietary habits and reduce dietary nutrient intake, and superimposed acute or chronic illnesses [26]. We have observed in our unit that hemodialysis patients either referred for checkup or following surgery overall received only 80% of the scheduled meals, thus resulting in a weekly deficit of about 2800 kcal per patient. The reasons for those missed meals were, for example, fasting states before diagnosis procedures or surgery, modified schedule of dialysis sessions, postdialysis fatigue, and inadequacy between meals and patient's preferences. It is therefore not surprising that in the French cohort, malnutrition was observed significantly more often in patients with diabetic and vascular kidney disease, even after adjustment for age [3]. Before starting maintenance dialysis therapy, low-protein and low-phosphate diets are routinely prescribed. These diets may be sometimes hypocaloric [27, 28] and therefore may be deleterious to the patient's nutritional status, if not adequately monitored by skilled dietitians.

The most important cause of inadequate nutrient intake is almost certainly anorexia. Anorexia may be caused by many factors, including: uremic toxins; gastrointestinal disorders such as peptic ulcers, gastritis, or esophagitis; unpalatable medicines; and psychosocial disorders [20, 29, 30].

Recent evidence suggest that protein calorie malnutrition often begins incipiently when the glomerular filtration rate (GFR) is about 28 to 35 mL/min/1.73 m^2 or even higher (abstract; Kopple et al, *J Am Soc Nephrol* 5:335, 1994) and continues to fall gradually as the GFR decreases below these values [31, 32]. However, patients usually do not become frankly malnourished until the GFR is 4 to 5 mL/min/1.73 m^2 or lower. As a result, pre-ESRD patients often have critically low levels of protein and energy intakes, and the spontaneous nutrient intake

does not normalize when maintenance dialysis treatment is started. Jacob et al reported that 45% of 61 MHD patients had a protein intake less than 1.0 g/kg body weight/day [33], whereas Bergström et al found that 12% of 117 unselected hemodialysis patients had a protein intake below 0.8 g/kg body weight/day [30]. A recent report of the HEMO pilot study in hemodialysis patients entering dialysis showed a low energy intake (22.8 kcal/kg body weight/day) and a protein intake of 0.94 g/kg body weight/day, much less than the 35 kcal/kg body weight/day usually recommended for hemodialysis patients or normal individuals [34, 35]. These protein energy intakes may strongly affect early outcomes of renal replacement therapy and explain why long-term hemodialysis patients are frequently malnourished.

A progressive decrease in protein calorie intake may also depend on taste disturbances. The neuroregulation of appetite is far from well understood in patients with chronic renal failure [36]. Zinc deficiency contributes to taste disturbances [37, 38]. It has also been suggested that, in addition to factors such as delayed gastric emptying, poorly palatable diets enhanced by salt and electrolyte restrictions, and postdialysis malaise, some uremic toxins appear to affect appetite directly. Anderstam et al recently infused uremic ultrafiltrate into the peritoneal cavity of rats. Compared with rats infused with saline or plasma ultrafiltrate from healthy humans, the rats infused with uremic ultrafiltrate demonstrated a net reduction in their spontaneous food intake [39]. Ultrafiltrate fractionation studies suggest that the molecular weight of compounds that may induce anorexia is between 1000 and 5000 D [39]. Another compound called leptin, a 15 kD polypeptidic hormone synthesized by adipocytes, has been shown to decrease appetite in rats and to induce weight loss when administered as a recombinant product in obese humans [40]. Leptin is abnormally high in hemodialysis patients as a consequence of reduced renal clearance, elevated insulin levels, and possibly chronic inflammation [41–44].

These observations suggest that more intensive dialysis therapy might increase appetite by removing uremic toxins. Lindsay and Spanner increased the dose of dialysis in a group of hemodialysis patients and observed a spontaneous increase in proteic catabolic rate without evidence of catabolic events, suggesting that patients had increased their protein intake [45]. On the other hand, in many patients, the proteic catabolic rate does not become normal when the Kt/V is increased. Although this might reflect the fact that Kt/V is not sufficiently high in these patients, it is possible that comorbid factors, poorly dialyzable compounds, or other factors may contribute to the anorexia and that a high dose of dialysis, within a range that is attainable routinely may improve but not eradicate anorexia in many patients.

Further studies are needed to evaluate the nutritional benefits of maneuvers designed to enhance the removal of uremic toxins through increased dialysis elimination or adsorption. A specific goal should be to lower plasma leptin by increasing dialysis clearance or decreasing its overproduction, which is likely associated with chronic inflammation [44].

