Nutrition and Outcome on Renal Replacement Therapy of Patients with Chronic Renal Failure Treated by a Supplemented Very Low Protein Diet

MICHEL APARICIO,* PHILIPPE CHAUVEAU,§ VALÉRIE DE PRÉCIGOUT,*
JEAN-LOUIS BOUCHET,† CATHERINE LASSEUR,‡ and CHRISTIAN COMBE‡

*Service de Néphrologie, Hôpital Pellegrin, †Centre de Traitement des Maladies Rénales Saint-Augustin,
‡Service de Néphrologie, Hôpital Saint-André, Bordeaux, France; and §Association pour l'Usage du Rein
Artificiel à Domicile en Aquitaine, Gradignan, France.

Abstract. Protein-restricted diets are prescribed in patients with chronic renal failure (CRF) to alleviate uremic symptoms and to slow the progression of CRF. The potential deleterious effects of protein restriction on nutritional status and clinical outcome of patients with CRF have raised concern. In this study, data were collected from 1985 to 1998 on 239 consecutive patients (age 50.2 ± 15.6 yr) with advanced CRF (GFR 13.1 ± 4.8 ml/min) to whom a supplemented very low protein diet (SVLPD) providing 0.3 g protein, 35 kcal, and 5 to 7 mg of inorganic phosphorus per kg per day was administered for a mean duration of 29.6 ± 25.1 mo. The diet was supplemented with essential amino acids and ketoanalogs, calcium carbonate, iron, and multivitamins. During SVLPD, protein intake decreased from 0.85 ± 0.23 to 0.43 ± 0.11 g/kg per d, and body mass index and serum albumin concentration remained unchanged overall. Fourteen patients died during SVLPD; death was unrelated to nutritional parameters. Hemodialysis was initiated after SVLPD in 165 patients at a mean GFR of 5.8 ± 1.5 ml/min. During an average of 54 mo on hemodialysis, mortality was low (2.4% after 1 yr) and correlated to age only, not to nutritional parameters observed at the end of SVLPD. Similar results were obtained in 66 transplanted patients (12 were not dialyzed before transplantation). SVLPD can be safely used in patients with CRF without adverse effects on the clinical and nutritional status of the patients. Due to the preservation of nutritional status and the correction of uremic symptoms, the initiation of dialysis was deferred in these patients. The outcome of patients on renal replacement therapy is not affected by prior treatment with SVLPD during the predialysis phase of CRF.

Protein restriction may be used to slow the progression of chronic renal failure (CRF), but its efficacy is debated. Although the primary results of the Modification of Diet in Renal Disease (MDRD) study were not conclusive (1), secondary analysis of the same study (2) and meta-analyses by Fouque *et al.* (3) and Pedrini *et al.* (4) supported the utilization of protein-restricted diets rather than conventional diets to slow the progression of CRF, particularly in patients with diabetic nephropathy (4). A recent reanalysis of the MDRD feasibility study suggests that supplementation of a very low protein diet (SVLPD) with a ketoacid-amino acid mixture slowed the progression of advanced CRF more than supplementation with an amino acid mixture (5). Furthermore, many authors have demonstrated previously that SVLPD has favorable effects on various metabolic consequences of uremia (6,7), including secondary hyperparathyroidism (8–11), peripheral resistance

to insulin (12–14), red cell lipid peroxidation (15), hyperlipidemia (16), and altered leukocytic functions (17,18). The correction of many such adverse metabolic effects of uremia by SVLPD may be useful to delay the start of renal replacement therapy (RRT) in patients with advanced CRF (19). However, concerns have been raised that dietary protein restriction and more specifically SVLPD could induce malnutrition in patients in the predialysis phase of CRF, whose nutritional status may already be altered by spontaneous decreases in energy and protein intake (20,21). Because malnutrition increases morbidity and mortality in dialysis patients (22–24), the use of SVLPD in the predialysis phase of CRF could have adverse effects on patient outcome on RRT (25). In the MDRD study, the low protein and very low protein diets used were safe for periods of 2 to 3 yr (26). However, both protein and energy intake declined and there were small but significant declines in various indices of nutritional status, indicating that "Physicians who prescribe low-protein diets must carefully monitor patients' protein and energy intake and nutritional status" (26). As a matter of fact, we have shown that energy production rate is increased in patients on SVLPD, which implies that the caloric intake should be increased when protein intake is restricted (14). In patients previously treated with SVLPD during the predialysis phase of CRF, the outcome on dialysis has been evaluated by only one group thus far (19,27,28). They found

that predialysis SVLPD substantially improved patient survival during the first 2 yr on dialysis.

