FORMACIÓN CONTINUADA

Hemodialysis, inflammation and malnutrition

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INTRODUCTION

In European hemodialysis patient, in spite of continuous progress in renal replacement therapy, a 10% annual mortality rate is still reported[1]. The role of undernutrition in this increased death risk is now admitted[2,3]. Serum albumin less than 35 g/l was shown to be associated with a mortality rate of 60% after one-year and 80% after 2 years[4]. Similarly, prealbumin less than 300 mg/l was shown to be associated with a mortality rate of 20% after one-year and 50% after 3 years[5]. Malnutrition in dialysis patients has been attributed to insufficient nutrient intake, dialysis inadequacy, acidosis, hormone derangement and, more recently, to uremia- and dialysis-induced inflammation. Moreover, the frequency and the severity of the association of malnutrition, inflammation and atherosclerosis during chronic renal failure have been underlined[6,7].

The present short review adresses: 1) the prevalence of malnutrition and its prognostic influence in hemodialysis patients, with respect to recent French Cooperative series[8,9]; 2) the role of inflammation in the occurrence of malnutrition; 3) the management of malnutrition.

PREVALENCE AND PROGNOSTIC INFLUENCE OF MALNUTRITION

The prevalence of malnutrition has been documented ten years ago in large series from North America[3] and Japan[10]. Because no large European study of hemodialyzed-patient nutritional status was available, a French National Cooperative Study was undertaken during 1996[8]. This study aimed to determine the prevalence of undernutrition during hemodialysis together with the relationships between nutritional and dialysis data. Thus, 7,123 patients, 4,108 males and 3,015 females whose mean age was 62, were included in the study. Table I gives main dialysis and nutritional data as well as the percentages of patients presenting with abnormal or non-recommended values for each parameter. This population was characterized by adequate dialysis in most of patients: weekly dialysis time was 12 hours or more in 77.8% of patients and Kt/V was equal to or higher than 1.1 in 74.9%. Mean Kt/V was 1.28 ± 0.35 in males and 1.47 ± 0.34 in females. The prevalence of undernutrition varied according to the considered nutritional parameter: 20% for body mass index to 62% for lean body mass. Protein intake, as estimated by mPCR, was less than 1 g/kg/day in one third of patients. Considering the prognosis value of plasma albumin and prealbumin, this study showed lifethreatening undernutrition in 20% to 36% of the studied patients. The study of the interrelations between nutritional parameters showed that prealbumin was the only one

Table I. French National Cooperative Study. Main dialysis and nutritional data[8]

	Mean ± SD	% patients with abnormal or non-recommended values	
Dialysis data			
Dialysis time (h/week)	12.4 ± 2.7	22%	< 12h/week
Kt/V	1.36 ± 0.36	25%	< 1.1
Nutritional data			
BMI (kg/m^2	23.3 ± 4.6	24%	< 20 kg/m^2
LBM (% expected value)	86 ± 21	62%	< 90%
Albumin (g/l)	38.8 ± 5.3	20%	< 35 g/1
Prealbumin (mg/l)	340 ± 90	36%	< 300 mg/1
NPCR (g/kg/day)	1.13 ± 0.32	35%	< 1 g/kg/day

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which correlated with each of the others, and, as previously reported[2,5], appeared as the most representative of nutritional status. Relationships between nutritional parameters and age showed that, as usually reported, albumin significantly decreased with age after 40 and prealbumin after 50. Lean body mass continuously decreased after 40. It should be noticed that the loss of muscle mass was much more pronounced in hemodialysis patients than it is in the general population, reaching 75% of ideal values after eighty years of age. Albumin and prealbumin were not significantly altered by vintage (months on dialysis) while body mass index continuously decreased in categories of patients with more than fifty months on dialysis. Lean body mass was higher in categories of patients hemodialyzed for more than a hundred months. The relationships between the dose of dialysis and nutritional status showed that patients with weekly dialysis time greater than 12 hours exhibited significantly higher levels of albumin and prealbumin independently of Kt/V. Lean body mass and body mass index values increased with weekly dialysis time until 14 hours/week. Lean body mass was higher in patients with Kt/V greater than 1.1 while body mass index was inversely related to Kt/V for values ranging between 0.9 and 2.1, traducing a less effective dialysis in patients with high body mass index as recently reported[11].