NUTRITIONAL CONSEQUENCES OF CHRONIC INFLAMMATION

In patients with chronic renal failure (CRF), chronic inflammation may be associated with immunologically-mediated primary renal diseases, treated by corticosteroids, which in turn induces a well-known catabolic state.

However, an important factor is likely repeated inflammatory bursts caused by bioincompatibility of dialysis membranes and fluids. The quality of dialysis water and dialysis fluid backfiltration play a major role, as suggested by cross-sectional studies in which plasma C-reactive protein levels are significantly higher in patients treated by low-flux hemodiafiltration than in patients treated by either high-flux hemodiafiltration, paired filtration dialysis, or conventional hemodialysis [46]. C-reactive protein is an acute phase reactant protein synthesized by the liver in response to inflammatory processes leading to an increase in IL-6 production. As a result, synthesis of acute phase reactants by the liver is associated with a decreased albumin production [47]. Moreover, chronic inflammatory status likely increases lipid and protein oxidation, and probably contributes to vascular disease and tissue amyloid deposition [48, 49].

DIALYSIS-RELATED NUTRIENT LOSSES

The hemodialysis procedure itself may promote wasting by removing nutrients and also by stimulating protein catabolism. Hemodialysis increases the urea nitrogen appearance (UNA or net urea generation), enhances net protein breakdown, and promotes negative nitrogen balance [50]. During sham hemodialysis in normal volunteers, Guttierez et al reported an increased release of amino acids from the leg, indicating enhanced net muscle protein breakdown [51]. The bioincompatible nature of dialyzer membranes may stimulate the release of cytokines, such as interleukin-1, which may be the cause of the enhanced protein catabolism.

During a routine hemodialysis treatment using a low-flux cuprophane membrane, 4 to 9 g of free amino acids are lost through the dialyzer during fasting and 8 to 10 g if patients are eating during the procedure [52, 53]. Peptides are also removed in a range of 2 to 3 g per dialysis [53], thus leading to a net amino acid of 10 to 13 g per dialysis [30]. With high-flux dialyzers in fasting patients, about 8 g of free amino acids are removed during a routine hemodialysis treatment [54]. However, the use

of high-flux membranes with an increased permeability to protein may result in albumin losses as high as 25 g per session when highest ultrafiltration rates are used during hemodiafiltration (abstract; Hillion et al, *J Am Soc Nephrol* 10:283A, 1999).

Reuse of dialyzers is a routine procedure in the United States [55]. Although usually small amounts of protein are lost during a single hemodialysis, Kaplan et al reported markedly increased protein losses when polysulfone membranes were reprocessed many times with bleach or formaldehyde [56]. After 20 to 25 reuses, up to 17 g of protein were lost during one hemodialysis session. Protein losses do not seem to increase markedly until reprocessing exceed 10 times. Interestingly, when the use of bleach for dialyzer reprocessing was discontinued, the patients underwent a significant increase in serum albumin, from 3.6 to 3.8 g/dL, which was considered to be due to reduced protein leakage through the dialyzers [56].

During hemodialysis with glucose-free dialysate, an average of 20 to 30 g of glucose is lost into the dialysate [57, 58]. If a dialysate containing 200 mg/dL (11 mmol/L) of glucose monohydrate (180 mg/dL of anhydrous glucose) is used, there is a net absorption of 10 to 30 g of glucose during each dialysis [57, 58].

Deficiency of water-soluble vitamins in hemodialysis patients results primarily from insufficient intake, losses into dialysate, or altered vitamin synthesis or metabolism or possibly the presence of inhibitors to the actions of the vitamins. Water-soluble vitamins and other bioactive compounds are removed by both hemodialysis and peritoneal dialysis [59–62]. These losses may be reduced by decreased urinary excretion and may be partially replaced by the vitamins provided in a normal diet [63–68]. If patients have low nutrient intakes, these losses may enhance malnutrition. In fact, the content of several vitamins in typical meals ingested by MHD patients is less than the Recommended Dietary Allowances of the Food and Nutrition Board. However, the need of water-soluble vitamins may vary with the new types of dialyzers used. The more porous, high-flux dialyzers remove greater quantities of vitamins. Some of the detrimental effects of losses of water soluble vitamins and other compounds might be alleviated by either intradialytic supplementation [69] or convective dialysis methods associated with reinfusion of regenerated ultrafiltrate.