In the present retrospective study, we have evaluated the influence of SVLPD on the clinical outcome and nutritional status of 239 patients with advanced chronic renal failure during the predialysis period and their evolution after initiation of dialysis and/or transplantation.

Materials and Methods
Study Population

From December 1985 to January 1998, an SVLPD has been proposed for all adult patients with advanced chronic renal failure (GFR <25 ml/min per 1.73 m^2) who were followed in the Service de Néphrologie, Hôpital Pellegrin, Bordeaux, France. Patients who required immediate initiation of dialysis, had excessively severe comorbid conditions, or were obviously incapable of following this vegetarian diet and its monitoring were not given SVLPD. In this period of time, it can be estimated that 30 to 40% of patients presenting with advanced CRF were administered a SVLPD in our department. Among the patients who gave informed consent to follow the dietary prescription, 239 were treated for more than 3 mo and were considered to be eligible for this study. Many of these patients have been included in previously published studies from our department about the metabolic effects of SVLPD (9,10,14,17,18,29).

Initially, dietary intake, nutritional indices, and renal function were assessed while patients were on their usual unrestricted diet during a 1-wk hospitalization. SVLPD was started after the patient and the patient's family had been introduced to the dietary prescription by a specifically trained dietitian familiar with the theoretical and practical aspects of SVLPD in patients with CRF.

Patients were evaluated every month as outpatients. Compliance with the prescribed diet was assessed by food diaries and 24-h urinary urea nitrogen excretion as an estimation of dietary protein intake (29,30). Routine blood and urine analyses were performed at the central laboratory of the hospital. After physical examination, a joint dietetic visit with a physician and a dietitian allowed for a readjustment of the prescription when necessary. GFR, which was evaluated as the urinary clearance of ^{51}Cr-ethylenediaminetetra-acetic acid normalized to 1.73 m^2 body surface area (29), anthropometrics, and nutritional proteins were assessed every 3 mo.

Treatment Regimen

All patients were prescribed a diet providing per kg per day 0.3 g of protein of vegetable origin and 5 to 7 mg of inorganic phosphorus. The energy supplied (35 kcal/kg per d) was furnished mainly by carbohydrates (67%), lipids accounting for 30% of the energy intake, and protein for only 3%. The diet was supplemented with one tablet for 5 kg body weight of a mixture of essential amino acids and ketoanalogs (Ketosteril®; Fresenius, Germany). Ketosteril® was unavailable from March 1994 to June 1995; therefore, amino acid supplementation was then given at the same dosage in the form of Cetolog® (Clintec, France), the production of which was stopped in June 1995. The composition of the tablets has been described in detail elsewhere (14,29). Calcium carbonate supplementation was given to maintain serum calcium within the normal range, at doses of 1 g/d (i.e., 400 mg elemental calcium) when amino-acids were provided by Ketosteril® and 2 g/d when amino acids were provided by Cetolog®, which contained less calcium (10,29). Patients were supplemented with iron and a multivitamin preparation providing 1000 UI of vitamin D2 per day. Patients who had proteinuria of >2 g/d were

supplemented with animal proteins of high biologic value calculated on the basis of 1.25 g for 1 g of protein in the urine. They also received antihypertensive medications and diuretics as needed according to standard clinical criteria. RRT was initiated as required on the basis of clinical symptoms and laboratory findings. Depending on age and comorbid conditions, willing patients were referred to the transplant unit to be evaluated for renal transplantation when isotopic GFR was <10 ml/min per 1.73 m^2.

Study Design

As stated above, the primary goal of this study was to evaluate the clinical and nutritional outcomes of patients treated by SVLPD. Clinical and biologic parameters were assessed before the beginning of the diet ($T0$), after 4 mo of SVLPD ($T4$), and at the end of SVLPD (T_{end}). We have shown previously that at 4 mo, an equilibration status is achieved for most of the metabolic parameters studied (10,14,18,29). For patients who were treated by dialysis after SVLPD, the 1-mo examination before starting dialysis treatment was considered as T_{end}.

The clinical outcome of the patients was evaluated at the date of completion of the study (February 1998), whether they were still treated by SVLPD, with a functioning graft, or on RRT. A questionnaire was sent to the transplant unit and to the dialysis centers of the Aquitaine region of France, asking for the status of the patients (dead or alive) and for the date and principal cause of death. Only two patients were considered lost to follow-up. Patients were grouped for the analysis according to their outcome at the end of treatment by SVLPD, 1 yr after cessation of SVLPD and at last follow-up in February 1998.

Statistical Analyses

Comparisons between groups were carried out using ANOVA and the Fischer exact test as applicable. For the same patients, comparisons between two periods were made using paired t test. The clinical outcome of all patients was evaluated at the end of treatment by SVLPD and 1 yr after if applicable, and at the end of follow-up (February 1998). Survival analyses were performed with the Kaplan–Meier method. Factors influencing survival were analyzed using the Cox proportional hazard method. All analyses were performed with two-tailed tests, using $P < 0.05$ as the level of significance.

