Effects of a Supplemented Hypoproteic Diet in Chronic Kidney Disease

Gabriel Mircescu, MD, PhD, Liliana Gârneaţă, MD, PhD,† Simona Hildegard Stancu, MD, PhD,‡ and Cristina Căpuşă, MD, PhD**

Objective: We assessed the effect of a severe hypoproteic diet supplemented with ketoanalogues (SVLPD) for 48 weeks on certain metabolic disorders of chronic kidney disease (CKD).

Design: We performed a prospective, open-label, parallel, randomized, controlled trial.

Setting: The study took place in the Nephrology Department at the Dr Carol Davila Teaching Hospital of Nephrology, Bucharest, Romania.

Patients: A total of 53 nondiabetic patients with CKD with an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 (Modification of Diet in Renal Disease formula), proteinuria less than 1 g/g urinary creatinine, good nutritional status, and anticipated good compliance with the diet were randomly assigned to two groups.

Intervention: Group I (n = 27) received the SVLPD (0.3 g/kg/d of vegetable proteins and ketoanalogues, 1 capsule for every 5 kg of ideal body weight per day). Group II (n = 26) continued a conventional low mixed protein diet (0.6 g/kg/d).

Outcome Measures: Nitrogen waste products retention and calcium-phosphorus and acid-base disturbances were primary efficacy parameters, and "death" of the kidney or the patient and the estimated glomerular filtration rate were secondary efficacy parameters. The nutritional status and compliance with the diet were predefined as safety variables. There were no differences between groups in any parameter at baseline.

Results: In the SVLPD group, serum urea significantly decreased (56 ± 7.9 mmol/L vs. 43.2 ± 10 mmol/L), and significant improvements in serum bicarbonate (23.4 ± 2.1 mmol/L vs. 18.1 ± 1.5 mmol/L), serum calcium (1.10 ± 0.17 mmol/L vs. 1.00 ± 0.15 mmol/L at baseline), serum phosphates (1.45 ± 0.66 mmol/L vs. 1.91 ± 0.68 mmol/L), and calcium-phosphorus product (1.59 ± 0.11 $mmol^2/L^2$ vs. 1.91 ± 0.10 $mmol^2/L^2$) were noted after 48 weeks. No death was registered in any group. Significantly lower percentages of patients in group I required renal replacement therapy initiation (4% vs. 27%). After 48 weeks, estimated glomerular filtration rate did not significantly change in patients receiving SVLPD (0.26 ± 0.08 mL/s vs. 0.31 ± 0.08 mL/s at baseline), but significantly decreased in controls (0.22 ± 0.09 mL/s vs. 0.30 ± 0.07 mL/s). The compliance with the keto-diet was good in enrolled patients. No significant changes in any of the parameters of the nutritional status and no adverse reactions were noted.

Conclusion: SVLPD seems to ameliorate the nitrogen waste products retention and acid-base and calcium-phosphorus metabolism disturbances and to postpone the renal replacement therapy initiation, preserving the nutritional status in patients with CKD.

© *2007 by the National Kidney Foundation, Inc.*

REDUCED DIETARY protein intake has been reported for more than a century to improve many uremic symptoms in advanced chronic renal failure.[1] More than two decades ago, it was reported that the hypoproteic diet may also slow down the rate of decline in renal function[2-6] and postpone the initiation of renal replacement therapy (RRT).[7,8] More recently, chronic kidney disease (CKD) stages and evidence-based strategies to delay progression were defined.[9] Although a dietary approach is mentioned, strong evidence is lacking.

Different dietary protein regimens have been proposed for the patients with CKD: (1) a conventional low protein diet (LPD) providing 0.6 g/kg per day, (2) a very LPD (0.3 g/kg per day) supplemented with essential amino acids, or (3) a very LPD (0.3 g/kg per day) supplemented

**Consultant in Nephrology and Internal Medicine, Dr Carol Davila Teaching Hospital of Nephrology, Bucharest, Romania.*

†*Consultant in Nephrology, Dr Carol Davila Teaching Hospital of Nephrology, Bucharest, Romania.*

‡*Specialist in Nephrology and Internal Medicine, Dr Carol Davila Teaching Hospital of Nephrology, Bucharest, Romania.*

Address reprint requests to Liliana Gârneaţă, Dr Carol Davila Teaching Hospital of Nephrology, 4 Calea Griviţei, sector 1, 010731 Bucharest, Romania. E-mail: lilianagarna@yahoo.com

© *2007 by the National Kidney Foundation, Inc.*

1051-2276/07/1703-0003$32.00/0

doi:10.1053/j.jrn.2006.12.012

with an isomolar mixture of essential amino acids and nitrogen-free ketoanalogues (severe hypoproteic diet supplemented with ketoanalogues [SVLPD]).[10]

The keto-diet allows the supplementation of nitrogen-free essential amino acids. Ketoanalogues of essential amino acids capture excessive nitrogen residues and use them for essential amino acids production. Thus, the nitrogen intake can be restricted and endogenous urea formation is reduced. Therefore, it was reported to control the metabolic disturbances of uremia[11,12] and to reduce the decline in renal function,[4–6] simultaneously preserving the nutritional status in patients with CKD.[13]

"The arguments whether a low-protein diet slows the rate of progression of renal disease continue to smolder and rage,"[14] but clear-cut conclusions are still to come.

