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Supplemented very low protein diet ameliorates responsiveness to erythropoietin in chronic renal failure

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Supplemented very low protein diet ameliorates responsiveness to erythropoietin in chronic renal failure.

Background. The aim of this study was to evaluate the relationship between uremic state and erythropoiesis in patients with predialytic chronic renal failure (CRF).

Methods. We monitored for 2 years the erythropoietin (EPO) requirement in patients with advanced CRF (creatinine clearance ≤25 mL/min), randomized to either low protein diet (LPD) group (0.6 g/kg body weight/day, $N = 10$) or very low protein diet (VLPD) group (0.3 g/kg body weight/day, $N = 10$) supplemented with a mixture of ketoanalogs and essential amino acids, both kept at target hemoglobin levels.

Results. The achieved protein intake after 6 months was 0.79 ± 0.02 g/kg body weight/day and 0.50 ± 0.02 g/kg body weight/day in LPD and VLPD, respectively; such a difference was maintained up to the end of follow up. The final hemoglobin values did not differ from the basal values in either group (11.5 ± 0.2 g/dL and 11.5 ± 0.3 g/dL). EPO dose, that was similar at baseline (62.4 ± 9.6 UI/kg body weight/week and 61.8 ± 8.8 UI/kg body weight/week subcutaneously), remained unchanged in LPD but progressively decreased in VLPD down to the final value of 41.2 ± 7.0 UI/kg body weight/week ($P < 0.0001$ vs. basal and LPD). VLPD was associated with a decrease of urinary excretion and serum levels of urea nitrogen and phosphate; however, EPO requirement was not correlated with the changes of these parameters. On the contrary, the variation of EPO dose directly correlated with the modification of parathyroid hormone (PTH) levels, that diminished from 229 ± 55 pg/mL to 118 ± 16 pg/mL ($P < 0.0001$) in VLPD and did not change in LPD.

Conclusion. In patients with advanced CRF, an effective decrease of protein intake of 0.3 g/kg body weight/day induces a reduction of about 35% of the EPO dose required to maintain the target hemoglobin levels. This effect appears dependent on the correction of a moderate secondary hyperparathyroidism.

Anemia is a major complication of dialytic and predialytic stages of chronic renal failure (CRF). In predialysis CRF patients, the International Guidelines recommend administration of erythropoietin (EPO) at dosage adequate to reach and maintain the hemoglobin level at the same target indicated for dialysis patients [1, 2]. Indeed, the major benefits of anemia correction on quality of life, cardiovascular outcome, and mortality are now well recognized, and, moreover, clinical studies have excluded the hypothesized worsening effect of EPO on progression of renal disease [3–5]. Nevertheless, the implementation of the guidelines on anemia correction in predialysis remains scarce [6, 7]. Effort must be therefore made to improve the control of anemia in this large subgroup of CRF patients.

Both experimental and clinical studies have generated evidence that the uremic state inhibits erythropoiesis [8–11]. Specifically, in hemodialysis patients treated with a fixed dose of EPO, an urea reduction ratio <65% is associated with a low hematocrit value that augments after increasing the efficiency of hemodialysis treatment [10]. On the other hand, inpatients constantly maintained at hematocrit values of 35% by EPO treatment, Kt/V and EPO dose are inversely correlated [11]. On the basis of these observations in hemodialysis, one may hypothesize that better control of uremia ameliorates responsiveness to EPO also in prehemodialysis patients.

It is well known that protein-restricted diets reduce signs and symptoms of uremia in CRF patients. In addition, the Modification of Diet in Renal Disease (MDRD) and recent metabolic studies have documented that the efficacy of either low protein diet (LPD) or very low protein diets (VLPD) is not weakened by detrimental effects on nutritional status [12–16]. More important, the dietary approach has been found efficacious in delaying the initiation of hemodialysis treatment [14, 16]. Despite the proven efficacy of dietary protein restriction in controlling uremia in pre hemodialysis patients, the potential impact of this effect on erythropoiesis has never been assessed. In patients with predialytic CRF, we therefore evaluated, by means of a prospective long-term study,

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the effect of a supplemented VLPD, as compared with standard LPD, on the requirement of EPO needed to maintain hemoglobin levels within the recommended range.