Results
Predialysis Period

Baseline Characteristics of the Population. The study included 239 patients. The causes of renal disease and baseline characteristics of the patients are shown in Table 1. Glomerulonephritis, interstitial nephritis, autosomal dominant polycystic kidney disease, and chronic rejection were the most common causes of CRF, while diabetes and nephrosclerosis represented only 7.4 and 10%, respectively. Such a distribution is comparable with other data published for France (31,32) for the years 1985 to 1992 and with the findings of a recent study concerning more than 7000 French hemodialyzed patients (33). The low prevalence of diabetes is comparable to other published data from French patients (34). Renal function was not different in patients with CRF of different etiologies, but proteinuria was more severe in patients with diabetes and chronic glomerulonephrites. The nutritional status was poorer in patients with chronic rejection.

Several significant differences ($P < 0.01$) between male and

Table 1. Clinical and biological characteristics of the 239 patients (140 male, 99 female) at the beginning of SVLPD[a]

Characteristic	Mean ± SD	Range	Normal Range
Age (yr)	50.2 ± 15.6	14 to 87	
Weight (kg)	63.9 ± 12	36 to 102	
males	69.4 ± 10.3		
females	56.2 ± 9.9		
BMI (kg/m^2)	22.3 ± 3.3	15 to 35	
males	23.2 ± 2.8		
females	21.2 ± 3.6		
Plasma urea (mmol/L)	21.8 ± 6.4	9.5 to 41	3.5 to 7
Plasma creatinine (μmol/L)	437 ± 120	221 to 822	62 to 124
Serum albumin (g/L)	38.4 ± 5.3	15 to 50	36 to 46
Plasma bicarbonate (mmol/L)	22.6 ± 3.7	12 to 34	24 to 32
Serum PTH (pg/ml)	213 ± 168	10 to 1080	<60
GFR (ml/min per 1.73 m^2)[b]	13.1 ± 4.8	4 to 23	90 to 120
Protein intake (g/kg body wt per d)	0.85 ± 0.23	0.4 to 1.6	
Proteinuria (g/d)	2 ± 2.3	0 to 19	
Follow-up (months)	29.6 ± 25.1	3.9 to 144	

[a] The various diagnoses in the patients were as follows: chronic glomerular nephritis, 23%; interstitial nephritis, 21%; diabetes mellitus, 7%; nephrosclerosis, 10%; polycystic kidney disease, 15%; chronic rejection, 12%; other and unknown, 12%. SVLPD, supplemented very low protein diet; BMI, body mass index; PTH, parathyroid hormone.
[b] Available in 142 patients.

female patients were found. Male patients were older and, as expected, their body weight and body mass index (BMI) were higher. GFR was similar in the two groups, but serum parathyroid hormone (PTH) levels were higher in the female group.

Classification according to the Outcome and Parameters Influencing Survival during the Predialysis Period. According to their clinical outcome, patients were classified into five groups. Twenty patients spontaneously stopped the treatment (group "discontinued") and 14 patients (5.9%) died (group "dead"), predominantly from cardiovascular and neoplastic causes. No cachexia or fatal infection occurred. Most of the patients, *i.e.*, 165, were treated by hemodialysis after SVLPD (group "dialyzed"). Twelve patients were transplanted before dialysis treatment (group "transplanted"), and 28 are still following the dietary regimen (group "SVLPD"). The mortality rate while patients were treated by SVLPD was 2.4% per year at risk over a total of 588.2 patient-years. The overall duration of treatment by SVLPD was 29.6 ± 25.1 mo (median 22.5). This duration was shorter in the "discontinued" and "dead" groups (16 and 25 mo, respectively). However, this should have been long enough to permit possible signs of malnutrition to appear. Age and duration of treatment by SVLPD in the different groups are shown in Figure 1. Age at the start of the study was significantly higher in the "dead" group than in the other groups, and in the "SVLPD" group than in the "transplanted" group ($P < 0.05$). However, neither age ($P = 0.06$) nor nutritional parameters such as BMI and serum albumin concentration at the initiation of SVLPD significantly influenced survival time in the predialysis period as determined by the Cox proportional model.
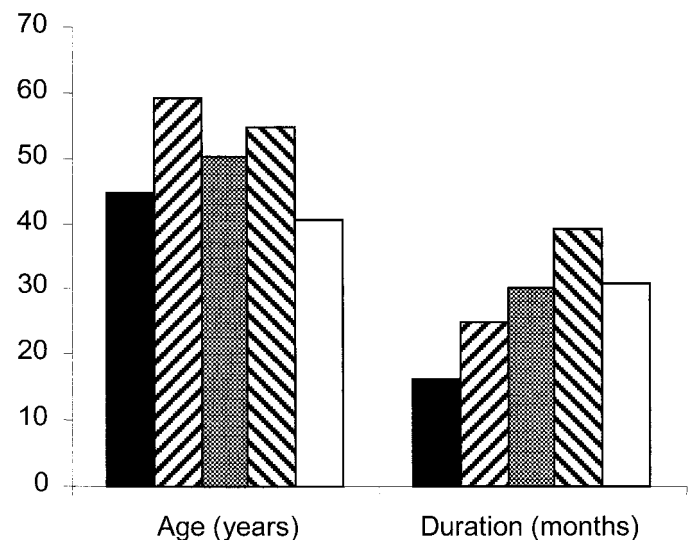