IMPAIRED UTILIZATION OF NUTRIENTS

Endocrine and metabolic disorders are frequently observed during chronic renal failure. There is a state of resistance to many anabolic hormones, including insulin, growth hormone, and insulin-like growth factor-1 (IGF-1) [70–72].

Acidemia, a condition frequently observed in renal failure patients, increases protein catabolism [73, 74]. Metabolic acidosis impairs protein metabolism by mainly increasing protein catabolism through a stimulation of the ubiquitin-proteasome pathway. In addition, acidosis increases insulin resistance and impairs the effects of insulin on glucose and amino acid utilization. Acidosis is also partially corrected by a low-protein diet [75].

Table 3. Therapeutic nutritional interventions

Interventions
Adequate dialysis dose
Daily dialysis
Correction of acidosis
Oral/enteral dietary supplements
Parenteral nutrition
Interdialytic
Intradialytic rHu-EPO
rHu-GH
rHu-IGF

PERSPECTIVES FOR NUTRITIONAL INTERVENTIONS

In face of numerous causes for malnutrition, it is not unexpected to find many different treatments for malnutrition. Some are still experimental, although pilot studies appear promising (Table 3).

A low serum bicarbonate level may be associated with higher protein intakes [3], and it is unclear from clinical studies whether those patients have a higher benefit of larger protein intakes as compared with the detrimental catabolism induced by acidosis per se. However, since dietary protein intake is not easy to assess routinely and because nPNA may not be a valid marker of protein intake in acidosis (for example, a nonstable metabolic state), acidosis control should be advised, through oral or dialytic route, to reach a minimum predialytic serum bicarbonate level of 22 mmol/L.

Oral and enteral dietary supports are generally not largely prescribed because of moderate taste acceptability, patients getting tired of them, and products overcost. In addition, a number of patients may present gastrointestinal discomfort or disease and may not benefit from these compounds. However, oral supplements may prevent the setting of malnutrition particularly due to low energy intakes and should therefore be proposed systematically before any intravenous nutrition therapy, because of almost no side effects and potential benefits. In particular states of severe malnutrition, we and others have observed unexpected recoveries after gastrostomy and sustained enteral nutrition.

Parenteral nutrition, either predialytic (IDPN) or continuous (TPN), has been proposed in response to the failure of increasing oral nutrients intake. Except during specific conditions such as surgery, trauma, severe sepsis,

or chronic digestive disease where this intravenous support will maintain an optimal intake, there are no convincing randomized controlled studies supporting the use of long-term intravenous nutrition [76]. Furthermore, side effects may occur such as nausea, malaise, liver test abnormalities, and sepsis, and in one study, IDPN has been associated with outcome worsening in patients with a serum albumin of greater than 35 g/L [77]. However, the fact that nutrients could be delivered without extra hospitalization and venous access during a regular dialysis, that new delivery systems and solutions (all-in-one) are proposed, and new formulas are under development still represent a large potential for future treatments, which should be adequately validated through clinical trials of best quality.

In order to stimulate protein synthesis, anabolic compounds have been administered during limited pilot trials in maintenance dialysis patients. It is now well accepted that recombinant growth hormone (rhGH) exerts a strong anabolic effect in chronic renal failure children, and benefits on growth and body composition have largely overcome limited side effects and high costs of treatment [78]. In chronic renal failure adults, rhGH has been associated with anabolic response during acute and chronic administration [79–81]. Since IGF-1 is the active compound released by growth hormone, rhIGF-1 has also been administered in adult chronic renal failure patients and showed anabolic properties as well [82]. Long-term administration of these compounds in adult MHD patients are still lacking, but it seems reasonable to try to boost the nutritional response by a short-term growth factor treatment combined with optimal protein and energy intakes.

Finally, recent data from short daily dialysis programs seem to offer a strong and rapid renutrition response by enlarging to almost unrestricted diets patients nutrient, salt, and beverage intakes. This last issue, debatable in terms of costs and patient comfort, deserves attention, at least as a rescue therapy (abstract; Traeger et al, *J Am Soc Nephrol* 10:197A, 1999).