The purpose of the study was to assess the effects of an SVLPD on nitrogen waste products accumulation, calcium-phosphorus metabolism disturbances, acid-base disorders, nutritional status, and the compliance with the prescribed diet for 48 weeks.

Methods

Study Design

We performed a single-center, prospective, open-label, parallel, randomized, controlled trial. The total study duration was 60 weeks. Eligible patients gave informed consent and entered a 12-week baseline phase. At the end of this phase, the subjects still fulfilling all the selection criteria were randomized (1:1 ratio) to receive the SVLPD or to continue the conventional LPD.

The trial was conducted with the provisions of the Declaration of Helsinki and Tokyo as amended in Venice (1983). The protocol was approved by the local Hospital Ethics Committee.

Selection Criteria

Inclusion and exclusion criteria were evaluated at the enrollment, after 4 weeks, and at randomization.

The inclusion criteria were as follows: adult age, CKD with an estimated glomerular filtration rate (eGFR) of less than 0.5 mL/s (30 mL/min per 1.73 m^2, Modification of Diet in Renal Disease [MDRD] formula), stable renal function at least 12 weeks before enrollment (a reduction in eGFR $\leq$ 4 mL/min/y, which is expected in nondiabetic patients, and with well-controlled arterial blood pressure[7]), proteinuria less than 1 g/g urinary creatinine, good nutritional status (Subjective Global Assessment score A/B and serum albumin $>$ 35 g/L [3.5 g/dL]), and anticipated good compliance with the prescribed diet.

The compliance with the restricted protein diet was assessed in all patients fulfilling all other selection criteria for at least 12 weeks before enrollment (Fig. 1). In all of these patients, the recommended dietary intake 3 months before inclusion consisted of a conventional LPD, with a daily protein intake of 0.6 g/kg ideal body weight (mixed protein regimen) and a total daily energy intake of 30 kcal/kg ideal body weight. The compliance with the conventional LPD was assessed every 2 weeks during this 3-month period before enrollment. Urinary urea nitrogen excretion was used to evaluate the protein intake (Mitch-Maroni's formula). The daily energy intake was estimated using the 3-day food diary. The compliance was considered to be good if both the achieved protein and the achieved energy intake were in the range of $\pm$10% of the recommended values. Once this very good compliance was proven, the patients were considered eligible. Before enrollment, these patients were informed that it could be necessary to follow a vegetarian diet. Only those agreeing to follow such a diet if assigned to this arm were considered to have "anticipated good compliance to the diet" per inclusion criterion.

Patients with poorly controlled arterial blood pressure ($>$145/85 mm Hg), relevant comorbid conditions (diabetes mellitus, heart failure, active hepatic disease, digestive diseases with malabsorption, inflammation/anti-inflammatory therapy), uremic complications (pericarditis, polyneuropathy), or feeding inability (anorexia, nausea) were excluded.

All of the enrolled patients received calcium and water-soluble vitamin supplementation, as required. The schedule of iron therapy was continued according to the *Romanian Best Practice Guidelines for the Treatment of Anaemia*.[15] Patients with serum ferritin less than 200 ng/mL (200 μg/L) received 100 mg intravenous iron sucrose (Venofer; Vifor, St. Galen, Switzerland) weekly. A dose of 100 mg intravenous iron sucrose was