Figure 1. Age (years) and duration of treatment (months) in the different groups of patients. ■, group "discontinued;" ▨, "dead;" ▤, group "dialyzed;" ▨, supplemented very low protein diet (group "SVLPD"); □, group "transplanted."

Outcome of Nutritional Parameters according to the Different Groups. An expected and significant reduction in protein intake was observed as soon as 1 mo after SVLPD was initiated (data not shown). The reduction in protein intake demonstrated after 4 mo of SVLPD was sustained until the end of the study (Figure 2). The dramatic reduction in estimated protein intake from urinary urea excretion from 0.85 ± 0.23 to 0.43 ± 0.11 g/kg per d is indicative of a satisfactory compliance by most of the patients to the prescribed diet (29). The
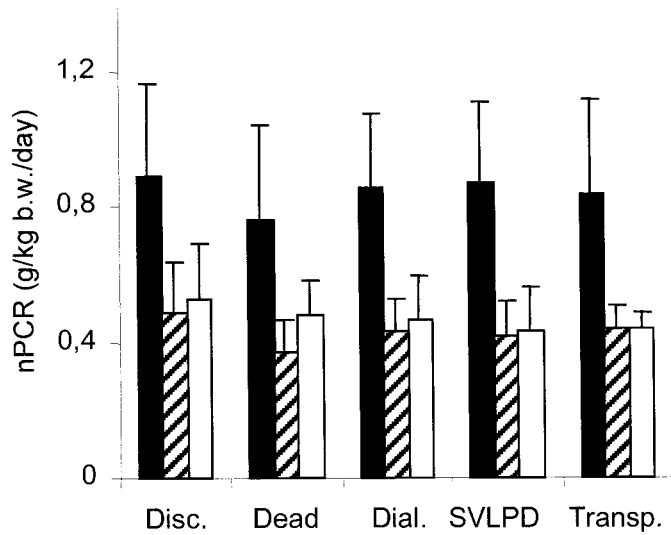
Figure 2. Evolution of the protein catabolic rate (nPCR) estimated from urinary urea excretion in the different groups of patients at the beginning (■), at 4 mo (▨), and at the end (□) of treatment by SVLPD.

courses of BMI and serum albumin are shown in Figure 3. At the start of the study, protein intake and BMI were identical in the different groups but serum albumin was significantly lower in the "discontinued" than in the other groups ($P < 0.05$). Serum albumin concentrations were not significantly modified overall (from 38.4 ± 5.3 to 39.2 ± 5.1 g/L, $P = 0.052$), but increased significantly in the "SVLPD" group from 39.3 ± 5.9 to 42.2 ± 5.3 g/L ($P < 0.02$). BMI remained unchanged in all groups.

Proteinuria.   In the 41 patients who had proteinuria >3.5 g/d at the start of SVLPD, daily urinary protein excretion decreased from 5.7 ± 2.8 to 3.0 ± 2.1 g/d at the end of the survey ($P < 0.001$). During the same period of time, serum albumin concentration increased significantly in these patients from 33.8 ± 6.4 to 37.8 ± 5.4 g/L ($P < 0.002$).

GFR, Serum PTH, and Serum Bicarbonate.   GFR was measured every 3 mo in all 142 patients included since 1989. Figure 4 shows the changes in GFR. No difference existed among the various groups at the start of the study. GFR in the "dead" group was unchanged during the 25-mo follow-up. Dialysis therapy was initiated at a mean GFR of 5.8 ± 1.5 ml/min per 1.73 m^2. No patient was dialyzed earlier because of malnutrition. Serum PTH levels were significantly reduced from 213 ± 68 pg/ml (median 167) to 206 ± 264 pg/ml (median 131) ($P < 0.001$), and serum bicarbonate concentration increased significantly from 22.6 ± 3.7 to 24.5 ± 3.1 mmol/L ($P < 0.001$).

