Intradialytic Parenteral Nutrition Does Not Improve Survival in Malnourished Hemodialysis Patients: A 2-Year Multicenter, Prospective, Randomized Study

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ABSTRACT

Although intradialytic parenteral nutrition (IDPN) is a method used widely to combat protein-calorie malnutrition in hemodialysis patients, its effect on survival has not been thoroughly studied. We conducted a prospective, randomized trial in which 186 malnourished hemodialysis patients received oral nutritional supplements with or without 1 year of IDPN. IDPN did not improve 2-year mortality (primary end point), hospitalization rate, Karnofsky score, body mass index, or laboratory markers of nutritional status. Instead, both groups demonstrated improvement in body mass index and the nutritional parameters serum albumin and prealbumin ($P < 0.05$). Multivariate analysis showed that an increase in prealbumin of >30 mg/L within 3 months, a marker of nutritional improvement, independently predicted a 54% decrease in 2-year mortality, as well as reduced hospitalizations and improved general well-being as measured by the Karnofsky score. Therefore, although we found no definite advantage of adding IDPN to oral nutritional supplementation, this is the first prospective study demonstrating that an improvement in prealbumin during nutritional therapy is associated with a decrease in morbidity and mortality in malnourished hemodialysis patients.

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Despite the continuing progress in hemodialysis therapy, the mortality rate of maintenance dialysis patients is unacceptably high. In this population, protein-calorie malnutrition is independently associated with an increase in morbidity and mortality.[1,2] Severe malnutrition has been reported in 25% of maintenance hemodialysis patients[2,3] and found to be associated with a yearly mortality rate of approximately 30%.[2,4,5] Intradialytic parenteral nutrition (IDPN) has been proposed to improve patient nutritional status and outcome. The interest of IDPN has been assessed in terms of metabolic effect and nutritional benefit[6]: IDPN has been shown to improve energy and protein balance, albumin synthesis rate, and, in randomized trials, nutritional parameters.[7–11] Retrospective studies have suggested that IDPN may improve survival in hypoalbuminemic hemodialysis patients.[4,5,12] However, to date, the effects of IDPN on patient morbidity and mortality have not been assessed in a

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prospective, randomized manner. More precise, the impact of albumin and prealbumin changes during nutritional therapy on survival has not been addressed.[13,14] This investigator-initiated, prospective, randomized, controlled, French Intradialytic Nutrition Evaluation study (FineS) was designed to evaluate in an intention-to-treat analysis the effects of a 1-yr IDPN given in addition to oral supplements on the 2-yr survival and morbidity. Moreover, this study aimed to define the determinants of the outcome in malnourished maintenance dialysis patients who receive nutritional therapies.

RESULTS

Patients

Between January 2001 and December 2002, 186 patients were randomly assigned to receive either IDPN plus oral supplements (IDPN group, $n = 93$) or oral supplements alone (control group, $n = 93$) during 1 yr, then followed during a subsequent year (Figure 1). The two groups were similar with respect to baseline characteristics (Table 1). At months 3, 6, and 12, IDPN provided the equivalent of 6.6 ± 2.6, 6.4 ± 2.1, and 6.1 ± 2.2 kcal and 0.26 ± 0.08, 0.25 ± 0.09, and 0.24 ± 0.10 g protein/kg per d, respectively. Patients who actually received IDPN at months 3, 6, and 12 represented 87, 79, and 67%, respectively, of the IDPN group. Causes for IDPN discontinuation were nutritional status improvement after 86 to 275 d in seven patients, wish of patient in nine cases, adverse events in 11 patients (nausea, 3; muscle pain, 2; hypertriglyceridemia, 1; arteriovenous fistula pain, 1; other adverse events, 4), and other reasons in five patients. At months 3, 6, and 12, oral supplements provided 5.9 ± 2.6, 5.8 ± 2.5, and 5.6 ± 2.7 kcal and 0.39 ± 0.18, 0.38 ± 0.18, and 0.37 ± 0.18 g protein/kg per d, without between-group difference. In control and IDPN groups, mean compliance to oral supplementation was respectively 72 and 69% after 3 mo, 68 and 75% after 6 mo, and 70 and 61% after 12 mo (NS).