A prospective longitudinal survey was undertaken in a subset of this population in order to assess the prognostic value of nutritional and dialysis parameters[9]. One thousand six hundred and ten patients were followed during 30 months. Overall survival in these prevalent patients was 89.7 ± 0.8% after one year and 78.4 ± 1.1% after two years. Univariate analysis using the Cox proportional hazard model showed that survival was significantly influenced by age, presence of diabetes, lean body mass, pre-dialysis concentrations of urea, creatinine, scrum albumin, serum prealbumin and nPCR. Body mass index, weekly dialysis time, vintage, urea reduction rate, Kt/V as well as pre-dialysis plasma of bicarbonate and hemoglobin did not influence the outcome. The lack of influence of Kt/V on survival in this study may be due to the fact that most patients received adequate dialysis. Multivariate analysis showed that among the variables which significantly influenced survival in univariate analysis only age, diabetes, albumin and prealbumin remained significant predictors of the outcome.

Because serum albumin[12] and prealbumin[13] are nutritional proteins which behave as negative acute-phase proteins in renal disease as in other pathological settings[14,15], their high predictive value for survival may be due to this dependance on both nutrition and inflammation.

CAUSES OF MALNUTRITION DURING HEMODIALYSIS, ROLE OF INFLAMMATION

Malnutrition in hemodialysis patients has been attributed to three main mechanisms: insufficient feeding, abnormal nutrient metabolism and nutrient losses due to dialysis procedures. This paper focuses on some aspects concerning nutrient intake and metabolism.

Table II gives the main causes of anorexia in dialysis patients. Data from the French National Cooperative Study[8] underlined the crucial role of protein intake: when patients were stratified in categories of protein intake varying from less than 0.6 g/kg/day to more than 1.5 g/kg/day, albumin and prealbumin values were significantly lower in patients with protein intake below the recommended value of 1.2 g/kg/day. Moreover, lean body mass was strikingly correlated with nPCR from the lowest protein intake category to the highest one while body mass index did not vary beween these categories.

In stable patients with chronic renal failure, studies of forearm protein metabolism using ^{3}H-phenylalanine kinetics showed an increase in protein synthesis, proteolysis and protein turnover without change in net proteolysis[16]. In the same studies, proteolysis was shown to be positively correlated with plasma cortisol and inversely correlated with arterial bicarbonate. From these studies one can expect that any pathological event able either to increase plasma cortisol or to induce acidosis would result in a net loss of muscle mass. Main established causes for increased protein catabolism and decreased protein synthesis in hemodialysis patients are unsufficient energy-protein intakes, acidosis and hormone disturbances. Data on isolated perfused rat muscle showed that acidosis induced a cortisol-dependent activation of both branched-chain amino acid catabolism and ATP-ubiquitin-dependent proteolysis[17]. Longitudinal leucine kinetic studies in chronic renal failure (CRF) patients showed that the correction of acidosis either by sodium bicarbonate or by adequate dialysis

Table II. Cause of anorexia in dialysis patients

- Inadequate dialysis.
- Retention of anorexigen molecules.
- Elevated serum leptin.
- Dysgueusia
- Anemia.
- Digestive discomfort, nausea, vomiting, gastroparesis..
- Polymedication, hospitalisations
- Low economical status.
- Depression

Table III. Effects of hormone disturbances on protein metabolism

Hormone disturbances	Effects on protein metabolism
Insulin resistance	Altered effects on protein synthesis and breakdown.
Lack of 1,25-OH vit. D synthesis	Altered protein synthesis due to an increase in intracellular Ca+. Decrease insulin secretion.
Lack of erythropoietin secretion	Resistance to insulin.
Altered growth factor production and metabolism	Reduced peripheral and hepatocyte sensitivity to GH. Altered IGF-1 metabolism and effects, increase in IGF-1 binding protein BP3.

was followed by a decrease in amino acid oxydation and protein breakdown[18]. Acidosis due to renal failure may also alter hepatosplanchnic amino acid uptake, ureagenesis and albumin synthesis[19-23].