METHODS

Study population

In our outpatient clinic for the conservative treatment of CRF, we selected patients with creatinine clearance ≤25 mL/min/1.73 m^2 and treated with LPD (0.6 g/kg body weight/day) and EPO for a period of 6 to 12 months. Patients with bleeding or diseases potentially affecting EPO response, such as neoplastic diseases, infectious diseases, and severe malnutrition, were excluded. Out of a pool of 33 eligible patients, 20 gave their informed consent to the study. These 20 patients were therefore randomized into two groups; one group started a VLPD supplemented by ketoanalogs and essential amino acids ($N = 10$), while the remaining patients continued their usual LPD and constituted the control group ($N = 10$).

Treatment regimens

The LPD provided 0.6 g of protein/kg body weight/day with a caloric intake of 35 kcal/kg body weight/day, while the VLPD supplied the same caloric intake but with 0.3 g/kg body weight/day of protein of vegetable origin. This diet was supplemented with a mixture of ketoanalogs and essential amino acids (Alfa Kappa) (Kedrion, Lucca, Italy) administered at the dose of 1 tablet/5 kg body weight; each tablet contained calcium keto-isoleucine 67 mg, calcium keto-leucine 101 mg, calcium phenylpyruvate 68 mg, calcium keto-valine 86 mg, calcium hydroxy-methionine 59 mg, L-lysine monoacetate 105 mg, L-threonine 53 mg, L-histidine 38 mg, and L-tyrosine 30 mg. All patients were required to restrict their dietary sodium intake.

Study design

Prior to randomization, we performed a 3 month run-in period in order to verify the stability of hemoglobin coefficient of variation (<3%). Follow-up on the diets lasted 24 months. Patients were seen every month to measure renal function, hemoglobin levels, adherence to dietary prescription, and blood pressure. For the statistical analysis, we used the data at the 6-month interval. The patient terminated the study if the value of creatinine clearance decreased to ≤ 7 mL/min/1.73 m^2 or because of development of uremic complications requiring hemodialysis treatment.

Pharmacologic treatment

EPO therapy (β-epoietin) was administered subcutaneously once a week and the dose was adjusted in each patient to maintain hemoglobin levels in the 11 to 12 g/dL range. Iron supplementation was performed to keep tranferrin saturation (TSAT) >20% and serum ferritin between 100 and 500 mg/dL. Antihypertensive therapy was administered in all patients to maintain blood pressure levels <140/90 mm Hg. Patients also received 2 to 3 g/day of sodium bicarbonate and folic acid/vitamin B_{12} supplements. Phosphate binders were administered to maintain serum phosphate levels ≤ 5.5 mg/dL.

Measurements

Blood pressure was measured by mercury sphygmomanometer, with the first and fifth Korotkoff sounds being used to identify systolic and diastolic blood pressure, respectively. The reported values were the mean of three consecutive measurements obtained after 15 minutes of rest. Serum albumin, serum and urinary levels of creatinine, urea, sodium, phosphate, and potassium were measured by an autoanalyzer (Olympus AU 400) (Olympus Italia, Segrate, Italy). Dietary protein intake was estimated from 24-hour urea N excretion according to Maroni, Steinman, and Mitch [17]. To determine the dietary energy intake, patients recorded on dietary diaries the amount of ingested food and the daily number of meals (breakfast, lunch, dinner, and snacks) once each month. A skilled dietitian trained patients how to record the total food intake in the diary by household measures, and also instructed them to take the measures of the utensils before starting food record. The same person analyzed all food records over the study period, computing dietary protein and energy intake.