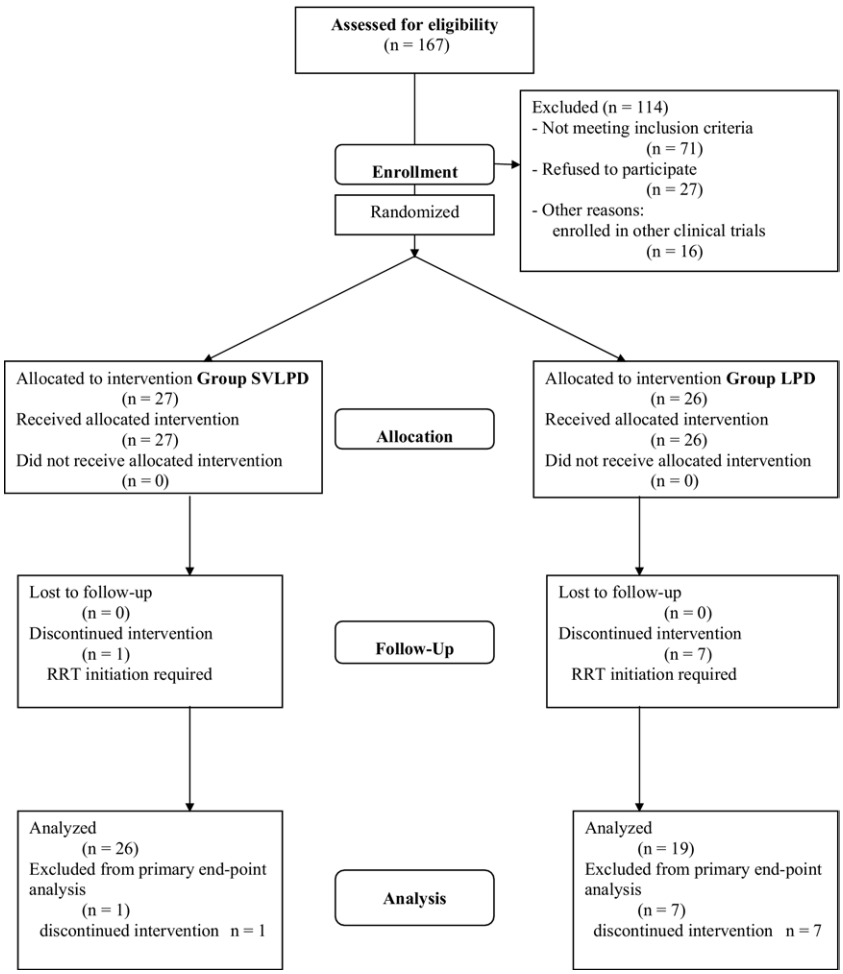

Figure 1. Participant flow chart. RRT, renal replacement therapy; SVLPD, severe hypoproteic diet supplemented with ketoanalogues.

administered every other week in patients with serum ferritin levels of 200 to 400 ng/mL (200-400 μg/L) and monthly in patients with serum ferritin levels of 400 to 500 ng/mL (400-500 μg/L). Iron administration was stopped if serum ferritin exceeded 500 ng/mL.[15] Oral iron supplementation was not used in any of the enrolled patients.

Therapeutic Intervention

Fifty-three patients were enrolled and randomly assigned to two treatment groups.

The patients in the SVLPD group (n = 27) received 0.3 g/kg per day of vegetable proteins and ketoanalogues of essential amino acids (Ketosteril, Fresenius Kabi, Bad Homburg, Germany), 1 capsule for every 5 kg of ideal body weight per day.

The patients in the control group (n = 26) continued their conventional LPD, with 0.6 g/kg per day (including high biological value proteins).

The total recommended energy intake was 30 kcal/kg per day in both arms.

Parameters

Primary efficacy parameters were as follows:

- Nitrogen waste products: serum urea and creatinine
- Calcium-phosphorus metabolism: serum calcium, serum phosphate, calcium-phosphorus product, and alkaline phosphatase activity
- Acid-base balance: serum bicarbonate

Death of the patient or "death" of the kidney and the eGFR were predefined as secondary efficacy parameters. RRT initiation was decided by the Ethical Committee of the Hospital, considering the clinical and biochemical status of the patient (presence of the uremic symptoms, acute pulmonary edema, feeding inability, uncontrolled acid-base, and/or hydroelectrolyte disturbances

were used as criteria to start RRT). The members of the Ethical Committee were aware of the patients' inclusion in the clinical trial but were unaware of the arm to which the patients had been assigned.

The parameters of the nutritional status were predefined as primary safety parameters: subjective global assessment, anthropometric markers (body mass index, tricipital skinfold, mid-arm muscular circumference), and biochemical parameters (serum albumin and serum total cholesterol). The compliance with the prescribed diet, occurrence of any adverse event, and number of withdrawals were also used as safety variables.

Monitoring Schedule

Sixteen blood samplings were scheduled for each patient, to be drawn at weeks −12, −8, −4, and 0, and monthly thereafter. The laboratory reports included the nitrogen compounds, calcium-phosphorus metabolism parameters, acid-base balance, biochemical nutritional markers, serum C-reactive protein, hemoglobin, blood cell count, and biochemical safety parameters (sodium, potassium, liver enzymes, and bilirubin).

The anthropometric measurements and subjective global assessment were evaluated at enrollment, at randomization, and every 3 months thereafter.

The compliance with the prescribed diet was assessed weekly for the first month, every 4 weeks during the next 8 weeks, and every 12 weeks thereafter, using the urinary urea nitrogen excretion to evaluate the protein intake using Mitch-Maroni's formula[16] and the 3-day food diary to estimate the daily energy intake.

The blood pressure levels, drug therapy requirements for hypertension, and occurrence of adverse events were recorded monthly.

Statistical Analysis

Data are presented as mean and standard deviation for the parameters with normal distribution or median and interquartile range for skewed data. Student *t* test, chi-square, and nonparametric tests were used to determine statistical significant differences in baseline parameters between study groups.

In individuals with significant variations in dietary intake, the estimation equations for GFR are not reliable, leading to overestimation.[17,18] When the patients were switched to a meat-restricted diet (creatine-free), serum creatinine and urinary creatinine decreased and stabilized after 3 months. Because it takes approximately three half-lives of creatinine (4 months) to reach a new equilibrium, a period of at least 12 weeks is necessary to estimate (according to the changes in serum creatinine) whether such a diet has a beneficial effect on the course of renal failure. An assessment phase including weeks 16 to 48 was therefore defined, and the statistical analyses addressed to the decline in eGFR included only the data from this assessment phase.