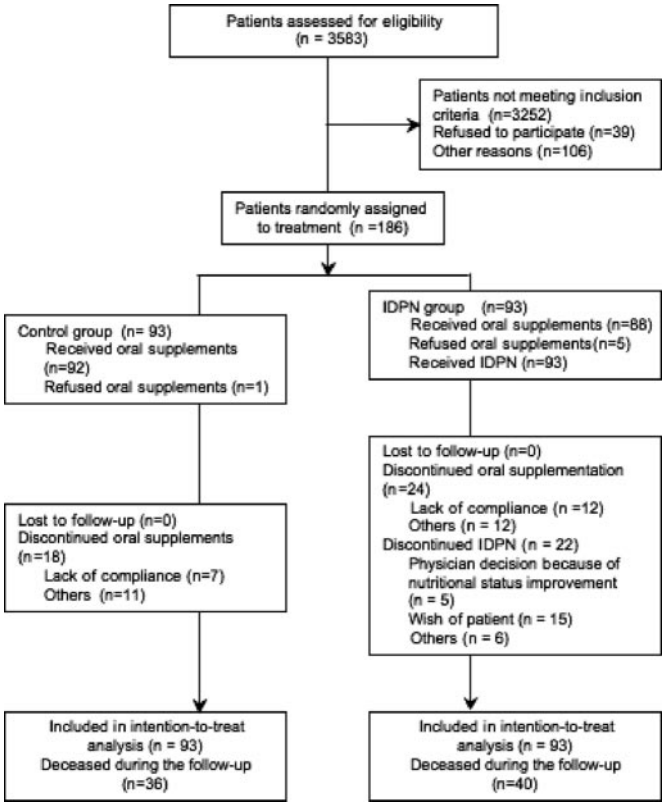

Figure 1. Number of patients who entered the study, were assigned to intradialytic parenteral nutrition (IDPN) or control group, completed the protocol, and were included in intention-to-treat analysis.

Primary Outcome

Thirty-six patients died during the 2-yr follow-up in the control group and 40 in the IDPN group. Causes of death did not differ between groups (Table 2). Mean cumulative survival was 0.77 and 0.58 after 1 and 2 yr, respectively, similar in IDPN and control groups (Figure 2). No difference appeared after adjustment for diabetes, serum C-reactive protein (CRP), and comorbidities. As compared with control subjects, patients with diabetes showed a similar survival at month 12 ($\chi^2 = 0.38$, $P = 0.538$), then tended to have a decreased survival from months 12 to 24 ($\chi^2 = 3.77$, $P = 0.052$).

Secondary Outcomes

Karnofsky score was 66 ± 17 and 66 ± 14 in control and IDPN groups, respectively, on day 0 and remained unaffected and similar in the two groups during the follow-up (data not shown). All patients but 27 were hospitalized at least once during the follow-up. The median hospitalization length was 21 d. Hospitalization rate was 0.06 ± 0.10 and 0.06 ± 0.15 in control and IDPN groups from day 0 to month 12 and 0.06 ± 0.11 and 0.08 ± 0.16 from month 12 to month 24, respectively. Cardiovascular diseases represented 22.3% of hospitalization causes, infections 18.9%, digestive diseases 13.4%, disability 7.9%, neurologic complications 7.1%, falls and fractures 4.6%, cancer 4.6%, and other causes 21%, without between-group statistical difference.

Figure 3 shows nutritional data from day 0 to month 24. As compared with control subjects, IDPN patients exhibited lower spontaneous protein intake at month 12 and higher total energy intake at months 3 and 6. No between-group difference was observed regarding other nutritional data. More than 50% of patients received nutritional support after the 1-yr randomized treatment as per physician's decision. At months 18 and 24, oral supplements were given to 44 and 55% of control subjects and 54 and 50% of IDPN patients, respectively; IDPN was administered in 6 and 9% of control patients and in 13 and 17% of IDPN patients (NS). In both groups, spontaneous intake was stable during the follow-up. Paired tests showed that in both groups, total energy, total protein intake, and normalized protein nitrogen appearance (nPNA) increased from day 0 to months 3, 6, and 12. Nutritional support was followed by

Table 1. Baseline data in control and IDPN groups[a]

