Long-term outcome on renal replacement therapy in patients who previously received a keto acid–supplemented very-low-protein diet1,2

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ABSTRACT

Background: The consequences of a supplemented very-low-protein diet remain a matter of debate with regard to patient outcome before or after the onset of renal replacement therapy. Objective: We evaluated the long-term clinical outcome during maintenance dialysis and/or transplantation in patients who previously received a supplemented very-low-protein diet. Design: We assessed the outcome of 203 patients who received a supplemented very-low-protein diet for >3 mo (inclusion period: 1985–2000) and started dialysis after a mean diet duration of 33.1 mo (4–230 mo).

Results: The survival rate in the whole cohort was 79% and 63% at 5 and 10 y, respectively. One hundred two patients continued with chronic dialysis during the entire follow-up, and 101 patients were grafts at least once. Patient outcomes were similar to those of the French Dialysis Registry patients for the dialysis group and similar to the 865 patients who were transplanted in Bordeaux during the same period for the transplant group. There was no correlation between death rate and duration of diet.

Conclusions: The lack of correlation between death rate and duration of diet and the moderate mortality rate observed during the first 10 y of renal replacement therapy confirm that a supplemented very-low-protein diet has no detrimental effect on the outcome of patients with chronic kidney disease who receive renal replacement therapy.  Am J Clin Nutr 2009;90:969–74.

INTRODUCTION

The consequences of dietary protein restriction, particularly those of a supplemented very-low-protein diet (SVLPD), on the outcome of patients with chronic kidney disease (CKD) have been a matter of debate and controversy (1–6). Indeed, some authors have reported a nutritional risk and negative consequences on morbidity and mortality when patients previously receiving dietary protein restriction underwent renal replacement therapy (RRT) (4–6). However, until recently, no report has addressed the long-term outcome on RRT of patients previously treated with SVLPD. An extended follow-up of the Modification of Diet in Renal Disease (MDRD) Study recently published (7), which reported a gloomy prognosis late after the end of the study, prompted us to assess the long-term outcome on RRT (dialysis and/or transplantation) in our own series of patients.

SUBJECTS AND METHODS

Study population

From December 1985 to January 2000, an SVLPD was prescribed to patients with CKD stage IV-V who did not have too many severe comorbid conditions and were a priori able to follow a vegetarian diet and to be monitored. These patients represented 25% of all stage IV-V CKD patients followed during this period in our unit.

Two hundred fifty-one patients were enrolled. Twenty-one patients received the SVLPD for <3 mo and 24 died before RRT after a mean SVLPD duration of 25 mo (5–76 mo), ie, a mortality rate of 3.5%/y, and were excluded from the present analysis. Three other patients were still alive but were drafted in another center and were also excluded (Figure 1). The final analysis focused on 203 patients who received the dietary treatment for >3 mo without stopping their diet at any time before a diagnosis of end-stage renal disease (ESRD). The patients were divided into 2 groups: 1) HD group (102 patients treated with hemodialysis who never received a kidney transplant) and 2) TR group (101 patients who received at least one kidney transplant).

All patients were prescribed a diet providing 0.3 g protein · kg body wt−1 · d−1 of vegetable origin and 5–7 mg phosphate. The energy supply (35 kcal · kg−1 · d−1) was mainly provided by carbohydrates (67%), lipids (30%), and protein (3%). The diet was supplemented with one tablet for 5 kg body weight of a mixture of essential amino acids and the ketoanalogs Ketos-teril (Fresenius, Bad Homburg, Germany) or cetolog (Clintec, Maurepas, France). The population, methodology, composition of tablets, survey, and short- and middle-term follow-up were previously described (8). Briefly, until the initiation of RRT, the same physician and the same dietitian jointly followed patients as outpatients every month. Compliance with the prescribed diet was assessed monthly from 24-h urinary urea nitrogen excretion.

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by using standard equations (9) as an estimation of dietary protein intake and every 3 mo by food diaries to estimate protein and energy intakes. Routine blood and urinalysis were performed monthly at the central laboratory of the hospital. The glomerular filtration rate (GFR), determined from the urinary clearance of $^{51}$Cr-EDTA normalized to $1.73 \text{ m}^2$ body surface area, and nutritional proteins were assessed every 3 mo and were available for 152 patients. The study was approved by the local ethical committee (Hospital University Center, Bordeaux, France).