Reprint requests to Maurice Laville, M.D., Department of Nephrology, Claude-Bernard University, Edouard-Herriot Hospital, 69437 Lyon Cedex 03, France.
E-mail: maurice.laville@chu-lyon.fr

REFERENCES

1. Wolfson M, Strong CJ, Minturn D, Gray DK, Kopple JD: Nutritional status and lymphocyte function in maintenance hemodialysis patients. *Am J Clin Nutr* 39:547–555, 1984
2. Cano N, Fernandez JP, Lacombe P, Lankester M, Pascal S, Defayolle M, Labastie J, Saingra S: Statistical selection of nutritional parameters in hemodialysed patients. *Kidney Int Suppl* 22:S178–S180, 1987
3. Aparicio M, Cano N, Chauveau P, Azar R, Canaud B, Flory A, Laville M, Leverve X: Nutritional status of haemodialysis patients: A French national cooperative study. *Nephrol Dial Transplant* 14:1679–1686, 1999
4. Held PJ, Brunner FB, Odaka M, Garcia JR, Port FK, Gaylin DS: Five-year survival for end-stage renal disease patients in the United States, Europe, and Japan, 1982 to 1987. *Am J Kidney Dis* 15:451–457, 1990
5. Valderrabano F, Berthoux F, Jones E, Mehls O: Report on management of renal failure in Europe, XXV, 1994: End stage renal disease and dialysis report. *Nephrol Dial Transplant* 11(Suppl 1):2–21, 1996
6. Shinzato T, Nakai S, Akiba T, Yamazaki C, Sasaki R, Kitaoka T, Kubo K, Shinoda T, Kurokawa K, Marumo F, Sato T, Maeda K: Survival in long term haemodialysis patients: Results of the annual survey of the Japanese society for dialysis therapy. *Nephrol Dial Transplant* 12:884–888, 1997
7. Bergström J: Nutrition and mortality in hemodialysis. *J Am Soc Nephrol* 6:1329–1341, 1995
8. Iseki K, Kawazoe N, Fukiyama K: Serum albumin is a strong predictor of death in chronic dialysis patients. *Kidney Int* 44:115–119, 1993
9. Goldwasser P, Mittman N, Antignani A, Burrell D, Michel MA, Collier J, Avram MM: Predictors of mortality in hemodialysis patients. *J Am Soc Nephrol* 3:1616–1622, 1993
10. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. *J Am Soc Nephrol* 7:728–736, 1996
11. Oksa H, Ahonen K, Pasternak A, Marnela KM: Malnutrition in hemodialysis patients. *Scand J Urol Nephrol* 25:157–161, 1991
12. Avram MM, Mittman N, Bonomini L, Chattopadhyay J, Fein P: Markers for survival in dialysis: A seven-year prospective study. *Am J Kidney Dis* 26:209–219, 1995
13. Sreedhara R, Avram MM, Blanco M, Batish R, Avram MM, Mittman N: Prealbumin is the best nutritional predictor of survival in hemodialysis and peritoneal dialysis. *Am J Kidney Dis* 28:937–942, 1996
14. Acchiardo SR, Moore LW, Latour PA: Malnutrition as the main factor of morbidity and mortality in hemodialysis patients. *Kidney Int* 24(Suppl 16):S199–S203, 1983
15. Lowrie EG, Lew LN: Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 5:458–482, 1990
16. Churchill DN, Taylor DW, Cook RJ, Laplante P, Barre P, Cartier P, Fay WP, Goldstein MB, Jindal K, Mandin H: Canadian hemodialysis morbidity study. *Am J Kidney Dis* 3:214–234, 1992
17. Owen WF, Lew NL, Liu Y, Lowrie EG, Lazarus JM: The urea reduction ratio and serum albumin concentrations as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 329:1001–1006, 1993
18. Collins AJ, Ma JZ, Umen A, Keshaviah P: Urea index (Kt/V) and other predictors of hemodialysis patient survival. *Am J Kidney Dis* 23:272–282, 1994
19. Blummenkrantz MJ, Kopple JD, Gutman YK: Methods for assessing nutritional status of patients with chronic renal failure. *Am J Clin Nutr* 33:1567–1585, 1980
20. Bergström J: Why are dialysis patients malnourished? *Am J Kidney Dis* 26:229–241, 1995
21. Hakim RM, Breyer JA, Ismail NM, Schulman GM: Effect of dose of dialysis on morbidity and mortality. *Am J Kidney Dis* 23:661–669, 1994
22. Held PJ, Port FK, Wolfe RA, Stannard DC, Carroll CE, Daugirdas JT, Bloembergen WE, Greer JW, Hakim RM: The dose of hemodialysis and patient mortality. *Kidney Int* 50:550–556, 1996
23. Parker TF III, Wingard RL, Husni L, Alp Ikizler T, Parker RA, Hakim RM: Effect of the membrane biocompatibility on nutritional parameters in chronic hemodialysis patients. *Kidney Int* 49:551–556, 1996
24. Hakim RM, Held PJ, Stannard DC, Wolfe RA, Port FK, Daugirdas JT, Agodoa L: Effect of the dialysis membrane on mortality of chronic hemodialysis patients. *Kidney Int* 50:566–570, 1996
25. Carlson DM, Duncan DA, Naessens JM, Johnson WJ: Hospitalization in dialysis patients. *Mayo Clin Proc* 59:769–775, 1984
26. Grodstein GP, Blumenkrantz MJ, Kopple JD: Nutritional and