Main hormone impairments during CRF are listed in table III. It is noteworthy that many of these hormone dysfunctions are related to acidosis[24]: correcting acidosis was shown to improve parathyroid cell sensitivity to calcium[25] as well as insulin sensitivity and secretion[26]. Similarly, acidosis appeared as the main factor of abnormal growth factor action[27,28] and thyroid-cell resistance to thyroid-stimulating hormone[29].

Numerous recent papers emphasized the role of systemic inflammatory response as a cause of[6,12,13,30] protein catabolism and malnutrition in dialysis patients. Causes of inflammatory response associated to chronic renal failure and hemodialysis are given in table IV. The systemic inflammatory response is an adaptative phenomenon to stress. This adaptative response aims to satisfy the new metabolic priorities associated to stress condition such as providing fuel and amino acids for immune cells and trauma areas requirements. The inflammatory response involves a release of catecholamines, cortisol, glucagon and growth hormone which induces an insulin resistance and a mobilization fuel stores. Cytokine activation, mainly interleukin-1 and tumor necrosis factor-alpha, promotes muscle protein degradation while interleukin-6 induces the synthesis of acute phase proteins in the liver. As described 20 years ago, decreased concentrations of serum albumin and prealbumin and increased C-reactive protein and α-1 glycoprotein are markers of the systemic inflammatory response syndrome whatever is the origin of stress[31,32]. In stressed patients, the prolongation of this adaptative phenomenon can be deleterious by inducing a massive loss of muscle protein, a lack of adaptation to starvation and a decreased response to adequate nutritional support. In hemodialysis patients, the participation of inflammation to malnutrition seems to be likely. Of course, inflammation is associated with a decrease in serum albumin, but serum albumin cannot be considered as a nutritional marker during inflammation[31]. The prevalence of C-reactive protein more than 20 mg/l was reported to be higher in patients with severe malnutrition than in patients without malnutrition or with moderate malnutrition as estimated by the Subjective Global Assessment[33]. However, whether this relationship was independent from other factors such age is difficult to establish[33]. Expected effects of inflammation on nutritional status would be an increase in protein catabolism and a decrease in protein intake and lean body mass. In a 1054-hemodialysis patient series, C-reactive protein failed to be associated with a decrease in muscle mass as estimated by plasma creatinine[13]. Similarly in a 260-hemodialysis patient series we did not found any correlation between C-reactive protein and weight loss or protein catabolic rate (NC, unpublished data). Thus, as pointed by Lim and Kopple[34], data are needed concerning the effect of chronic uremia-induced inflammation on protein kinetics.

Table IV. Causes of inflammatory response in hemodialysis patients

Dialysis-unrelated inflammatory response	Inflammatory causal disease of uremia. Uremic state *per se*. Reduced renal clearance of cytokines. Associated inflammatory diseases. Unrecognized chronic infections. Chronic heart failure.
Dialysis-related inflammatory response	Membrane bioincompatibility. Complement activation. Backfiltration of pyrogens and endotoxins from contaminated dialysate. Fistula or graft infections.

The abnormalities of nutrient metabolism are responsible for an increase in energy and protein requirements (table V). It is noteworthy that, in spite of these metabolic abnormalities, malnutrition is rare when the nutritional needs are satisfied. As an example, patients with high protein intakes are most often characterized by normal lean body mass in spite of a frequently decreased predialysis plasma bicarbonate[35]. These data underlines the crucial role of inadequate feeding in the pathogenesis of undernutrition during dialysis.

Table V. Recommended daily intakes in hemodialysis patients

	NKF*[42]	ESPEN**[43]
Protein (g/kg/day)	1.2 (> 50% HBV)	1.2-1.4 (> 50% HBV)
Energy (kcal/kg/day)	< 60 ans: 35 > 60 ans: 30 - 35	≥ 35
Vitamins (daily supplements)	–	Pyridoxin: 10 - 20 mg Vitamin C: 30 - 60 mg Folic acid: 1 mg 1-25 $(OH)_2$ D_3[§]

*NKF: National Kidney Foundation; **ESPEN: European Society of Parenteral and Enteral Nutrition. [§]according to calcemia monitoring.