Hemoglobin was measured by Coulter counter (Coulter Electric, Hialeah, FL, USA). Three different amounts of hemoglobin standards (8.2, 13.2, and 15.5 g/dL) were analyzed during the analytic session to evaluate the stability of the method. Analysis of hemoglobin standards was performed during the single analytic session and over the study time. Results are expressed as coefficient of variation 1.1%, 1.1%, and 1.2% for 8.2, 13.2, and 15.5 g/dL standards for daily variation. Iron and transferrin values were obtained by automated methods. TSAT was calculated by means of the following formula: TSAT% = [plasma iron (g/dL)/transferrin (mg/dL) × 1.41] × 100. The ferritin value was determined by enzyme-linked immunosorbent assays (ELISA). The parathyroid hormone (PTH) level was assessed by standard radioimmuno assay (RIA) method using two affinity-purified goat antibodies specific for two different regions of the PTH molecule (PTH 1-34; and PTH 39-84) (Sorin, Saluggia, Italy). C-reactive protein (CRP) was quantified by nephelometry by using a BNA II Nephelometer (Dade Behring, Inc., Newark, DE, USA).

Patients were trained to correctly collect 24-hour urine. The collection was considered incomplete if total volume was less than 750 mL and creatinine excretion was less than 10 mg/kg body weight.

Statistical analysis

All the values are reported as mean ± SD. Analysis of variance (ANOVA) for repeated measures followed by the Newman Keuls as post hoc test and paired Student *t* test were used for intragroup statistical analysis. Unpaired Student *t* test was used for intergroup comparisons. Fisher's exact test was used to compare categorical variables. Correlations between individual parameters were evaluated using linear regression analysis. A two-tailed P value < 0.05 was considered significant. The primary efficacy variable considered to calculate the sample size was the percent reduction (versus baseline) of the EPO dose. A mean basal EPO dose of 65.3 ± 10.6 IU/kg body weight/week was detected in the eligible patients with CRF attending our outpatient clinic. Considering as clinically relevant a reduction of 30%, we predicted a decrease of EPO dose from 65.3 to 45.7. Thus, it was estimated that to give the study a 90% power to have such a difference as statistically significant ($P < 0.05$), a minimum sample size of eight patients in each group was required.

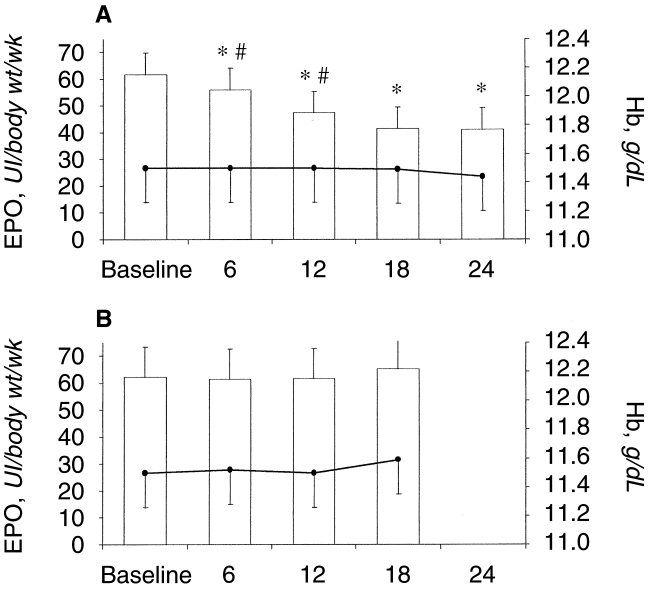

Fig. 1. Erythropoietin (EPO) dose (bars) and hemoglobin concentration (line) at baseline and during follow-up in very low protein diet (VLPD) (*A*) and low protein diet (LPD) (*B*) patients. In VLPD, at 24 months, data refer to eight patients; in LPD, at 18 months, data refer to nine patients. *$P < 0.05$ vs. baseline; #$P < 0.05$ vs. following point.