Outcome of Patients on Dialysis Therapy and Transplantation

Outcome and Factors Influencing Survival in Patients Treated by Hemodialysis.   Hemodialysis was used as RRT in 165 patients. Their mean characteristics at the start of the dialysis treatment are summarized in Table 2. The mean time
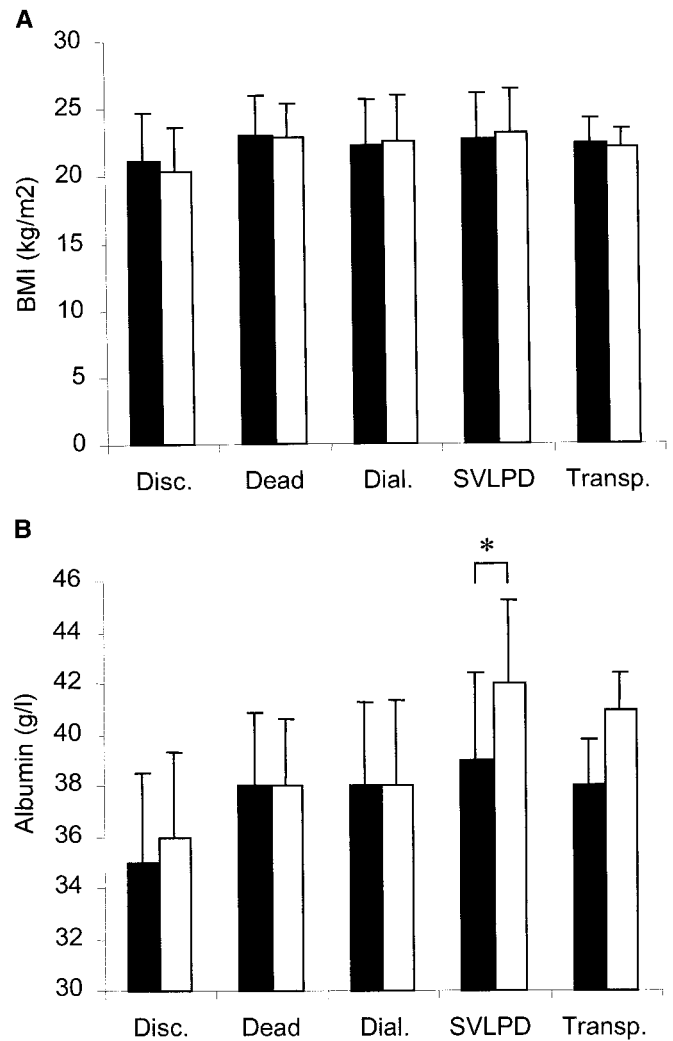

Figure 3. Nutritional parameters at the beginning (■) and end (□) of treatment by SVLPD in all patients. (A) Body mass index (BMI). (B) Serum albumin concentration. *$P < 0.02$ between beginning and end of SVLPD.

of follow-up was 70 mo (median 68 mo) including 54 mo on dialysis (median 48 mo). Figure 5 shows a Kaplan–Meier curve of the survival of the patients treated by hemodialysis after cessation of SVLPD. On dialysis treatment, the mortality rate was 2.4, 25, and 50% after 1, 5, and 10 yr, respectively. Four of the 66 patients who received a renal transplant died. During the first year on dialysis, four patients died (2.4%), 28 patients were grafted, and one was lost for follow-up. In February 1998, after a mean follow-up of 8 yr, 63 patients were still on dialysis, 26 were grafted, 42 were dead, and one patient was lost to follow-up. Most of the deaths were due to cardiovascular or cerebrovascular causes. Only four patients died with cachexia after, respectively, 48, 49, 51, and 89 mo of dialysis treatment, and all of them were older than 80 yr.

The influence of age on the outcome of dialysis is depicted in Figure 6, with a shorter survival observed in older patients. Five years after the initiation of dialysis (*i.e.*, after the discontinuation of SVLPD), 50% of patients were still alive in the
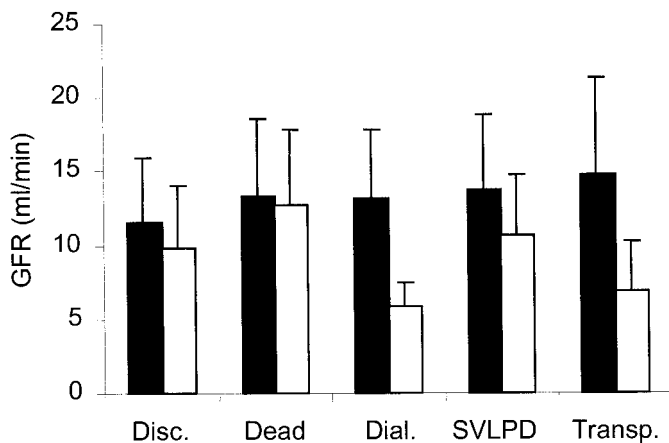
Figure 4. Isotopic GFR in the different groups of patients at the beginning (■) and end (□) of treatment by SVLPD.