Moreover, individualized predialysis patient nutritional care was systematically performed with the help of a renal nurse several times for each patient until the initiation of RRT. As a result, definitive vascular access was available in 87% of patients at dialysis initiation, and only 6 patients required emergency admission to start dialysis. The primary goal of this retrospective study was to evaluate, by the end of October 2008, the long-term clinical outcome of patients previously treated with an SLVPD.

**Composition of tablets**

*Ketosteril*

One tablet of Ketosteril consisted of ketoisoleucine, calcium salt (67 mg); ketoleucine, calcium salt (101 mg); ketophenylalanine, calcium salt (68 mg); ketovaline, calcium salt (86 mg); ketornithine, calcium salt (59 mg); l-Lysine acetate (105 mg); l-threonine (53 mg); l-tryptophan (23 mg); l-histidine (38 mg); l-Tyrosine (30 mg); and calcium (50 mg).

*Cetolog*

One tablet of Cetolog consisted of ketoisoleucine, L-ornithine (153 mg); ketoleucine, L-lysine (162 mg); ketoleucine, L-histidine $\text{H}_2\text{O}$ (51 mg); ketovaline, L-ornithine (73 mg); ketovaline, L-lysine (77 mg); DL-hydroxymethionine, calcium salt (28 mg); l-threonine (74 mg); and l-tyrosine (151 mg).

**Calculation and statistical analysis**

Patients were pooled according to their outcome: deceased, lost to follow-up, or alive (still receiving dialysis or received a kidney transplant). Results are given as means ± SDs. Each variable was analyzed according to outcome by using one-factor analysis of variance. Group comparisons were done by using exact Fischer’s test. Significance was set at $P < 0.01$. Categorized variables were compared by using a chi-square test. For the survival analysis, patients who were grafted, lost to follow-up, or transferred to another dialysis technique were censored at the date of change. Time was calculated from the start of RRT to the date of death, lost to follow-up, or 31 October 2008. Data with potential influence on survival at the time of RRT were analyzed by using the Cox proportional hazard model.

For the transplanted group, survival analysis of the SLVPD patients (patient survival rate in transplantation and graft survival rate) was compared with that of a cohort of 865 patients who received a transplant during the same period in the same center in Bordeaux and who received conventional dietary recommendations during the pre-ESRD period. The outcomes of a second transplantation were analyzed only when treatment with an SLVPD had been provided at the end of the first transplantation. Patient who received a third transplantation were excluded because none of them was present in the SLVPD group. Survival analysis was performed by using Kaplan-Meier representations and log-rank tests. Time was calculated from the time of transplantation to the date of death, the date of dialysis, or 31 October 2008. Data with potential influence on survival at the time of RRT were tested by using the Cox proportional hazard model. JMP 7.0 software (SAS institute, Cary, NC) was used for the analysis.

**RESULTS**

Two hundred three patients who received the dietary treatment for >3 mo were included (Figure 1): 102 patients were treated...
with hemodialysis and never underwent transplantation, whereas 101 patients underwent at least one transplantation. The main clinical and biological characteristics of patients at the time of initiation of RRT are summarized in Table 1. Comparison between dialyzed and transplanted patients showed that only age was significantly different (Student’s t test, P < 0.001).

Outcome of overall population at the end of follow-up

The mean duration of the SVLPD before ESRD was 33.1 ± 27.8 mo (4–230 mo). The mean time of follow-up of the overall population receiving RRT was 131 ± 74 mo (1–270 mo). Eighty-seven patients died, 31 patients were currently alive and receiving maintenance dialysis treatment (20 from the dialysis group and 11 from the transplant group), 78 patients are living with a functioning graft, and 7 patients were lost to follow-up. The crude survival rates in the whole cohort were 98%, 79%, and 63% at 1, 5, and 10 y, respectively (Figure 2). The annual mortality rate during RRT remained low, close to what we observed while the patients were receiving the SVLPD. Most deaths were related to cardiovascular and cerebrovascular causes. Five patients died of cachexia within 4 y of RRT, ranging in age from 81 to 88 y at the time of death.