RESULTS

The two study groups, LPD and VLPD, did not significantly differ for gender distribution (six males and four females in each group), age (52 ± 15 years vs. 57 ± 17 years, respectively) and body mass index (23.5 ± 1.4 kg/m^2 vs. 23.2 ± 1.1 kg/m^2, respectively). Similarly, the systolic and diastolic blood pressure values did not significantly differ at baseline (135 ± 17/87 ± 5 mm Hg and 131 ± 12/86 ± 4 mm Hg, respectively). In the LPD and VLPD groups, the underlying renal disease was, respectively, diabetic nephropathy ($N = 3$ and 3), tubulointerstitial nephropathy ($N = 3$ and 0), glomerulonephritis ($N = 2$ and 3), hypertensive nephropathy ($N = 1$ and 1), and unknown ($N = 1$ and 3).

The duration of follow-up was significantly longer in VLPD than LPD (23.2 ± 1.9 months vs. 19.6 ± 4.0 months, respectively, $P < 0.02$); in VLPD, in fact, eight out ten patients completed the 24-month period of follow-up, while seven out ten patients of the LPD group stopped the study after month 18 having reached the end point. Therefore, we did not perform statistical analysis of the LPD data at month 24 ($N = 3$).

At baseline, in VLPD and LPD, EPO dose was 61.8 ± 8.8 U/kg body weight/week and 62.4 ± 9.6 U/kg body weight/week, and hemoglobin levels were 11.5 ± 0.3 g/dL and 11.5 ± 0.2 g/dL, respectively. The hemoglobin values remained unchanged during the follow-up in both groups, being 11.4 ± 0.2 g/dL in VLPD at month 24 and 11.6 ± 0.2 g/dL in LPD at month 18. The pattern of changes of EPO dose and hemoglobin levels in VLPD and LPD is reported in Figure 1. In this group, EPO requirement progressively decreased during the first year, reaching a plateau at 18 months; EPO dose, in fact, was reduced down to 56.1 ± 9.0, 47.5 ± 8.3, 41.5 ± 6.4, and 41.2 ± 7.0 after 6, 12, 18, and 24 months, respectively. On the contrary, EPO requirement in LPD did not differ throughout the study from baseline, being 65.4 ± 10.8 U/kg body weight/week at month 18.

The markers of compliance to dietary prescription are depicted in Table 1. During follow-up, dietary energy intake remained constantly above 30 kcal/kg/day in both groups. In VLPD, a stable reduction of daily excretion of urinary urea nitrogen became manifest within the initial 6 months; this corresponded to a decrease of protein intake from 0.81 ± 0.02 g/kg body weight/day to 0.50 ± 0.02 g/kg body weight/day. The reduced protein intake was coupled with the decline of blood urea nitrogen and serum and urinary phosphate levels. On the contrary, no major change of these parameters was detected in LPD. No correlation was found between the percentual change of blood urea nitrogen or serum phosphate and EPO dose at any time interval. At baseline, the mean values of serum calcium levels were similar between VLPD and LPD (9.4 ± 0.7 mg/dL and 9.5 ± 0.5 mg/dL, respectively) and did not change throughout the study.

In Table 2, we report the values of the main markers associated with EPO responsiveness. In both groups, the mean values of body weight and serum albumin did not

Table 1. Indexes of compliance to dietary prescription in very low protein diet (VLPD) and low protein diet (LPD) patients