metabolic response to catabolic stress in chronic uremia. *Am J Clin Nutr* 33:1411–1416, 1980
27. Fouque D, Joly MO, Laville M, Beaufrere B, Goudable J, Pozet N, Chatelain P: Zech Increase of serum insulin-like growth factor I (IGF 1) during chronic renal failure is reduced by low-protein diet. *Miner Electrolyte Metab* 18:276–279, 1992
28. Ciancaruso B, Capuano A, D'amaro E, Ferrara N, Nastasi A, Conte G, Bellizzi V, Andreucci VE: Dietary compliance to a low protein and phosphate diet in patients with chronic renal failure. *Kidney Int Suppl* 27:S173–S176, 1989
29. Evans RW, Manninen DL, Garrison LP Jr, Hart LG, Blagg CR, Gutman RA, Hull AR, Lowrie EG: The quality of life of patients with end-stage renal disease. *N Engl J Med* 312:553–559, 1985
30. Bergström J: Nutrition and adequacy of dialysis in hemodialysis patients. *Kidney Int Suppl* 41:S261–S267, 1993
31. Ikizler TA, Greene JH, Wingard RL, Parker RA, Hakim RM: Spontaneous dietary intake during progression of chronic renal failure. *J Am Soc Nephrol* 6:1386–1391, 1995
32. Pollock CA, Ibels LS, Zhy FY, Warnant M, Caterson RJ, Waugh DA, Mahony JF: Protein intake in renal disease. *J Am Soc Nephrol* 8:777–783, 1997
33. Jacob V, Le Carpentier JE, Salzano S, Naylor V, Wild G, Brown CB, el Nahas AM: IGF-1, a marker of undernutrition in hemodialysis patients. *Am J Clin Nutr* 52:39–44, 1990
34. Dwyer JT, Cunniff PJ, Maroni BJ, Kopple JD, Burrowes JD, Powers SN, Cockram DB, Chumlea WC, Kusek JW, Makoff R, Goldstein DJ, Paranandi L: The hemodialysis pilot study: Nutrition program and participant characteristics at baseline: The HEMO Study Group. *J Ren Nutr* 8:11–20, 1998
35. National Kidney Foundation DOQI guidelines in nutrition. *Am J Kidney Dis* 2000 (in press)
36. Astback J, Fernstrom A, Hylander B, Arvidson K, Johansson O: Taste buds and neuronal markers in patients with chronic renal failure. *Perit Dial Int* 19(Suppl 2):S315–S323, 1999
37. Atkin-Thor E, Goddard BW, O'Nion J, Stephen RL, Kolff WJ: Hypogueusia and zinc depletion in chronic dialysis patients. *Am J Clin Nutr* 31:1948–1951, 1978
38. Mahajan SK, Bowersox EM, Rye DL, Abu-Hamdan DK, Prasad AS, McDonald FD, Biersack KL: Factors underlying abnormal zinc metabolism in uremia. *Kidney Int Suppl* 27:S269–S273, 1989
39. Anderstam B, Mamoun AH, Södersten P, Bergström J: Middle-sized molecule fractions isolated from uremic ultrafiltrate and normal urine inhibit ingestive behavior in the rat. *J Am Soc Nephrol* 7:2453–2460, 1996
40. Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, Lubina JA, Patane J, Self B, Hunt P, McCamish M: Recombinant leptin for weight loss in obese and lean adults: A randomized, controlled, dose-escalation trial. *JAMA* 282:1568–1575, 1999
41. Merabet E, Dagogojack S, Coyne DW, Klein S, Santiago JV, Hmiel SP, Landt M: Increased plasma leptin concentration in end-stage renal disease. *J Clin Endocrinol Metab* 82:847–850, 1997
42. Fouque D, Juillard L, Lasne Y, Tabakian A, Laville M, Joly MO, Laville M: Acute leptin regulation in end-stage renal failure: The role of growth hormone and IGF-1. *Kidney Int* 54:932–937, 1998
43. Meyer C, Robson D, Rackovsky N, Nadkarni V, Gerich J: Role of the kidney in human leptin metabolism. *Am J Physiol* 36:E903–E907, 1997
44. Stenvinkel P, Lonnqvist F, Schalling M: Molecular studies of leptin: Implications for renal disease. *Nephrol Dial Transplant* 14:1103–1112, 1999
45. Lindsay RM, Spanner E: A hypothesis: The protein catabolic rate is dependent upon the type and amount of treatment in dialyzed uremic patients. *Am J Kidney Dis* 13:382–389, 1989
46. Panichi V, Migliori M, De Pietro S, Taccola D, Metelli MR, Palla R: Plasma C-reactive protein in haemodialysis. *Blood Purif* 17:142–148, 1999
47. Kaysen GA: Biological basis of hypoalbuminemia in ESRD. *J Am Soc Nephrol* 9:2368–2376, 1998
48. Nguyen AT, Lethias C, Zingraff J, Herbelin A, Naret C, Descamps-Latcha B: Hemodialysis membrane-induced activation of phagocyte oxidative metabolism detected in vivo and in vitro within microamounts of whole blood. *Kidney Int* 28:158–167, 1985