Figure 5. Survival curve of the 165 patients treated by hemodialysis after cessation of SVLPD.

Table 2. Clinical and biological characteristics at the beginning and end of treatment by SVLPD of the 165 patients (103 male, 62 female) treated by hemodialysis[a]

Characteristic	Beginning	End
Age (yr)	50.1 ± 15.8	52.6 ± 16.1
Body weight (kg)	64.2 ± 12.1	64.6 ± 12.1
BMI (kg/m^2)	22.4 ± 3.3	22.5 ± 3.4
Protein intake (g/kg per d)	0.86 ± 0.22	0.48 ± 0.13[b]
Creatinine (μmol/L)	458 ± 123	748 ± 183[b]
Urea (mmol/L)	22.6 ± 6.9	16.6 ± 6.4[b]
Bicarbonate (mmol/L)	22.4 ± 3.6	24.1 ± 2.9[b]
Albumin (g/L)	38.7 ± 4.4	38.8 ± 4.8
GFR (ml/min per 1.73 m^2)[c]	13.1 ± 4.8	5.8 ± 1.5[b]
PTH (pg/ml)	211 ± 49	206 ± 193
Urinary protein (g/d)	1.9 ± 1.9	1.5 ± 1.4
Follow-up (months)		29.8 ± 23.1

[a] Abbreviations as in Table 1.
[b] $P < 0.0001$, start *versus* end of SVLPD.
[c] Available in 93 patients.

group older than 60 and more than 70% in the younger groups. In the Cox proportional hazards model, older age significantly influenced survival ($P < 0.00002$), whereas BMI and serum albumin concentration at the beginning of hemodialysis treatment (*i.e.*, at the end of SVLPD), and BMI and serum albumin concentration at the beginning of SVLPD had no significant influence on survival.

Transplanted Patients. Twelve patients were grafted without prior initiation of dialysis. Fifty-four were transplanted while treated by hemodialysis. None of these 66 patients died during the first year. Among these 66 patients, there were four deaths overall involving neoplasia, myocardial infarction, a cerebrovascular cause, and cytomegalovirus infection.

Discussion

In this study, we assessed the evolution of the nutritional status of 239 predialysis patients treated by SVLPD during a
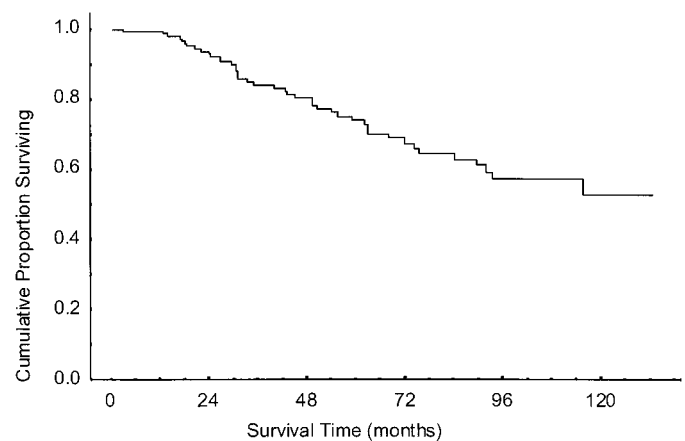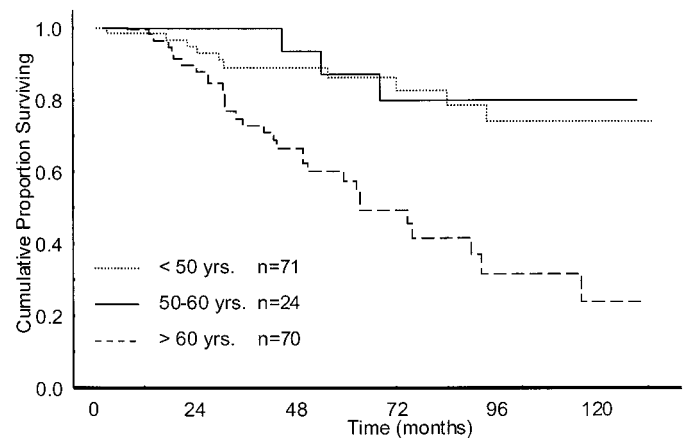

Figure 6. Survival curve of the 165 patients treated by hemodialysis after cessation of SVLPD, according to age.

mean period of nearly 30 mo and their outcome after initiation of end-stage renal disease treatment.