Parameter	Control (n = 93)	IDPN (n = 93)
Age (yr; mean ± SD)	67.2 ± 10.8	68.8 ± 9.9
Gender ratio (M/F)	0.90	0.94
Diabetes (n [%])	19 (20)	26 (27)
Comorbidities (n [%])		
chronic infection	1 (1)	3 (3)
cardiovascular event	16 (17)	19 (20)
congestive heart failure	10 (11)	16 (17)
liver insufficiency	3 (3)	1 (1)
respiratory insufficiency	7 (8)	7 (8)
cancer	6 (6)	9 (10)
no comorbidity	57 (61)	43 (46)
Karnofsky score (mean ± SD)	66.0 ± 16.8	65.0 ± 13.9
Dialysis vintage (mo; mean ± SD)	109 ± 104	84 ± 91
Dialysis time (h/wk; mean ± SD)	12.8 ± 1.9	13.3 ± 2.8
Highly permeable membrane (n [%])	55 (59)	49 (53)
Hemodiafiltration/hemodialysis	0.16	0.13
Residual diuresis >500 ml/d (n [%])	4 (4)	4 (4)
Predialysis blood urea (μmol/L; mean ± SD)	19.2 ± 7.3	19.1 ± 6.7
Kt/V urea (mean ± SD)	1.7 ± 0.3	1.7 ± 0.3
nPNA (g/kg per d; mean ± SD)	1.09 ± 0.40	1.10 ± 0.33
Hemoglobin (g/dl; mean ± SD)	10.6 ± 1.3	10.7 ± 1.3
BMI (mean ± SD)	22.4 ± 3.7	23.1 ± 4.7
Serum albumin (g/L; mean ± SD)	31.5 ± 3.7	31.6 ± 4.4
Serum prealbumin (mg/L; mean ± SD)	239 ± 55	240 ± 49
Serum C-reactive protein (mg/l, median [min to max])	11 (0.5 to 168)	10 (0.5 to 197)
Predialysis creatinine (μmol/L; mean ± SD)	652 ± 178	642 ± 177
Plasma cholesterol (mmol/L; mean ± SD)	4.47 ± 1.15	4.54 ± 1.25
Plasma triglycerides (mmol/L; mean ± SD)	1.49 ± 0.64	1.56 ± 0.87
Serum ALAT (UI/L; mean ± SD)	18.5 ± 10.6	18.6 ± 10.4
Serum GGT (UI/L; mean ± SD)	50.4 ± 46.5	61.2 ± 118.0

[a]No significant difference was found between the two groups. ALAT, alanine amino transferase; BMI, body mass index; IDPN, intradialytic parenteral nutrition; GGT, γ -glutamyl transferase; nPNA, normalized protein nitrogen appearance.

an increase in body weight at months 3, 6, and 12 in IDPN patients and at month 3 in control subjects. In addition, both groups showed an increase in serum albumin and prealbumin from day 0 to month 3. Serum albumin remained elevated until month 18 and serum prealbumin until the end of the follow-up (month 24). In the two groups, serum CRP did not vary during the follow-up.

Predictors of Primary Outcome

Because the two groups did not differ with respect to outcomes, the predictors of primary and secondary end points were studied in all patients as a single group. Univariate analysis showed that diabetes and the number of comorbidities increased the mortality risk, whereas dialysis vintage and baseline values of Karnofsky score, serum albumin, and creatinine were negatively correlated with mortality. Mean cumulative survival was 0.74 and 0.37 after 1 and 2 yr in patients with diabetes and 0.78 and 0.64 in patients without diabetes ($P <$ 0.01 at 2 yr). The increase in Karnofsky score and serum prealbumin from day 0 to month 3 predicted an improved survival. Baseline serum CRP did not predict any of the outcomes. Multivariate analysis showed four independent predictors of the 2-yr mortality (Figure 4): Number of comorbidities (odds ratio [OR] 1.53; 95% confidence interval [CI] 1.14 to 2.05 per comorbidity), baseline serum albumin (OR 0.93; 95% CI 0.89 to 0.98 per g/L) and creatinine (OR 0.98; 95% CI 0.97 to 0.99 per 10 μmol/L), and serum prealbumin increase >30 mg/L from day 0 to month 3 (OR 0.46; 95% CI 0.27 to 0.79).

Predictors of Secondary Outcomes

The activity score weakly correlated with serum prealbumin changes from day 0 to month 3 ($r = 0.286$, $P < 0.01$ for Karnofsky score change from day 0 to month 18). Multivariate logistic regression showed that only a serum prealbumin increase independently predicted the risk to be hospitalized for >21 d (OR 0.24; 95% CI 0.10 to 0.59 for a serum prealbumin increase >30 mg/L). Albumin and prealbumin changes from day 0 to month 3 were negatively correlated with CRP changes during the same period ($r = -0.474$, $P < 0.001$, and $r = -0.461$, $P < 0.001$, respectively). However, at uni- and multivariate logistic regression analyses, CRP changes did not predict the serum albumin increase over the critical threshold of 35 g/L or the prealbumin increase by >30 mg/L from day 0 to month 3. Only nPNA determined the 30 mg/L increase of serum prealbumin from day 0 to month 3 (OR 1.34; 95% CI 1.16 to 1.55 per 0.1 g/kg per d). The increase in serum albumin and prealbumin during the follow-up was independent from baseline serum CRP. At day 0, 50% of patients presented with serum CRP >10 mg/L. When all patients were separated into two groups according to their baseline serum CRP levels, it seemed that patients with inflammation, as defined by serum CRP >10 mg/L, were characterized by lower baseline serum albumin and prealbumin concentrations. However, the increase in serum albumin and prealbumin during nutritional support was observed independent from baseline serum CRP (Figure 5). At month 18, the increase in serum albumin was even greater in patients with inflammation.