49. Miyata T, Wada Y, Cai Z, Iida Y, Horie K, Yasuda Y, Maeda K, Kurokawa K, van Ypersele de Strihou C: Implication of an increased oxidative stress in the formation of advanced glycation end products in patients with end-stage renal failure. *Kidney Int* 51:1170–1181, 1997
50. Borah M, Schoenfeld PY, Gotch FA, Sargent JA, Wolfson M, Humphreys MH: Nitrogen balance in intermittent hemodialysis therapy. *Kidney Int* 14:497–500, 1978
51. Guttierez A, Alvestrand A, Wahren J, Bergstrom J: Effect of in vivo contact between blood and dialysis membranes on protein catabolism in humans. *Kidney Int* 38:487–494, 1990
52. Giordano C, DePascale C, De Cristofaro D, Capodicasa G, Balestrieri C, Baczyck K: Protein malnutrition in the treatment of chronic uremia, in *Nutrition in Renal Disease*, edited by Berlyne GM, Baltimore, Williams and Wilkins, 1968, p 23
53. Kopple JD, Swendseid ME, Shinaberger JH, Umezawa CY: The free and bound amino acids removed by hemodialysis. *Trans Am Soc Artif Intern Organs* 19:309–313, 1973
54. Ikizler TA, Flakoll PJ, Parker RA, Hakim RM: Amino acid and albumin losses during hemodialysis. *Kidney Int* 46:830–837, 1994
55. Levin NW: Dialyzer reuse: A currently acceptable practice. *Semin Dial* 6:89–90, 1993
56. Kaplan AA, Halley SE, Lapkin RA, Graeber CW: Dialysate protein losses with bleach processed polysulphone dialyzers. *Kidney Int* 47:573–578, 1995
57. Wathen RL, Keshaviah P, Hommeyer P, Caldwell K, Comty CM: The metabolic effects of hemodialysis with and without glucose in the dialysate. *Am J Clin Nutr* 31:1870–1875, 1978
58. Gutierrez A, Bergström J, Alvestrand A: Hemodialysis-associated protein catabolism with and without glucose in the dialysis fluid. *Kidney Int* 46:814–822, 1994
59. Kopple JD, Swenseid ME: Vitamin nutrition in patients undergoing maintenance hemodialysis. *Kidney Int Suppl* 2:S79–S84, 1975
60. Andersen KEH: Folic acid status of patients with chronic renal failure maintained by dialysis. *Clin Nephrol* 8:510–513, 1977
61. Rostand SG: Vitamin B12 levels and nerve conduction velocities in patients undergoing maintenance hemodialysis. *Am J Clin Nutr* 29:691–697, 1976
62. Sullivan JF, Eisenstein AB, Mottola OM, Mittal AK: The effect of dialysis on plasma and tissue levels of vitamin C. *Trans Am Soc Artif Intern Organs* 18:277–281, 1972
63. Sullivan JF, Eisenstein AB: Ascorbic acid depletion during hemodialysis. *JAMA* 220:1697–1699, 1972
64. Whitehead VM, Comty CH, Posen GA, Kaye M: Homeostasis of folic acid in patients undergoing maintenance hemodialysis. *N Engl J Med* 279:970–974, 1968
65. Sullivan JF, Eisenstein AB: Ascorbic acid depletion in patients undergoing chronic hemodialysis. *Am J Clin Nutr* 23:1339–1346, 1970
66. Descombes E, Hanck AB, Fellay G: Water soluble vitamins in chronic hemodialysis patients and need for supplementation. *Kidney Int* 43:1319–1328, 1993
67. Dobbelstein H, Korner WF, Mempel W, Grosse-Wilde H, Edel HH: Vitamin B6 deficiency in uremia and its implications for the depression of immune responses. *Kidney Int* 5:233–239, 1974
68. Kopple JD, Mercurio K, Blumenkrantz MJ, Jones MR, Tallos J, Roberts C, Card B, Saltzman R, Casciato DA, Swendseid ME: Daily requirement for pyridoxine supplements in chronic renal failure. *Kidney Int* 19:694–704, 1981
69. Cristol JP, Bosc JY, Badiou S, Leblanc M, Lorrho R, Descomps B, Canaud B: Erythropoietin and oxidative stress in hemodialysis: Beneficial effects of vitamin E supplementation. *Nephrol Dial Transplant* 12:2312–2317, 1997
70. De Fronzo RA, Tobin JD, Rowe JW, Andres R: Glucose intolerance in uremia: Quantification of pancreatic beta cell sensitivity to glucose and tissue sensitivity to insulin. *J Clin Invest* 62:425–435, 1978
71. Fouque D: Insulin-like growth factor-1 (IGF-1) resistance in renal failure. *Miner Electrolyte Metab* 22:133–137, 1996
72. Fouque D, Peng S, Kopple JD: Impaired metabolic response to