	Baseline	6 months	12 months	18 months	24 months
VLPD					
Patients *number*	10	10	10	10	8
BUN *mg/dL*	82 ± 13[a]	43 ± 10[b]	41 ± 9[b]	42 ± 8[b]	44 ± 7
UUN *g/day*	6.52 ± 0.85[a]	3.21 ± 0.37[b]	3.22 ± 0.42[b]	3.20 ± 0.40[b]	3.14 ± 0.37
Serum phosphate *mg/dL*	3.7 ± 0.8[a]	3.2 ± 0.2[b]	3.2 ± 0.3[b]	3.2 ± 0.3[b]	3.1 ± 0.2
Urinary phosphate *mg/day*	808 ± 178[a]	503 ± 122[b]	518 ± 143[b]	492 ± 155[b]	486 ± 95
DPI *g/kg/day*	0.81 ± 0.02	0.50 ± 0.02[b]	0.50 ± 0.01[b]	0.49 ± 0.02[b]	0.49 ± 0.02[b]
LPD					
Patients *number*	10	10	10	9	3
BUN *mg/dL*	89 ± 7	87 ± 11	86 ± 10	84 ± 9	—
UUN *g/day*	6.35 ± 0.64	6.26 ± 0.73	6.25 ± 0.74	6.26 ± 0.76	—
Serum phosphate *mg/dL*	3.8 ± 0.4	3.9 ± 0.3	4.0 ± 0.4	4.1 ± 0.5	—
Urinary phosphate *mg/day*	826 ± 212	830 ± 183	815 ± 216	794 ± 159	—
DPI *g/kg/day*	0.80 ± 0.01	0.79 ± 0.02	0.79 ± 0.02	0.79 ± 0.02	—

Abbreviations are: BUN, blood urea nitrogen; UUN, urinary urea nitrogen; DPI, dietary protein intake. The values are mean ± SD.
[a] $P < 0.001$ vs. following points; [b] $P < 0.05$ vs. LPD

Table 2. Markers of conditions associated with resistance to erythropoietin (EPO) in very low protein diet (VLPD) and low protein diet (LPD) patients

	Baseline	6 months	12 months	18 months	24 months
VLPD					
Patients *number*	10	10	10	10	8
Body weight *kg*	66.7 ± 8.9	66.7 ± 8.9	66.6 ± 8.8	66.7 ± 8.7	66.7 ± 8.7
ALB *g/dL*	3.9 ± 0.1	3.9 ± 0.2	3.9 ± 0.3	4.0 ± 0.2	3.9 ± 0.1
TSAT %	30 ± 5	29 ± 6	31 ± 7	29 ± 7	30 ± 6
Serum ferritin *ng/mL*	236 ± 52	234 ± 82	219 ± 55	232 ± 65	225 ± 72
PTH *mg/dL*	229 ± 55[a]	168 ± 39[b,c]	127 ± 18[b]	124 ± 20[b]	118 ± 16
CRP *μg/mL*	0.80 ± 0.26	0.66 ± 0.20	0.72 ± 0.30	0.60 ± 0.25	0.60 ± 0.21
LPD					
Patients *number*	10	10	10	9	3
Body weight *kg*	65.8 ± 7.3	65.9 ± 7.2	65.9 ± 7.2	65.6 ± 7.5	—
ALB *g/dL*	4.0 ± 0.3	4.1 ± 0.2	4.1 ± 0.2	4.0 ± 0.2	—
TSAT %	31 ± 4	30 ± 4	32 ± 4	33 ± 7	—
Serum ferritin *ng/mL*	256 ± 88	237 ± 97	257 ± 103	232 ± 76	—
PTH *mg/dL*	213 ± 52	229 ± 52	216 ± 36	218 ± 37	—
CRP *μg/mL*	0.72 ± 0.22	0.70 ± 0.20	0.75 ± 0.24	0.72 ± 0.25	—

Abbreviations are: ALB, serum albumin; TSAT, total saturation of transferrin; PTH, parathyroid hormone; CRP, C-reactive protein. The values are mean ± SD.
[a] $P < 0.001$ vs. following points; [b] $P < 0.05$ vs. LPD; [c] $P < 0.05$ vs. following points

change during the follow-up and between the two groups. Iron status was adequate in the two groups of patients; indeed, in our patients, iron was regularly administered to maintain the values of serum ferritin and total TSAT within the recommended range in VLPD and LPD throughout the study. Similarly, development of inflammatory status could be excluded on the basis of normal values of CRP. In contrast, PTH progressively decreased in VLPD patients; the reduction was of 25% ± 15% after 6 months and doubled by month 12 (−42% ± 16%, $P < 0.005$), remaining constant thereafter (Table 2). On the contrary, in LPD, PTH concentration did not vary during the whole study period (Table 2). As depicted in Figure 2, the percentage changes of PTH and EPO dose at month 18 were directly correlated ($N = 19$, $r = 0.762$, $P = 0.0001$). This correlation remained highly significant at month 12 ($N = 20$, $r = 0.661$, $P = 0.0015$) and at month 24 ($N = 11$, $r = 0.666$, $P = 0.025$).