At baseline, patients with diabetes exhibited a higher body mass index (BMI) than patients without diabetes (24.1 ± 0.7 *versus* 22.3 ± 0.3; $P < 0.05$) and similar serum albumin (31.1 ± 4.2 *versus* 31.7 ± 3.7 g/L) and prealbumin (235 ± 52 *versus* 241 ± 52 mg/L). As shown in Figure 6, similar to patients without diabetes, patients with diabetes exhibited a significant increase in serum albumin and prealbumin from day 0 to months 3 and 6. After month 6, serum albumin but not prealbumin decreased in patients with diabetes as compared with patients without diabetes.

Table 2. Adverse events observed during 2-yr follow-up[a]

Adverse Event	No. of Events	
	Control Group	IDPN Group
Event		
Deaths	36	40
heart failure	10	8
stroke	7	8
infection	8	7
cancer	1	7
Other causes	10	10
Hospitalizations for arteriovenous care	64	54
vascular access thrombosis	10	10
Hospitalization for other reasons	180	180
Events inducing discontinuation of IDPN	—	11
Nausea and vomiting	34	46
Diarrhea	14	8
Abdominal pain	9	8
Increase in plasma triglycerides >2 mmol/L	2	8
Increase in serum ALAT >1 N	1	0
Increase in serum GGT >1 N	1	9

[a]Some patients had more than one event.

Adverse Events

The most frequent adverse effects occurred with a similar frequency in the two groups: Digestive symptoms, hypotension, and muscle cramps (Table 2). They were responsible for IDPN discontinuation in nine cases. No between-group difference was observed according to liver function tests, vascular access–related symptoms, and plasma triglycerides. Arteriovenous fistula pain and hypertriglyceridemia caused IDPN discontinuation in one case each.

DISCUSSION

This study is the first prospective, randomized, controlled trial to address in an intention-to-treat design the effect of IDPN on mortality and morbidity in malnourished hemodialysis patients. Ninety-three patients were randomly assigned to receive IDPN at each hemodialysis session for 1 yr, and 93 were considered as control subjects and did not receive IDPN. The randomization procedure resulted in comparable study groups, although an NS trend to more comorbidities was observed in the IDPN group. Both control and IDPN groups received oral supplements. Both groups exhibited a similar improvement in nutritional status. Mortality rate was not different between the two groups (42% over 2 yr). Similarly, hospitalization rate and changes in Karnofsky score were not influenced by the addition of IDPN.

At first analysis, these negative results question the study power. Given the number of inclusions achieved and the initial hypothesis, the study power ($1 - \beta$ risk) was calculated to be 78%. Because no tendency to a lesser morbidity and mortality was noticed in the IDPN group, it seems unlikely that a higher number of patients would have allowed us to show a beneficial effect of IDPN. Indeed, a tentative estimation of sample size

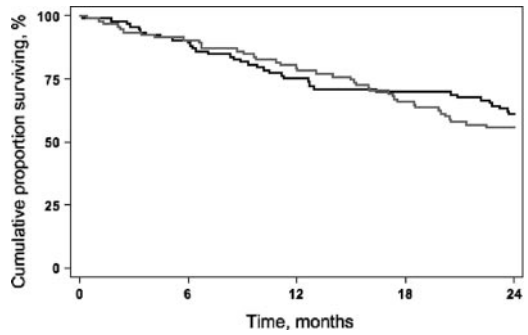

Figure 2. Kaplan-Meier survival analysis in control (black line) and IDPN (gray line) groups (NS). The number of patients on day 0 and months 3, 6, 12, 18, and 24 was, respectively, 93, 83, 70, 64, and 56 in the control group and 93, 80, 67, 55, and 46 in the IDPN group. One patient in the control group (day 530) and three patients in the IDPN group (days 208, 259, and 299) received a kidney transplant.