Results

A total of 53 adult nondiabetic patients (eGFR < 0.5 mL/s [30 mL/min]) were enrolled between January 15, 2004, and February 15, 2005. Eight patients required RRT initiation during the study: one patient from the SVLPD group and seven patients from the LPD group (Fig. 1).

The patients' characteristics at baseline are shown in Table 1. There were no statistically significant differences between the two treatment groups in demographic characteristics or any of the studied parameters at baseline.

Efficacy Parameters

Serum urea significantly decreased only in patients assigned to receive the keto-diet. Similarly, a significant increase in serum creatinine was noted only in the LPD group after 48 weeks (Table 2).

By the end of the study, serum bicarbonate significantly increased (23.4 ± 2.1 mmol/L vs. 18.1 ± 1.5 mmol/L at baseline [23.4 ± 2.1 mEq/L vs. 18.1 ± 1.5 mEq/L at baseline]) in patients receiving the keto-diet (Table 2).

After 48 weeks of therapeutic intervention, significant improvements in serum levels of mineral metabolism parameters were seen only in patients in the SVLPD group: Calcium increased (1.10 ± 0.17 mmol/L vs. 1.00 ± 0.15 mmol/L at baseline [4.4 ± 0.7 mEq/L vs. 4.0 ± 0.6 mEq/L at baseline]), phosphates decreased (1.45 ± 0.66 mmol/L vs. 1.91 ± 0.68 mmol/L at baseline [4.5 ± 1.7 mg/dL vs. 5.9 ± 2.1 mg/dL at

Table 1. Patients' Characteristics at Baseline

Parameter	Group SVLPD (n = 27)	Group LPD (n = 26)	*P*
Age (y)*	55.0 ± 12.7	53.6 ± 11.0	.66
Gender (males)	63%	58%	.69
Primary renal disease			
Primary glomerular nephropathies	59%	57%	.91
Tubulointerstitial diseases	27%	28%	.93
Vascular diseases	5%	6%	.97
Hereditary-congenital diseases	6%	7%	.63
Other renal diseases	3%	2%	.93
eGFR (mL/min/1.73 m^2)*	17.9 ± 4.8	16.1 ± 4.8	.18
SGA A, (%)	85%	80%	.95
BMI (kg/m^2)*	23.6 ± 3.4	22.9 ± 4.7	.34
Serum albumin (g/dL)*	3.9 ± 0.3	4.1 ± 0.7	.37
CRP (mg/L)†	4.0 (2.0; 8.0)	4.0 (3.0; 7.0)	.82

SVLPD, severe hypoproteic diet supplemented with ketoanalogues; LPD, low protein diet; eGFR, estimated glomerular filtration rate; SGA, subjective global assessment; BMI, body mass index; CRP, C-reactive protein.

*Data are presented as mean ± standard deviation.

†Data are presented as median (interquartile range). To convert eGFR in mL/min to mL/s, multiply by 0.01667; to convert serum albumin in g/dL to g/L, multiply by 10.

baseline]), and calcium-phosphorus product decreased (1.59 ± 0.11 $mmol^2/L^2$ vs. 1.91 ± 0.10 $mmol^2/L^2$ at baseline [39.6 ± 3.1 mg^2/dL^2 vs. 47.2 ± 4.3 mg^2/dL^2 at baseline]) (Table 2).

Estimated GFR did not significantly change in patients receiving SVLPD (0.26 ± 0.08 mL/s vs. 0.31 ± 0.08 mL/s at baseline) (15.4 ± 5.0 mL/min per 1.73 m^2 vs. 18.3 ± 4.6 mL/min per 1.73 m^2 at baseline), but significantly decreased in controls (0.22 ± 0.09 mL/s vs. 0.30 ± 0.07 mL/s) (13.4 ± 5.1 mL/min per 1.73 m^2 vs. 17.9 ± 4.3 mL/min 1.73 m^2 at baseline) (Fig. 2, Table 2).

Although the percentage of patients with declining renal function was similar in the two groups during the 12-week period before the enrollment (88.9% in SVLPD group vs. 80.8% in controls), a significantly smaller percentage of patients in the SVLPD group experienced a reduction in renal function during the assessment phase (63% vs. 88.5% in the control group).

No death was registered in any group during the study.

A significantly lower percentage of patients in the SVLPD group required RRT initiation throughout the therapeutic intervention (4% vs. 27%). Only 1 of the 27 patients receiving the keto-diet who had an eGFR of 0.15 mL/s (9.1 mL/min per 1.73 m^2) at randomization started hemodialysis after 21 weeks of therapeutic intervention. In the LPD group, seven patients (mean eGFR at randomization of 0.19 ± 0.02 mL/s [11.2 ± 0.9 mL/min per 1.73 m^2]) required RRT initiation after a mean observation period of 26.8 weeks (Fig. 3).