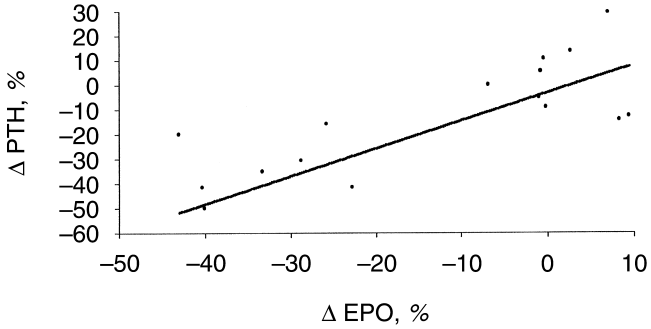

Fig. 2. Linear regression between the percentage changes of parathyroid hormone (PTH) level and erythropoietin (EPO) dose at 18 months in low protein diet (LPD) and very low protein diet (VLPD) patients ($N = 19$, $r = 0.762$, $P = 0.0001$).

Table 3. Main clinical parameters in very low protein diet (VLPD) and low protein diet (LPD) patients at baseline and during follow-up

	Baseline	6 months	12 months	18 months	24 months
VLPD					
Patients *number*	10	10	10	10	8
Creatinine clearance *mL/min/1.73 m²*	15.4 ± 4.2	15.7 ± 4.9	15.7 ± 6.4	15.6 ± 6.6	18.5 ± 4.7
Mean arterial pressure *mm Hg*	103 ± 7[a]	96 ± 6	95 ± 8	96 ± 10	91 ± 7
Urinary sodium *mEq/day*	170 ± 22[a]	138 ± 20[b]	147 ± 18[b]	139 ± 16[b]	130 ± 16
Triglycerides *mg/dL*	180 ± 20[a]	151 ± 17[b]	150 ± 10[b]	145 ± 12[b]	148 ± 15[b]
Cholesterol *mg/dL*	201 ± 47[a]	172 ± 20	159 ± 17[b]	157 ± 16[b]	158 ± 16
LPD					
Patients *number*	10	10	10	9	3
Creatinine clearance *mL/min/1.73 m²*	17.3 ± 3.5[a]	16.2 ± 4.0[a]	14.2 ± 5.1[a]	12.4 ± 5.3	—
Mean arterial pressure *mm Hg*	101 ± 4	99 ± 5	99 ± 6	98 ± 4	—
Urinary sodium *mEq/day*	171 ± 24	168 ± 24	165 ± 19	166 ± 22	—
Triglycerides *mg/dL*	175 ± 21	178 ± 19	173 ± 30	180 ± 21	—
Cholesterol *mg/dL*	198 ± 29	187 ± 27	190 ± 19	206 ± 26	—

The values are mean ± SD.
[a]$P < 0.01$ vs. following points; [b]$P < 0.05$ vs. LPD

As shown in Table 3, the decline of renal function was greater in the latter group (−0.30 ± 0.16 mL/min/month) with respect to VLPD patients (0.01 ± 0.22 mL/min/month, $P < 0.003$). Arterial blood pressure was adequately controlled in the two groups of patients with no value exceeding 140/90 mm Hg. Of note, in VLPD patients, mean arterial pressure significantly decreased during follow-up, while no significant change was detected in LPD; in addition, urinary sodium excretion significantly decreased during follow up in VLPD but not in LPD patients (Table 3). Similarly, plasma triglycerides and cholesterol decreased in VLPD group but not in LPD.