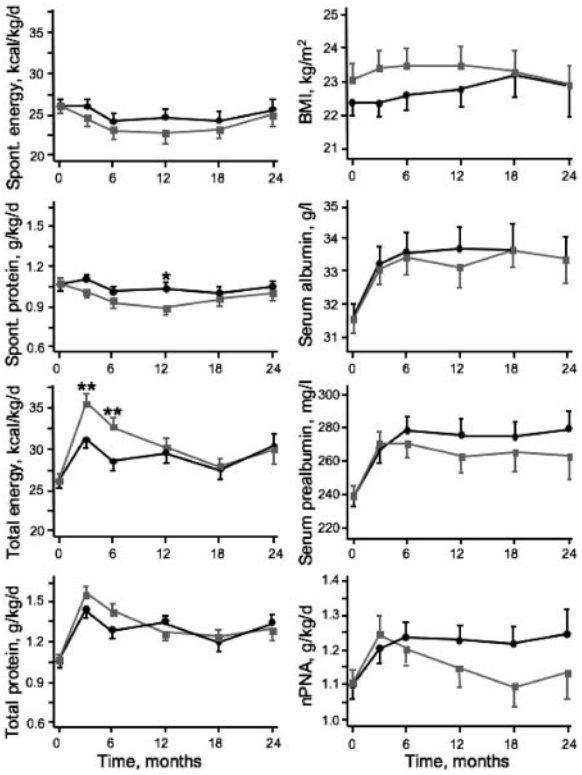

Figure 3. Changes in spontaneous (spont.) and total energy and protein intakes, body mass index (BMI), serum albumin, prealbumin, and normalized protein nitrogen appearance (nPNA) during the 2-yr follow-up in control (black line) and IDPN (gray line) groups (means ± SEM). Between-group differences: $*P < 0.05$; $**P < 0.01$. Nutritional therapies were followed by a significant increase in BMI at months 3, 6, and 12 in the IDPN group ($P < 0.01$) and at month 3 in the control group ($P < 0.05$). In both groups, nutritional support induced an increase in serum albumin at months 3, 6, 12, and 18 ($P < 0.01$) and in serum prealbumin at months 3 to 24 ($P < 0.02$).

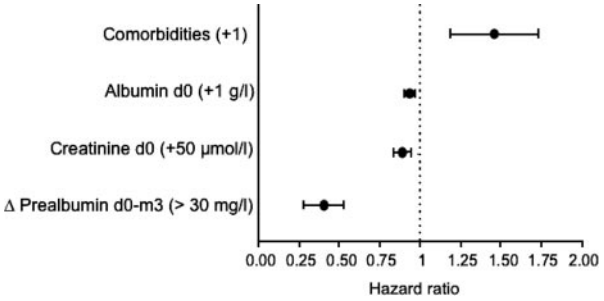

Figure 4. Independent predictors of mortality: Multivariate Cox regression analysis.

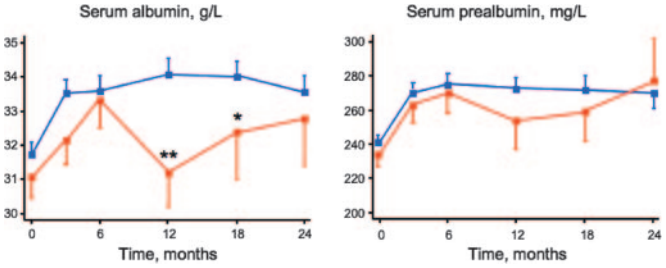

Figure 6. Serum albumin and prealbumin changes from day 0 to month 24 in patients without ($n = 141$, blue line) and with ($n = 45$, red line) diabetes. Between-group differences: $*P < 0.05$; $**P < 0.01$. Nutritional therapies were followed by a significant increase in serum albumin, from months 3 to 24 in patients without diabetes ($P < 0.01$) and at months 3 and 6 in patients with diabetes ($P < 0.01$). Serum prealbumin increased from months 3 to 24 in the two groups.

using the 1-yr efficacy observed in this study showed that a minimum of 1364 patients in each group would have been necessary to observe potentially a difference in the treatment effect with a power of 80%. Such a large 2700-patient study is unlikely to be planned in this area. The lack of effect of adding IDPN to oral supplements was consistent with the nutritional response: No nutritional benefit was noted at each time point from day 0 to month 24. The tendency to a decrease in survival from months 12 to 24 in patients with diabetes from IDPN group may have been due to a deleterious effect of IDPN-induced hyperglycemia, as reported in intensive care unit patients[15] and during total parenteral nutrition.[16]