When the patients were divided according to their outcome (dead or alive), only age was significantly different between the 2 groups (Student’s t test, P < 0.001) (Table 2). On one hand, there was no relation between patient outcome and the duration of SVLPD before RRT, whereas, on the other hand, there was no relation between the nutritional variables (serum albumin, body mass index, and protein catabolic rate) and renal function at the initiation of RRT. The multivariate survival analysis using the Cox proportional hazard model, also only found age as a significant variable. Because transplanted patients were significantly younger than dialysis patients and because it has been analyzed the 2 groups of patients separately.

Clinical outcome of patients receiving maintenance dialysis

The mean duration of the SVLPD before RRT was 33 ± 24 mo. One hundred two patients continued to receive maintenance dialysis therapy for a mean time of 90 ± 63 mo. The patient survival rates were 97%, 88%, 60%, and 33% at 1, 2, 5, and 10 y, respectively (Figure 3). As in the overall population, age was the main factor affecting mortality (Cox analysis). Compared with the French Registry it was noticeable that, despite a lower GFR at the initiation of RRT, SVLPD patients experienced a delayed initiation of dialysis by 15.4 mo.

Clinical outcome of transplanted patients

The mean duration of the SVLPD before RRT was 33 ± 31 mo. As previously mentioned, 101 patients (ie, 50% of the overall population) were transplanted between August 1986 and May 2005 in the same center. Eight patients received a preemptive graft. Dialysis therapy was initiated in all other patients. Forty-six patients were grafted during the first year of dialysis treatment, 15 during the second year, 21 between 2 and 5 y of dialysis treatment, and 11 beyond 5 y of dialysis. The mean duration of hemodialysis treatment before transplantation was 24.8 ± 25.1 mo (1–121 mo). Fourteen of the 101 kidney grafts were second transplantations. All but one patient received a cadaveric donor transplant.

The mean time of follow-up after transplantation was 112 ± 67 mo (1–244 mo). The sex ratio (M/F) was 52/49 in the SLVPD group compared with 573/292 (P = 0.0004) in the control group of the 865 consecutive kidney transplant recipients during the same period in the same center. The mean age was similar in the 2 groups: 41.2 ± 10.7 and 41.6 ± 13.4 y, respectively. Fourteen of 101 patients in the SLVPD group and 86 of 865 patients in the control group received a second transplant (P = 0.2). Patient survival rates were 97%, 95%, and 86% at 5, 10, and 15 y, respectively, in the SLVPD group when compared with 91%, 84%, and 75% in the control group (P = 0.01, log-rank test). Similarly, the graft survival rate was significantly higher in the SLVPD group (79%, 69%, and 64% at 5, 10, and 15 y, respectively) than in the control group (72%, 56%, and 42% at 5, 10, and 15 y, respectively) (P = 0.003, log-rank test; Figure 4).

DISCUSSION

We assessed the long-term outcome of 203 patients treated with an SVLPD for a mean duration of 3 y before receiving RRT (eg, chronic dialysis and/or kidney transplantation) for a subsequent period of 10 y. The results were not significantly different from those reported in France during the same period.

### TABLE 1

Clinical and biochemical characteristics of patients at the onset of renal replacement therapy (RRT)