No significant changes were noted in the urinary protein excretion in any group (Table 2).

There were no differences between groups in the blood pressure control or the percentage of patients receiving angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers throughout the study (Table 2).

Safety Parameters

There were no significant changes in the parameters of the nutritional status in any group of patients.

The compliance with the prescribed diets, assessed by protein and energy intake, was good throughout the study in both arms (Table 3).

Ketoanalogues supplementation was well tolerated. No relevant changes in laboratory safety parameters (blood cell count, potassium, liver enzymes, and bilirubin) were noted (data not shown). No adverse reactions to Ketosteril (Fresenius Kabi) administration were noted.

Discussion

Several studies have shown that a high protein diet worsens renal damage and increases proteinuria, hypertension, and mortality in experimental

Table 2. Metabolic Parameters, Renal Function, Blood Pressure, and Requirements for Antihypertensive Treatment in Patients Completing the Study

	Baseline	Week 48
Nitrogen waste products		
Serum urea (mg/dL)		
Group SVLPD (n = 26)	157 ± 33	121 ± 28*
Group LPD (n = 19)	135 ± 24	144 ± 26
Serum creatinine (mg/dL)		
Group SVLPD (n = 26)	4.1 ± 1.3	4.8 ± 1.5
Group LPD (n = 19)	3.9 ± 1.4	5.0 ± 1.7*
Acid-base balance		
Serum bicarbonate (mEq/L)		
Group SVLPD (n = 26)	18.1 ± 1.5	23.4 ± 2.1*
Group LPD (n = 19)	18.3 ± 1.3	17.6 ± 1.9
Calcium-phosphorus metabolism		
Serum calcium (mg/dL)		
Group SVLPD (n = 26)	4.0 ± 0.6	4.4 ± 0.7*
Group LPD (n = 19)	4.1 ± 0.9	3.9 ± 0.5
Serum phosphates (mg/dL)		
Group SVLPD (n = 26)	5.9 ± 2.1	4.5 ± 1.7*
Group LPD (n = 19)	5.7 ± 2.3	6.0 ± 1.9
Calcium-phosphorus product (mg^2/dL^2)		
Group SVLPD (n = 26)	47.2 ± 4.3	39.6 ± 3.1*
Group LPD (n = 19)	46.7 ± 4.4	46.8 ± 4.8
Alkaline phosphatase activity (U/L)		
Group SVLPD (n = 26)	146.6 ± 17.8	151.1 ± 22.1
Group LPD (n = 19)	155.2 ± 28.6	159.7 ± 31.1
Renal function		
eGFR ($mL/min/1.73m^2$)		
Group SVLPD (n = 26)	18.3 ± 4.6	15.4 ± 5.0
Group LPD (n = 19)	17.9 ± 4.3	13.4 ± 5.1*
Proteinuria (g/d)		
Group SVLPD (n = 26)	0.56 ± 0.19	0.63 ± 0.17
Group LPD (n = 19)	0.67 ± 0.21	0.65 ± 0.15
Blood pressure and requirements for antihypertensive treatment		
Systolic blood pressure (mm Hg)		
Group SVLPD (n = 26)	125.2 ± 27.1	123.1 ± 16.9
Group LPD (n = 19)	125.3 ± 24.5	129.8 ± 14.9
Diastolic blood pressure (mm Hg)		
Group SVLPD (n = 26)	74.6 ± 15.7	70.9 ± 12.4
Group LPD (n = 19)	70.8 ± 14.0	70.5 ± 10.2
Patients with optimal blood pressure control†		
Group SVLPD (n = 26)	92.4%	96.2%
Group LPD (n = 19)	89.8%	94.8%
Patients on antihypertensive drugs		
Group SVLPD (n = 26)	87%	89%
Group LPD (n = 19)	83%	87%
No. of antihypertensive drugs per treated patient		
Group SVLPD (n = 26)	2.2 ± 1.3	2.2 ± 1.2
Group LPD (n = 19)	2.1 ± 1.2	2.2 ± 1.2
Patients receiving ACEIs and/or ARBs		
Group SVLPD (n = 26)	64%	65%
Group LPD (n = 19)	68%	70%

SVLPD, severe hypoproteic diet supplemented with ketoanalogues; LPD, low protein diet; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

*Statistically significant versus baseline.

†Arterial blood pressure less than 130/75 mm Hg. To convert eGFR in mL/min to mL/s, multiply by 0.01667; serum urea in mg/dL to mmol/L, multiply by 0.357; serum creatinine in mg/dL to μmol/L, multiply by 88.4; serum bicarbonate in mEq/L to mmol/L, multiply by 1; serum calcium in mg/dL to mmol/L, multiply by 0.2495; serum phosphates in mg/dL to mmol//L, multiply by 0.3229; serum albumin in g/dL to g/L, multiply by 10.