In both groups, BMI, serum albumin and prealbumin increased during oral supplementation without additional effect of IDPN. For ethical reasons, no control group without nutritional support was studied. However, the beneficial effect of nutritional supplementation is supported by the analysis of body weight and serum albumin changes during the 6 mo before inclusion and during nutritional therapies: Although the two parameters significantly worsened before inclusion, they strikingly improved during supplementation (Figure 7). This dramatic spontaneous degradation of nutritional status before intervention, which was similar in control and IDPN-randomized patients, argues in favor of the design of our study, which included a minimal nutritional support in the control group. Previous randomized studies showed that IDPN was able to improve body weight, serum albumin, and prealbumin in malnourished hemodialysis patients.[9–11] In this study, protein and energy requirements were obtained apart from the administration of IDPN. Such an efficacy of oral supplements may explain the lack of benefit from IDPN addition.

A limitation of this study is that urine collection was not performed. However, because the number of patients with urine output >500 ml/d was similar in the two groups and represented only four patients in each group (Table 1), it is unlikely that this limitation affected the between-group comparison of nPNA values. IDPN was discontinued in seven patients who were randomly assigned to IDPN as a result of an improvement of nutritional status. Such decision by physicians in charge of patients corresponds to a "real life" situation that should be considered in the intention-to-treat analysis. The follow-up of these seven patients led to two deaths, one transplantation, and four living patients at 2 yr. Because such a death rate was slightly lower than for all patients, it seems un-

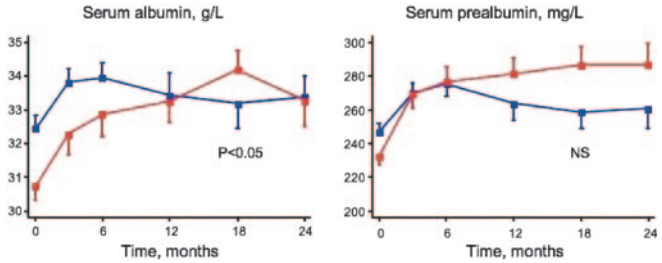

Figure 5. Serum albumin and prealbumin changes from day 0 to month 24 in patients with serum C-reactive protein (CRP) <10 mg/L ($n = 88$, blue line) or ≥10 mg/L ($n = 86$, red line). Baseline albumin and prealbumin were lower in patients with serum CRP ≥10 mg/L ($P < 0.05$). A significant increase in serum albumin and prealbumin was observed irrespective of baseline CRP. At month 18, the increase in serum albumin was greater in patients with the higher baseline CRP concentrations.

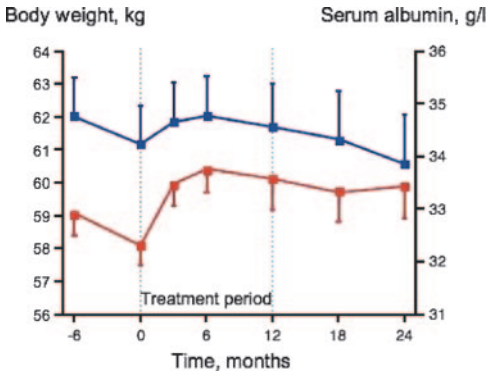

Figure 7. Body weight (blue line) and serum albumin (red line, $n = 121$) changes before, during, and after nutritional therapies. Both body weight and serum albumin decreased from month −6 to day 0 then increased after nutritional support initiation ($P < 0.05$).

likely that IDPN discontinuation influenced the comparisons between the two groups.

In all patients, mean changes in serum albumin and prealbumin from day 0 to month 3 were, respectively, 1.6 g/L and 30 mg/L. Among the 167 patients who presented with serum albumin <35 g/L, one of the criteria for inclusion, 62 reached albumin levels ≥35 g/L at month 3. Similarly, among the 159 patients who presented with serum prealbumin <300 mg/L, another criterion for inclusion, 62 reached prealbumin levels ≥300 mg/L at month 3. It is interesting that during the same period, 80 (43%) patients exhibited a serum prealbumin increase of >30 mg/L, associated with a two-fold improvement of the 2-yr survival. This study is the first to address the predictors of mortality in hemodialysis patients who receive nutritional therapy. Four independent parameters associated with mortality were identified. Besides the well-documented influence of comorbidities, baseline serum albumin, and creatinine,[1,17] it is worth emphasizing that the early increase in serum prealbumin during nutritional support independently predicted survival. This finding demonstrates that nutritional therapy was associated with increased survival when nutritional status, as assessed by serum prealbumin, was improved. Moreover, these results allow physicians to identify patients in whom an improvement of survival could be expected, depending on the early nutritional response. Previous reports showed that hospitalization risk is determined by nPNA and serum albumin.[18–20] In this study, serum prealbumin increase during nutritional support also appeared as an independent predictor of hospitalization. Serum prealbumin is now widely accepted as a sensitive and reliable marker of nutritional status in maintenance hemodialysis patients.[20–23] These data exhibit the prognostic value of serum prealbumin changes during nutritional support. They also show the major role of protein intake because only nPNA determined serum prealbumin increase.