recombinant human insulin-like growth factor-1 in dialysis patients. *Kidney Int* 47:876–883, 1995
73. May RC, Kelly RA, Mitch WE: Mechanisms for defects in muscle protein metabolisms in rats with chronic uremia. *J Clin Invest* 79:1099–1103, 1987
74. Reaich D, Channon S, Scrimgeour CM, Daley SE, Wilkinson R, Goodship THJ: Correction of acidosis in humans with CRF decreases protein degradation and amino acid oxidation. *Am J Physiol* 265:E230–E235, 1993
75. Rigalleau V, Combe C, Blanchetier V, Aubertin J, Aparicio M, Gin H: Low protein diet in uremia: effects on glucose metabolism and energy production rate. *Kidney Int* 51:1222–1227, 1997
76. Wolfson M: Use of intradialytic parenteral nutrition in hemodialysis patients. *Am J Kidney Dis* 23:856–858, 1994
77. Chertow GM, Ling J, Lew NL, Lazarus JM, Lowrie EG: The association of intradialytic parenteral nutrition administration with survival in hemodialysis patients. *Am J Kidney Dis* 24:912–920, 1994
78. Fine R: Growth hormone treatment of children with chronic renal insufficiency, end-stage renal disease and following renal transplantation: Update 1997. *J Pediatr Endocrinol Metab* 10:361–370, 1997
79. Ikizler TA, Wingard RL, Flakoll PJ, Schulman G, Parker RA, Hakim RM: Effects of recombinant human growth hormone on plasma and dialysate amino acid profiles in CAPD patients. *Kidney Int* 50:229–234, 1996
80. Iglesias P, Diez JJ, Fernandez-Reyes MJ, Aguilera A, Burgues S, Martinez-Ara J, Miguel JL, Gomez-Pan A, Selgas R: Recombinant human growth hormone therapy in malnourished dialysis patients: A randomized controlled study. *Am J Kidney Dis* 32:454–463, 1998
81. Johannsson G, Bengtsson BA, Ahlmen J: Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis: Anabolic effect and functional improvement. *Am J Kidney Dis* 33:709–717, 1999
82. Fouque D, Peng SC, Shamir E, Kopple JD: Recombinant human IGF-1 induces an anabolic response in malnourished CAPD patients. *Kidney Int* 57:646–654, 2000