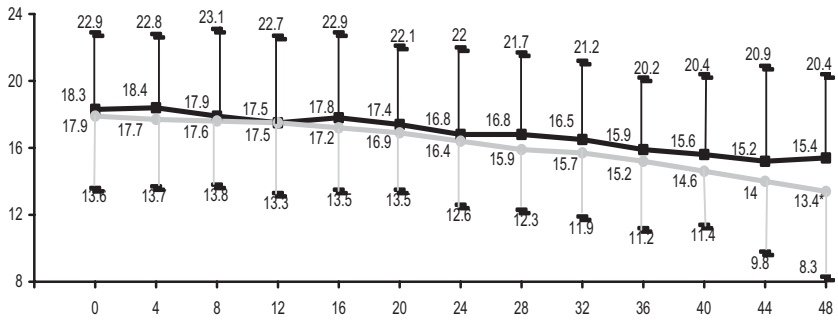

Figure 2. eGFR (mL/min/1.73 m^2, mean ± standard deviation) at randomization and during the study phase: SVLPD group (■, n = 26) and LPD group (●, n = 19). *Statistically significant difference versus baseline. To convert eGFR in mL/min to mL/s, multiply by 0.01667. eGFR, estimated glomerular filtration rate; SVLPD, severe hypoproteic diet supplemented with ketoanalogues; LPD, low protein diet.

models of CKD. In contrast, a long-term LPD can slow the rate of progression of renal failure, attenuating the impact of hemodynamic and metabolic factors.[1,19]

These findings have prompted numerous investigators to examine whether LPD could slow the rate renal function loss in patients with CKD. The results of various clinical trials have not been concordant: Some studies have reported positive effects of the LPD,[20–22] and other studies have shown no benefit.[5,7,23–25]

The role of dietary protein restriction in the progression of CKD has not been settled,[26] but available data support that an SVLPD is associated with a significant decrease in serum urea and allows a better control of the acid-base and phosphocalcic disorders and insulin resistance, thus postponing the occurrence of the uremic symptoms and delaying RRT initiation.[1,11,12] The improvement of metabolic acidosis with SVLPD is explained by the alkalinizing effect of this diet, because it is poor in cysteine and methionine and therefore has low acidic residues.

The decrease of serum phosphate levels results from a reduced phosphate intake, because the same nutrients provide protein and phosphate. At the same time, calcium salts included in the ketoanalogues preparation, acting both as calcium providers and as phosphate binders, are involved in the correction of calcium-phosphorus metabolism disturbances.[11]

The present study is a randomized, controlled trial to test the effect of an SVLPD on certain metabolic disorders in nondiabetic patients with stage 4 CKD (eGFR < 0.5 mL/s [30 mL/min per 1.73 m^2]), optimal blood pressure control, proteinuria less than 1 g/g urinary creatinine, good nutritional status, and anticipated good compliance with the diet.

Our results support an amelioration of nitrogen balance and the correction of acid-base imbalances and calcium-phosphorus metabolism disorders in patients receiving a keto-diet.

Only 4% of patients in the SVLPD group required RRT initiation during the study, a significantly lower percentage compared with 27% of subjects assigned to continue the conventional LPD. Similar results were reported by Pedrini et al.,[4] who assessed the effects of LPD on 1413 nondiabetic patients enrolled in five randomized, controlled trials, including MDRD; the risk of end-stage renal disease or death was reduced by 33%.[4]

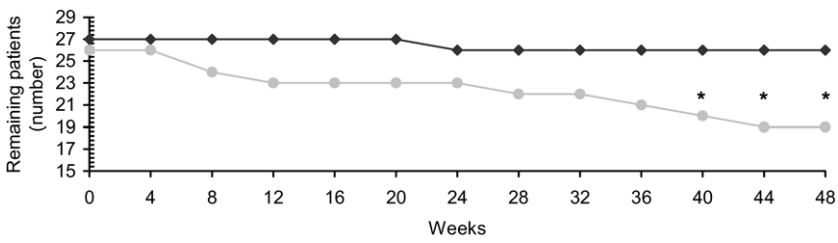

Figure 3. Need for RRT initiation throughout the study: ■, SVLPD group (n = 27); ●, LPD group (n = 26). *Statistically significant difference between groups. RRT, renal replacement therapy; SVLPD, severe hypoproteic diet supplemented with ketoanalogues; LPD, low protein diet.