Clinical Outcome and Nutritional Status of the Patients while Treated by SVLPD

Between 1985 and 1998, an SVLPD was proposed to all adult patients with advanced CRF, excluding those with severe comorbid conditions that might superimpose a hypercatabolic state. Because of the potential risk of malnutrition, patients who obviously could not adapt to the dietary prescription or to close monitoring were also excluded. However, "healthy" patients with insulin-dependent diabetes mellitus or with advanced chronic renal rejection who could be considered as *a priori* high-risk nutritional patients were included in the study. Older age was not considered a contra-indication.

According to these conditions, 239 patients, *i.e.*, roughly 30 to 40% of all the patients who presented with advanced CRF during this period of time, were given an SVLPD. Compliance with the diet was satisfactory in most of them as demonstrated by the mean alimentary protein intake, which was 0.39 g/kg per d (the amino acid supplements affording 0.5 to 0.7 g N/d).

Furthermore, only 16 patients dropped out after the first 3 mo of SVLPD during the survey. In cases of intercurrent illness that could interfere with the adaptation to low-protein intake, SVLPD was stopped and patients were given a conventional protein intake. In most studies concerning long-term survey of predialysis patients on SVLPD, no signs of protein malnutrition were found, with one exception in which protein intake was restricted to 0.2 g/kg per d (35). This resulted in an abrupt decrease in body weight and anthropometrics during the first 3 mo, after which these parameters tended to be more stable. In the MDRD study B, patients on SVLPD displayed minor but statistically significant declines in serum transferrin, urinary creatinine excretion, and anthropometrics while serum albumin rose; therefore, it is believed that the very low protein diets used in the MDRD Study are safe for periods of 2 to 3 yr. (7,26).

In the present patients, a close clinical follow-up permitting a better control of anemia, fluid balance, and BP associated with a monthly dietary counseling has enabled us to maintain a satisfactory nutritional status during the predialysis period, as demonstrated by stable body weight, BMI, and serum albumin levels. Similarly, maintenance of neutral nitrogen balance as well as stability of serum protein levels and anthropometric values indicative of muscle mass have been observed in CRF patients on long-term SVLPD treatment (36). This close monitoring explains the difference in the results observed in predialysis patients who do not follow a dietary prescription and whose spontaneously reduced protein and energy intake results in malnutrition in 25 to 50% of cases at the start of RRT (37,38). As reported in other long-term protocols of dietary protein restriction, the present study confirms that such diets have no or minor adverse effects on the nutritional status of patients when they are carefully followed (39). Moreover, as already reported by others, in patients with nephrotic syndrome, protein intake restriction results in a significant increase in serum albumin levels (40).

In addition, proper observance of SVLPD has allowed the correction or improvement of various catabolic factors, which may have resulted in improved protein anabolism. The correction of metabolic acidosis is explained by a marked reduction in the production of H^+ ions linked to high intake of metabolizable organic anions and low intake of sulfur-containing amino acids (29,41). The mean serum bicarbonate concentration of our patients was 24.4 ± 3.0 mmol/L at the beginning of RRT (before discontinuing SVLPD), and less than 4% of patients had serum bicarbonate levels below 20 mmol/L. Normalization of serum bicarbonate levels is important because metabolic acidosis stimulates amino acid and protein degradation, reduces albumin synthesis, induces negative nitrogen balance, and blocks the ability of uremic patients to adapt to a reduced-protein diet (41). Because of its very low content in phosphorus and preserved calcium intake through calcium carbonate supplementation (and calcium salts of ketoanalogs in the Ketosteril® supplementation) (10), a SVLPD reduces phosphorus retention, which inhibits calcitriol production and decreases the calcemic response to PTH, thus representing two of the main mechanisms implicated in the genesis of secondary hyperparathyroidism (9,10,29). Serum phosphorus and PTH levels were close to normal in the majority of the patients; only 16% of them had PTH levels >300 pg/ml at the discontinuation of SVLPD. This last result is of paramount importance given the various deleterious effects of PTH. Furthermore, it is possible that SVLPD, which improves the altered insulin sensitivity of uremic patients (12,13), also has positive effects on their protein metabolism. On the other hand, because SVLPD increases carbohydrate and lipid oxidation as well as energy expenditure (14), and because nitrogen balance is markedly influenced by the importance of caloric intake in both uremic patients and healthy control subjects (42), efforts must be made to improve energy intake. Finally, the reduced accumulation of nitrogen-containing waste products may have contributed to maintaining a better appetite. These different factors may explain why none of the patients needed a hastening of the initiation of dialysis on nutritional grounds. During the predialysis period, only 14 patients died, mostly from cardiovascular disorders. It must be considered that such a low mortality rate was observed in patients with advanced renal failure who could have been treated by dialysis according to current medical standards (43). Death rate was weakly influenced by the age of patients. Conversely, there was no correlation with the duration of dietary treatment or with the evolution of nutritional parameters.