Besides comorbidities, causes of protein loss that may have influenced the response to nutritional therapy include acidosis, dialysis procedure, inflammation, and diabetes.[24,25] Our data did not make it possible to evaluate the role of acidosis in the response to nutritional support. Kt/V values (1.7 ± 0.3 on day 0) did not vary during the follow-up, attesting to dialysis adequacy. In these conditions, dialysis procedure, as assessed by Kt/V, the use of high-permeability membranes, hemodialysis, or hemodiafiltration, did not influence nutritional and outcome parameter changes during the 2-yr follow-up. In hemodialysis patients, inflammation was reported to decrease appetite and to induce protein catabolism.[26] In 79 well-dialyzed patients without nutritional intervention, Kaysen *et al.*[27] demonstrated that inflammation and reduced albumin synthesis were the principal cause of decrease in serum albumin, whereas protein intake remained stable. Conversely, protein energy supplementation by IDPN was demonstrated to enhance albumin synthesis[8] and to increase serum albumin as well as prealbumin.[9,11] The effect of inflammation on the response to nutritional therapy is poorly documented. In a pilot study, Leon *et al.*[28] reported that serum CRP did not alter the response to nutritional intervention, as assessed by serum albumin. In this study, inflammation, as assessed by serum CRP on day 0, did not alter the nutritional response to nutritional support. Although albumin and prealbumin changes were negatively correlated with CRP changes from day 0 to month 3, logistic regression analyses failed to show a predictive value of CRP changes for the serum albumin increase over the critical threshold of 35 g/L or the prealbumin increase by >30 mg/L. Furthermore, the beneficial effect of the prealbumin increase on mortality was independent from baseline serum CRP concentration. These data strongly argue for the provision of a nutritional supplementation in malnourished hemodialysis patients, irrespective of their inflammatory status.

Diabetes did not alter the early response to nutritional support but was associated with a less sustained increase in serum albumin. Patients with diabetes were characterized by an increased mortality during the second year of follow-up. It is noticeable that, opposite to the picture observed in patients without diabetes, the increase in serum prealbumin by >30 mg/L from day 0 to month 3 did not predict an improvement of survival in patients with diabetes. These data are consistent with a previous report showing that, despite a higher prevalence of protein malnutrition, survival of patients with diabetes was independent from nutritional status.[29] Besides insulin resistance,[30] increased inflammatory process and oxidative stress have been advocated as possible causes of lower survival in hemodialysis patients with diabetes. In this study, serum CRP was not influenced by diabetes. In patients with diabetes, glycosylated hemoglobin was 6.98 ± 1.16% on day 0 and not influenced by oral supplementation or IDPN.

This study showed three main findings: (*1*) In malnourished hemodialysis patients, the intention-to-treat analysis failed to show any advantage of adding IDPN to oral supplements; (*2*) in patients without diabetes, nutritional supplementation was associated with a dramatic and sustained improvement in nutritional status; and (*3*) the increase in serum prealbumin during nutritional therapy was an independent predictor of mortality and hospitalization risk during a 2-yr follow-up.

CONCISE METHODS

Study Design

Our first objective was to determine the effects of IDPN on survival, morbidity, and nutritional status of malnourished hemodialysis patients receiving oral supplements. The additional objective was to identify the factors that determine primary and secondary end points. The 3583 patients from the 38 hemodialysis centers belonging to the French Study Group of Nutrition in Dialysis were screened. Inclusion criteria were age between 18 and 80 yr; hemodialysis vintage >6 mo; and two of the following markers of malnutrition: BMI <20 kg/m^2, body weight loss within 6 mo >10%, serum albumin <35 g/L, and serum prealbumin <300 mg/L. Exclusion criteria were weekly dialysis time <12 h; urea Kt/V <1.2; comorbidities compromising the 1-yr

survival (evolutive cancer and AIDS); treatment by oral, enteral, or parenteral feeding during the past 3 mo; and hospitalization at time of randomization.