Table 3. Safety Parameters

	Baseline	Week 48
Anthropometric markers		
BMI (kg/m^2)		
Group SVLPD (n = 26)	23.9 ± 3.1	23.8 ± 2.4
Group LPD (n = 19)	23.2 ± 4.4	23.4 ± 4.4
Tricipital skinfold (cm)		
Group SVLPD (n = 26)	19.9 ± 3.3	20.1 ± 3.0
Group LPD (n = 19)	19.2 ± 4.3	19.3 ± 4.6
Mid-arm muscular circumference (cm)		
Group SVLPD (n = 26)	23.2 ± 2.7	23.1 ± 2.5
Group LPD (n = 19)	22.9 ± 3.8	23.0 ± 4.0
Biochemical markers		
Serum albumin (g/dL)		
Group SVLPD (n = 26)	3.9 ± 0.3	4.2 ± 0.6
Group LPD (n = 19)	4.1 ± 0.4	4.0 ± 0.5
Serum total cholesterol (mg/dL)		
Group SVLPD (n = 26)	205.3 ± 41.6	197.1 ± 33.6
Group LPD (n = 19)	212.4 ± 23.1	206.5 ± 31.4
Lymphocytes count ($\times 10^3/\mu$L)		
Group SVLPD (n = 26)	2.133 ± 0.458	2.076 ± 0.500
Group LPD (n = 19)	2.054 ± 0.367	1.965 ± 0.412
SGA (A, %)		
Group SVLPD (n = 26)	87	87
Group LPD (n = 19)	90	90
Protein intake (g/kg/d)		
Group SVLPD (n = 26)	0.31 ± 0.09	0.32 ± 0.07
Group LPD (n = 19)	0.62 ± 0.1	0.59 ± 0.08
Energy intake (kcal/d)		
Group SVLPD (n = 26)	31.2 ± 2.3	31.8 ± 2.1
Group LPD (n = 19)	32.3 ± 2.1	31.0 ± 1.9

BMI, body mass index; SVLPD, severe hypoproteic diet supplemented with ketoanalogues; LPD, low protein diet; SGA, subjective global assessment.

To convert serum albumin in g/dL to g/L, multiply by 10; serum total cholesterol in mg/dL to mmol/L, multiply by 0.02586; white blood cell count in $\times 10^3/\mu$L to $\times 10^9$/L, multiply by 1.

During the 48 weeks of therapeutic intervention, eGFR did not significantly change in the SVLPD group, whereas a significant reduction in renal function was noted in the LPD group. Analysis of differences in progression may be confounded because some of the patients received angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, which are known to influence progression. Consequently, the outcome could be biased. Moreover, with a 25% probability to reach end-stage renal disease or to experience a greater than 50% reduction in eGFR,[5,27] and a difference between groups of 10% for significance, 96 patients per arm would be required, for a probability of 95% and a power of 80%.[28] The sample size was not large enough to determine whether the regimen changes the rate of progression of renal insufficiency. A longer observation period with the number of patients projected by our power analysis is required to judge the effect of a ketoacids-supplemented LPD on the progression of CKD. In their seminal article concerning the MDRD equation, Levey et al.[29] did not consider it advisable to use this equation to assess the efficacy of dietary protein restriction on the progression of chronic renal disease.

The reduction in renal death in patients on the SVLPD seems to be related to the correction of uremic signs and to improved metabolic control, allowing an important delay in RRT initiation. From the point of view of the patient, this delay is certainly the most important factor to consider.[19]

On the other hand, the nutritional safety of LPD has been frequently questioned, specifically because a poor predialysis nutritional status can increase the morbidity and mortality of patients with CKD and, consequently, can negatively influence the outcome after RRT initiation.[30]

Our results showed no deleterious effect of the SVLPD on nutritional status, assessed by clinical, anthropometric, and biochemical parameters. It is noteworthy that nutritional status was not changed while preserving the daily energy intake in both arms, despite the LPD.

Compliance with LPDs is generally poor, when referring to both the energy and the protein intake,[30] and close nutritional monitoring is therefore required. Our selected patients had a very good compliance, as expected, at least regarding daily protein and energy intake. Unlike in large studies, in which the achieved protein intake largely surpassed the recommendations,[31] in our study the protein intake was very close to prescription (0.32 ± 0.07 vs. 0.30 and 0.59 ± 0.08 vs. 0.60 g/kg per day in SVLPD and LPD arms, respectively) as a consequence of careful initial selection and permanent dietary counseling. This remarkable compliance with the diet could be involved in the reported amelioration of metabolic disorders with SVLPD in our patients, because it has already been reported that correction of metabolic disturbances was dependent on the compliance of patients and usually not observed in patients on a conventional LPD, even when they were compliant with the dietary prescription. There were no adverse reactions to the ketoanalogues.

The recently revealed high prevalence of CKD raises concerns all over the world.[9] In the time when the focus in nephrology care moves toward predialysis patients, the nutritional support and particularly the SVLPD could be a new link to the elegant RRT integrated care described by Van Biesen et al.[32] In addition, the possible delay of RRT initiation through nutrition could have a major economic impact, which is particularly important in developing countries where the dialysis facilities still do not meet the needs.[33] However, close nutritional monitoring, dietary counseling, and a careful selection of motivated patients who could benefit from such a diet are required.

Conclusion

The SVLPD seems to be effective and safe in ameliorating nitrogen waste products retention and acid-base and calcium-phosphorus metabolism disturbances, and in delaying the RRT initiation, with no deleterious effect on the nutritional status of patients with CKD.