Clinical Outcome of the Patients on RRT (after Cessation of SVLPD)

The low mortality of dialysis patients reported in the present study seems to refute the concern that has been raised about the possibility that SVLPD could induce malnutrition and result in poor outcome of patients once dialysis is initiated, with nutritional status of patients at the onset of end-stage renal disease therapy a major determinant of short- and long-term survival (24,44–46).

At the beginning of treatment by hemodialysis, GFR was 5.8 ± 1.5 ml/min per 1.73 m², lower than in the MDRD study (9.1 ± 3 ml/min per 1.73 m²) but nearly identical to the final GFR of 5.6 ± 1.9 ml/min at which RRT was initiated in the patients reported by Walser and Hill (19), and very close to the mean value of 7.1 ± 3.1 ml/min per 1.73 m² recently reported in the U.S. end-stage renal disease population involving more than 90,000 patients. In the latter study, the proportion of patients with GFR >10 ml/min, between 5 and 10 ml/min, and <5 ml/min was 14, 63, and 23%, respectively (47,48). Besides the disputed influence of SVLPD on the progression of CRF (not evaluated in the present study), which could delay the onset of RRT (19), it is likely that the dramatic reduction in serum urea levels and other putative uremic toxins derived from alimentary protein intake (49) and the correction of several metabolic disorders alleviated some of the uremic symptoms and in this manner postponed the beginning of HD treatment (19).

It does not appear that the initiation of RRT at a level of residual renal function lower than usually recommended (25,37,43,50–52) had a negative influence on the survival of patients on dialysis. This conclusion is all the more straight-

forward in that, in the present study, the clinical outcome of the patients on RRT was considered from the beginning of dialysis, and not after the first 3 mo as in the USRDS registry. During the first year of dialysis, four patients (2.4%) died (none during the first 3 mo), all from cardiovascular causes. The mortality rate was 6.8% during the second year and the patient survival was 75 and 50% at 5 and 10 yr, respectively. These results compare favorably with those recently reported in France and Western Europe (31), in the USRDS case mix (24,32), and in the Japanese registry (53), but our patients represent a highly selected population with different underlying nephropathies and comorbid conditions. Unfortunately, no registry exists in France to compare our data with those of a "standard" French dialysis population. However, despite the absence of a control group, one may consider that SVLPD had no adverse effects on the survival of patients subsequently treated by dialysis.

Most of the deaths were related to cardiovascular and cerebrovascular causes. Only four patients died with cachexia after 48, 49, 51, and 89 mo on dialysis. They were, respectively, 81, 82, 81, and 81 yr old at the time of death.

These data confirm the results of Coresh *et al.* (27), who, after a mean duration of dietary treatment before dialysis of 27 mo, observed a particularly low number of deaths: during 37 person-years of follow-up, only one patient died in the first year of dialysis. Rayner *et al.* (54) found no difference in mortality on dialysis between their group of 79 patients previously on a low-protein diet (0.6 g/kg per d) and those without dietary prescription. These various results suggest that when carefully monitored, protein-restricted diets have no direct harmful effects on the short- and long-term outcome of patients subsequently treated by hemodialysis.

In the current patients treated by SVLPD before the initiation of RRT, peritoneal dialysis was not proposed because we were concerned about the possibility of protein malnutrition (55). However, in view of the results obtained in patients treated by hemodialysis, one may speculate that such treatment would not have major side effects.

The results observed in the 66 patients who received a cadaveric renal transplant (without prior RRT or while they were on RRT) are comparable to those reported in the French Transplant Registry (56), in which the patient survival rate was 95.2% at 1 yr and 89.6% at 5 yr. Only four of the present transplant recipients died (from stroke, neoplasia, myocardial infarction, and cytomegalovirus infection).

Conclusion

The results of the present study, conducted in a single center, demonstrate that a very low protein diet in patients with advanced chronic renal failure carefully selected, motivated, and followed had no deleterious influence on their nutritional status in the predialysis phase of CRF. Furthermore, the clinical outcome of the patients when they reached end-stage renal failure, whether they were treated by hemodialysis or transplanted, compares favorably to data reported in the literature. What is more, the reduction in serum urea levels reflecting the correction of several metabolic disorders alleviated uremic symptoms and in this manner delayed the onset of end-stage renal failure treatment until GFR levels lower than those currently recommended were attained.

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