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Hemodialysis group (n = 102)</th>
<th>Transplant group (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at start of SVLPD (y)</td>
<td>49.7 ± 15.2</td>
<td>59.5 ± 11.0</td>
<td>39.8 ± 11.9^2</td>
</tr>
<tr>
<td>Age at start of RRT (y)</td>
<td>52.5 ± 15.4</td>
<td>62.4 ± 11.3</td>
<td>42.4 ± 12.2^2</td>
</tr>
<tr>
<td>SVLPD duration (mo)</td>
<td>33.1 ± 27.8</td>
<td>33.4 ± 24.0</td>
<td>32.9 ± 31.5</td>
</tr>
<tr>
<td>Serum albumin at start of RRT (g/L)</td>
<td>38.8 ± 4.6</td>
<td>38.8 ± 4.7</td>
<td>40.0 ± 5.1</td>
</tr>
<tr>
<td>BMI at start of SVLPD (kg/m²)</td>
<td>22.4 ± 3.3</td>
<td>22.2 ± 3.6</td>
<td>21.7 ± 2.7</td>
</tr>
<tr>
<td>BMI at start of RRT (kg/m²)</td>
<td>22.5 ± 3.3</td>
<td>23.3 ± 3.5</td>
<td>21.8 ± 2.8</td>
</tr>
<tr>
<td>Protein intake at start of RRT (g · kg⁻¹ · d⁻¹)</td>
<td>0.47 ± 0.13</td>
<td>0.46 ± 0.13</td>
<td>0.49 ± 0.12</td>
</tr>
<tr>
<td>Plasma urea at start of RRT (mmol/L)</td>
<td>15.7 ± 6.7</td>
<td>15.4 ± 7.3</td>
<td>15.9 ± 6.1</td>
</tr>
<tr>
<td>Plasma creatinine at start of RRT (µmol/L)</td>
<td>710 ± 205</td>
<td>688 ± 217</td>
<td>732 ± 190</td>
</tr>
<tr>
<td>GFR at start of RRT (mL/min)</td>
<td>5.9 ± 1.6</td>
<td>5.8 ± 1.6</td>
<td>5.9 ± 1.6</td>
</tr>
</tbody>
</table>

^1 All values are means ± SDs. SVLPD, supplemented very-low-protein diet; GFR, glomerular filtration rate.

^2 Significantly different from the hemodialysis group, P < 0.001 (Student’s t test).
TABLE 2
Clinical characteristics of patients according to their outcomes at the end of follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dead (n = 87)</th>
<th>Alive (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at start of SVLPD (y)</td>
<td>58.9 ± 11.7</td>
<td>42.1 ± 13.6(^2)</td>
</tr>
<tr>
<td>SVLPD duration until RRT (mo)</td>
<td>32.3 ± 22.3</td>
<td>34.3 ± 32.2</td>
</tr>
<tr>
<td>Serum albumin at start of RRT (g/L)</td>
<td>38.5 ± 4.5</td>
<td>40.2 ± 5.3</td>
</tr>
<tr>
<td>BMI at start of RRT (kg/m(^2))</td>
<td>23.3 ± 3.5</td>
<td>22.1 ± 3.0</td>
</tr>
<tr>
<td>Protein intake at start of RRT (g·kg(^{-1})·d(^{-1}))</td>
<td>0.45 ± 0.12</td>
<td>0.48 ± 0.13</td>
</tr>
<tr>
<td>GFR at start of RRT (mL/min)</td>
<td>5.9 ± 1.7</td>
<td>5.7 ± 1.5</td>
</tr>
</tbody>
</table>

\(^1\) All values are means ± SDs. SVLPD, supplemented very-low-protein diet; RRT, renal replacement therapy; GFR, glomerular filtration rate.

\(^2\) Significantly different from the Dead group, \(P < 0.001\) (Student’s \(t\) test).

After the onset of RRT, the crude survival rate in the whole cohort was similar to that reported by Jungers et al (11) in a cohort of 1057 patients who started RRT (hemodialysis and/or transplantation) from 1989 to 1998. The overall 5-y survival rate of this cohort was 65%.

Patient survival rates during maintenance dialysis in the present series were at least as good as those of the French National Dialysis Registry, which started in 2002: 97%, 88%, and 76% in the present study compared with 82%, 72%, and 63% in the French Registry at 1, 2, and 3 y respectively. The main characteristics of our patients (age and sex) were similar in at the start of RRT (12). Renal function at the start of RRT was lower in our patients: 5.9 ± 1.6 compared with 9.2 ± 5.4 mL/min (estimated by the MDRD formula), whereas serum albumin was higher (38.9 compared with 33.4 g/L). As compared with the French Registry, patients who received the SVLPD experienced a delayed initiation of dialysis by \(\approx 16\) mo.