Two arms were considered: A treated group, receiving IDPN during 1 yr, and a control group. For ethical reasons, given the poor outcome associated with malnutrition in maintenance dialysis, both control and IDPN groups received oral supplements during the same period. Standard oral supplements were given on a basis of 500 kcal/d and 25 g/d protein, according to each physician's usual practice, and the compliance was assessed during dietary interviews at each time point (see End Points). Rules for IDPN delivery were given to physicians who cared for patients: (*1*) The nonprotein energy and protein supply should fulfill the difference between spontaneous intakes as estimated by dietary interview and recommended intakes (*i.e.* 30 to 35 kcal/d and 1.2 g protein/kg per d[31]; (*2*) a standard lipid emulsion should represent 50% and glucose 50% of nonprotein energy supply; (*3*) nitrogen supply should be a standard amino acid solution; and (*4*) the rate of infusion should be constant and not exceed 125 ml/h during the first week, then 250 ml/h during the dialysis session. The amount of fluid infused was fully compensated by ultrafiltration. Four grams of sodium chloride was added per liter of IDPN solution to compensate Na losses as a result of ultrafiltration.[4]

End Points

The primary end point was all-cause mortality decrease in the IDPN group, and secondary end points were hospitalization rate, Karnofsky score,[32] BMI, serum albumin, and prealbumin. Mortality, causes of death, causes and length of hospitalizations, Karnofsky score, nutritional parameters, and adverse events were collected at day 0 and after 3, 6, 12, 18, and 24 mo by two clinical data monitors. The hospitalization rate was defined as the ratio of the number of days of hospitalization per day of follow-up. Spontaneous dietary intake was determined at each time point by a 3-d food report including one dialysis day using the SU-VI-MAX food picture book.[33] Data were computed (Bilnut 4.0 SCDA Nutrisoft, Le Hallier, Cerelles, France) using the French Data Base CIQUAL (*Centre Informatique sur la Qualité des Aliments, Agence Française de Sécurité Sanitaire des Aliments*). Pre- and postdialysis body mass was recorded from a single midweek dialysis session. On the same day, predialysis hemoglobin, serum CRP, albumin, prealbumin, alanine amino transferase, γ glutamyl transferase, triglycerides, cholesterol, and pre- and postdialysis urea and creatinine concentrations were determined by the usual laboratories of the different centers using conventional autoanalyzers. Immunonephelometry was used for serum CRP, albumin, and prealbumin measurements. This method was reported to exhibit the lower inter-center variations and to be the most reproducible method for measuring these plasma proteins.[34] Dialysis adequacy was estimated by urea Kt/V.[35,36] nPNA, a reflection of protein intake in stable conditions, was calculated from urea generation rate after measurements of pre- and postdialysis plasma urea.[37]

Statistical Analyses

Sample sizes were determined according to the primary end point. Considering a spontaneous yearly mortality rate of 30% and α and β error types of 5 and 20%, respectively, the number of patients required to show a 10% reduction of mortality rate (from 30 down to 20%) was 102 in each group (NCSS-PASS software, Kaysville, UT). Randomization was stratified by center: Each center received one or more blocks of six sequentially numbered opaque sealed envelopes.

Data are presented as means $\pm$ SD. OR are given with a 95% CI. Statistical tests were realized with Stata8 (Stata Corp., College Station, TX). The level of significance was set at 0.05. Between-group comparisons were performed in intention-to-treat analysis using *t* test for continuous variables, χ^2 tests for categorical variables, and generalized estimating equations method for longitudinal data. Survival analysis was performed using Kaplan-Meier graphs and log-rank tests.

Age; gender; presence of diabetes; serum CRP; number of comorbidities; baseline nutritional parameters; energy and protein supplies through oral supplementation, IDPN, and whole energy and protein intakes; number of IDPN sessions; and changes in BMI, serum albumin, prealbumin, and nPNA during nutritional support were tested for their predictive value of survival using the univariate Cox proportional hazard model. Variables exhibiting a significant (with $P < 0.20$) predictive value of survival in univariate analysis were then tested in a multivariate Cox model integrating IDPN, diabetes, and age. The same parameters were tested for their predictive value of secondary outcomes using simple regression or uni- and multivariate logistic regression studies.

Ethics

The protocol was approved by the Ethics Committee of Grenoble, France, and registered on clinicaltrials.gov (NCT00314834). Data were analyzed by H.R. and N.J.M.C.

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DISCLOSURES

None.

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