References

1. Mitch WE: Dietary protein restriction in chronic renal failure: nutritional efficacy, compliance, and progression of renal insufficiency. J Am Soc Nephrol 2:823-831, 1991

2. Brenner BM: Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. Kidney Int 23:647-655, 1983

3. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM: Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol 241: F85-F93, 1981

4. Pedrini MT, Levey AS, Lau J, et al: The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. Ann Intern Med 124:627-632, 1996

5. Fouque D, Wang P, Laville M, et al: Low protein diets delay end-stage renal disease in non-diabetic adults with chronic renal failure. Nephrol Dial Transplant 15:1986-1992, 2000

6. Kasiske BL, Lakatua JD, Ma JZ, et al: A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. Am J Kidney Dis 31:954-961, 1998

7. Klahr S, Levey AS, Beck GJ, et al for The Modification of Diet in Renal Disease Study Group: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. N Engl J Med 330:877-884, 1994

8. Walser M, Hill S: Can renal replacement be deferred by a supplemented very low protein diet? J Am Soc Nephrol 10:110-116, 1999

9. Nickolas TL, Frisch GD, Opotowsky AR, Arons R, Radhakrishnan J: Awareness of kidney disease in the US population: findings from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000. Am J Kidney Dis 44(2):185-197, 2004

10. Mitch WE: Dietary therapy in uremia: the impact on nutrition and progressive renal failure. Kidney Int 57:S38-S43, 2000

11. Lafage M-H, Fournier A: Keto-diet, physiological calcium intake and native vitamin D improve renal osteodistrophy. Kidney Int 42:1217-1225, 1992

12. Price SR, Mitch WE: Metabolic acidosis and uremic toxicity: protein and amino acid metabolism. Semin Nephrol 14:232-237, 1994

13. Aparicio M, Chauveau P, De Précigout V, et al: Nutrition and outcome on renal replacement therapy of patients with chronic renal failure treated by a supplemented very low protein diet. J Am Soc Nephrol 11:708-716, 2000

14. Martinez-Maldonado M, Sattin RW: Rate of progression of renal disease and low-protein diet. Am J Kidney Dis 31:1048-1049, 1998

15. Mircescu G, Gherman-Căprioară M, Covic A, et al: [Best Practice Guidelines. Anemia secondary to chronic kidney disease], Bucharest, Ed. Infomedica, 2005

16. Maroni BJ, Steinman TI, Mitch WE: A method for estimating nitrogen intake of patients with chronic renal failure. Kidney Int 27:58-65, 1985

17. Garcia-Naveiro R, Rodriguez-Carmona A, Perez-Fontan M: Agreement between two routine methods of estimation of

glomerular filtration rate in patients with advanced and terminal chronic renal failure. Clin Nephrol 64:271-280, 2005

18. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM: Performance of the modification of diet in renal disease and Cockroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 16:459-466, 2005

19. Mitch WE, Maroni BJ: Nutritional considerations and indications for dialysis. Am J Kidney Dis 31:185-189, 1998

20. D'Amico G, Gentile MG, Fellin G, et al: Effect of dietary protein restriction on the progression of renal failure: a prospective randomized trial. Nephrol Dial Transplant 9:1590-1594, 1994

21. Ihle BU, Becker GJ, Whitworth JA, et al: The effect of protein restriction on the progression of renal insufficiency. N Engl J Med 321:1773-1777, 1989

22. Prakash S, Pande DP, Sharma S, et al: Randomized, double-blind, placebo-controlled trial to evaluate efficacy of ketodiet in predialytic chronic renal failure. J Ren Nutr 14:89-96, 2004

23. Locatelli F, Alberti D, Graziani G, et al: A. Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group [see comments]. Lancet 337:1299-1304, 1991

24. Rosman JB, Langer K, Brandl M, et al: Protein-restricted diets in chronic renal failure: a four year follow-up shows limited indications. Kidney Int 27:S96-S102, 1989

25. Hansen HP, Tauber-Lassen E, Jensen BR, et al: Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. Kidney Int 62:220-228, 2002

26. Mandayam S, Mitch WE: Dietary protein restriction benefits patients with chronic kidney disease. Nephrology 11:53-57, 2006

27. Modification of Diet in Renal Disease Study Group (prepared by Beck GJ, Berg RL, Coggins CH, et al.): Design and statistical issues of the Modification of Diet in Renal Disease Trial. Control Clin Trials 12:566-586, 1991

28. Jones B, Jarvis P: Trials to assess equivalence: the importance of rigorous methods. Br Med J 313:36-39, 1996

29. Levey AS, Bosch JP, Lewis JB, et al: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 16:461-470, 1999

30. Johnson DW: Dietary protein restriction as a treatment for slowing chronic kidney disease progression: the case against. Nephrology 11:58-62, 2006

31. Levey AS, Adler S, Caggiula AW, et al. and Modification of Diet in Renal Disease Study Group: Effects of dietary protein restriction on the progression of advanced renal disease in the modification of diet in renal disease study. Am J Kidney Dis 27:652-663, 1996

32. Van Biesen W, Davies S, Lameire N: An integrated approach to end-stage disease. Nephrol Dial Transplant, 16(suppl 6):7-9, 2001

33. Mircescu G, Capşa D, Covic M, et al: Nephrology and renal replacement therapy in Romania: transition still continues (Cinderella story revisited). Nephrol Dial Transplant 19:2971-2980, 2004