Table VII. Management of malnutrition in dialysis patients

Detection and treatment of intercurrent disease or of any other cause of anorexia or catabolism:

1. correction of inadequate diet;
2. correction of inadequate dialysis;
3. use of biocompatible membrane;
4. use of bicarbonate dialysis;
5. treatment of anemia by erythropoïetin;
6. detection and treatment of depression;
7. detection and treatment of associated gastro-intestinal disorders.

Mild or moderate malnutrition (inadequate diet without criteria of severe malnutrition)

Diet counselling and oral supplements

Severe malnutrition:

– Spontaneous intakes > 20 kcal/kg/day: intradialytic parenteral nutrition + oral supplements
– Spontaneous intakes < 20 kcal/kg/day: daily enteral nutrition

NUTRITIONAL MANAGEMENT OF DIALYSIS PATIENTS

Because of the influence of malnutrition on the outcome, the nutritional management of dialysis patients appears of the first importance. A regular nutritional assessment is necessary in order to verify the diet adequacy and to detect malnutrition (table VI). Severe malnutrition, which indicates an active nutritional support, can be detected by serum albumin less than 35 g/l, prealbumin < 300 mg/l and nPCR < 1 g/kg/day. Table VII gives a decisional schema for the management of malnutrition during dialysis according to nutritional monitoring[36]. In patients with severe malnutrition, intradialytic parenteral nutrition makes it possible to ensure a 15-20 kcal/kg/hemodialysis and 0.5-1 g amino acid/kg/hemodialysis session and to reach nutritional requirements in most of the depleted patients[37]. However, when spontaneous intakes are less than 20 kcal/kg/day, intradialytic parenteral nutrition cannot provide enough nutrients to reach the nutritional requirements. In these patients, total enteral nutrition, given through a nasogastric tube or a gastrostomy, is necessary[36]. More than 20 retrospective studies[36, 38] and one controlled study of intradialytic parenteral nutrition[37] reported an improvement of nutritional status. However, prospective controlled studies are still needed concerning the effect of nutritional support on the outcome of hemodialysis patients.

Promising nutritional effects have been reported using growth factors: in malnourished HD patients, studies on forearm ^{3}H-phenylalanine kinetics, showed that recombinant human growth hormone (rhGH) increased protein synthesis and reduced net protein catabolism[39]. A randomized controlled study of a 4-week administration of rhGH in depleted hemodialysis patients, showed an increase in body weight and plasma transferrin together with a decrease of BUN level, suggesting an anabolic reaction[40]. Similarly, beneficial nutritional effects of nandrolone were reported[41]. These data need to be confirmed by large prospective controlled studies investigating the benefit of hormone therapies in terms of nutritional status and of survival.

Table VI. Recommended daily intakes in hemodialysis patients

Nutritional parameters	Intervals
Diet record (3 - 7 days)	6 - 12 months
Body weight	
Body mass index	1 month
NPCR	1 month
Predialysis creatinine	1 month
Serum albumin	1 - 3 months
Serum prealbumin	1 - 3 months

CONCLUSIONS

According to protein indicators, it seems likely that life-threatening malnutrition is present in about 25% of hemodialysis patients in Europe. Age, diabetes, nutrient intakes and dialysis adequacy appear as major determinants of nutritional status. Age, diabetes, albumin and prealbumin are independant predictors of survival. Serum albumin and prealbumin

behave as negative acute phase proteins and are negatively correlated to C-reactive protein in dialysis patients as in other pathological states. The prognosis value of albumin and prealbumin may be linked to their dependance on both nutrition and inflammation. Established causes for reduced protein anabolism and increased protein catabolism during chronic renal failure are proteincalorie deprivation, acidosis and hormone disturbances. Inflammation likely plays a role in the development of malnutrition in hemodialysis patients. However, data are lacking concerning the effect of chronic uremia-induced inflammation on protein kinetics.

The nutritional management of dialysis patients now appears of the first importance. A regular nutritional assessment is necessary in order to verify the diet adequacy and to detect malnutrition. Nutritional therapy in dialysis patients was shown to be able to improve nutritional status. However, more data are needed in order to assess is effect on patient outcome.

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