We performed a subgroup analysis in the kidney transplant patients because these patients were younger and transplantation modifies the mortality risk. Moreover, it was possible to compare this cohort with the overall population transplanted in Bordeaux during the same period. The clinical characteristics of the 101 transplanted patients who previously received an SVLPD were not different from those of the 865 patients in the control group. The long-term survival rate and the grafted survival rate were higher in the SVLPD group. These results suggest that an SVLPD fa-

FIGURE 2. Survival curve of the whole study population treated with hemodialysis and/or transplantation after stopping treatment with a supplemented very-low-protein diet.

As shown in Coresh et al’s study (1), the general health status of our patients was satisfactory at the onset of RRT, although they started RRT at a lower GFR than their counterparts, who did not benefit from dietary counseling. These findings may be explained by the beneficial effect of the diet on uremic symptoms. Indeed, the vegetarian protein-restricted diet also involved a reduction in sodium and phosphorus intakes and a low acidic ash content, which favors the correction of several hormonal and metabolic disorders responsible for uremic symptoms, such as metabolic acidosis, secondary hyperparathyroidism, insulin resistance, and high blood pressure (16). Thus, initiation of RRT may be substantially delayed because, for any given GFR, patients consuming an SVLPD experience lower urea generation and therefore become less symptomatic.

Beyond the various beneficial effects of SVLPD, patients consuming such a diet compulsory require regular clinical survey to monitor compliance with the diet and, as shown in previous studies, an unchanged body composition (24, 25). There was no routine follow-up of lean body mass and, as shown in previous studies, an unchanged body composition (24, 25). There was no routine follow-up of lean body mass and, as shown in previous studies, an unchanged body composition (24, 25).

FIGURE 4. Patient survival and graft survival in patients in the supplemented very-low-protein diet (SVLPD; n = 101) and control (n = 865) groups. The survival rate was higher in the SVLPD group than in the control group (P = 0.01, log-rank test).

Patients in the current study showed a satisfactory nutritional condition as evidenced by a stable body mass index, a serum albumin concentration that remained within the normal range, and, as shown in previous studies, an unchanged body composition (24, 25). There was no routine follow-up of food intake once patients started RRT. However, in a previous report of nutritional status during the first year of dialysis, we reported that protein intake was >1.2 g · kg⁻¹ · d⁻¹, whereas energy intake remained close to 30 kcal · kg⁻¹ · d⁻¹ (26). In agreement with a previous report by Bellizzi et al (27) in patients consuming an SVLPD, mean blood pressure was within the normal range in most of our patients at the start of dialysis. We observed similar results in our population (28). Blood pressure control is certainly improved with a regular medical survey and by the SVLPD, which potentiates the effects of antihypertensive treatment. Moreover, SVLPD has a vasodilatory effect through increased plasma concentrations of branched-chain amino acids. Correction of insulin resistance, hyperphosphatemia, and secondary hyperparathyroidism may also exert a cardiovascular protective effect in ESRD patients (29–31).

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Beyond the various beneficial effects of SVLPD, patients consuming such a diet compulsorily require regular clinical examination. The importance of a regular predialysis survey was previously emphasized (11, 20), which was the case in the current study. Indeed, a regular physical examination, concomitantly performed by a physician and a dietitian, allowed the maintenance of a satisfactory nutritional status, the control of blood pressure, and satisfactory preparation for RRT, which are among the main factors of a favorable outcome of ESRD patients (21–23).

In conclusion, the current study confirms the short- and long-term safety of pre-ESRD SVLPD once patients begin RRT. Patients prescribed to follow an SVLPD should receive regular physical examinations, which, in the present study, ensured that most patients maintained an optimal nutritional status, a satisfactory blood pressure, and appropriate dialysis access—indicators of a favorable prognosis in patients with ESRD. The lack of a correlation between the death rate and duration of SVLPD and the moderate mortality rate observed during the first 10 y of RRT strongly confirm that nutritional therapy before ESRD has no detrimental effect on the outcome of patients once RRT is initiated.

We thank Catherine Rio and Dominique Marot for their help. The authors’ responsibilities were as follows—BV, VdP, CC, and MA: responsible for the design of the experiment; PC, LC, and MA: responsible for the data analysis; and PC, LC, DF, and MA: responsible for writing the manuscript. All authors participated in the data collection. MA, DF, and PC received lecture honoraria from Fresenius-Kabi. None of the other authors had a conflict of interest.

REFERENCES