DISCUSSION

This study demonstrates that in patients with advanced CRF, a supplemented VLPD, as compared with a standard LPD, allows a long-lasting reduction of the EPO dose required to maintain hemoglobin level within the recommended range. This favorable effect on EPO resistance was determined by an achieved reduction in dietary protein intake of 0.3 g/kg body weight/day, that is, from 0.8 to 0.5 g/kg body weight/day. The study provides first-time evidence on the beneficial effects of protein restriction on anemia management of advanced CRF since all the early works on uremic patients have exclusively focused on the outcome of renal function and/or nutritional status [12–16, 18, 19].

To assess the isolated effect of dietary protein intake, we planned a careful control of the main determinants of resistance to EPO. It is well known that the response to EPO in predialytic CRF can be improved by some standard interventions, iron replacement being the most important one. During follow-up, serum ferritin and total TSAT remained constantly within the recommended range in VLPD and LPD patients by adequate administration of iron. Deficiencies of folate and vitamin B_{12} were avoided by periodic supplementation. The absence of malnutrition, that is, an uncommon cause of anemia in predialysis, was indicated by constancy of body weight and of normal values of serum albumin during the entire follow-up; indeed, dietary energy intake remained constantly above 30 kcal/kg body weight/day. Therefore, we can reasonably exclude that all these factors played a role in the different response to EPO.

On the contrary, the improvement of EPO response in VLPD was associated with a stable correction of the uremic state, as testified by the marked decrease of blood urea nitrogen. In uremic patients, Ifudu, Feldman, and Friedman [10] have demonstrated that an increase of dialytic dose is associated with increment of hemoglobin levels; however, the authors did not provide insights into the underlying pathophysiology. On this regard, experimental studies have shown that the substances exacerbating anemia in renal failure are of middle molecular weight [8, 9]. When serum drawn from an uremic patient is added to cultured bone marrow erythroid cells, a dose-dependent inhibition of the cell growth ensues; this effect, however, is not due to urea per se, since this substance does not possess inhibitory activity in vitro [8, 9]. The current clinical data tend to confirm these experimental findings; we did not detect in fact any correlation between EPO dose and blood urea nitrogen. Similarly, no correlation was found between EPO dose and phosphate levels. Finally, we can reasonably exclude that proinflammatory cytokines, which contribute to the pathogenesis of anemia in hemodialysis patients [20], may have played a role; in fact, the serum values of CRP were constantly normal in both LPD and VLPD patients throughout the study.

Interestingly, our long-term, prospective and controlled study demonstrates that, in agreement with previous short-term or retrospective or not-controlled works [21, 22, 23], supplemented VLPD decreases the serum

concentration of phosphate and, consequently, PTH levels. Experimental studies have shown an inhibitory effect of PTH on erythropoiesis [24, 25]. Furthermore, amelioration of responsiveness to EPO by parathyroidectomy or intravenous administration of calcitriol has been shown in hemodialysis patients affected by severe hyperparathyroidism [26, 27]. Despite this, the potential relevance of PTH to renal anemia has never been evaluated in prehemodialysis renal failure. In the present study, a strict correlation was found between the reduction of EPO dose and PTH, suggesting that the improvement of responsiveness to EPO was mediated by the correction of an even moderate hyperparathyroidism, secondary to the restriction of dietary phosphate intake. Nevertheless, we cannot exclude that the calcium salts of the keto-analogous preparation may have at least in part acted as intestinal phosphate-binding agent [21, 22]. Actually, the progressive decrease of EPO dose requirement in VLPD group paralleled the time-course reduction of PTH levels. Thus, the changes in EPO responsiveness may be the expression of a functional phenomenon related to the slow, progressive decline of PTH availability.

This relationship between EPO dose and PTH values has been sought but not found in hemodialysis patients [11, 28]. The discrepancy with our data may be related to the major contribution of factors other than PTH in determining the degree of anemia in the dialytic phase of CRF; under this condition, in fact, the marked deficiency of EPO, iron deficiency, inflammations, blood losses, bone marrow fibrosis, and aluminium overload, certainly play additional role.

At baseline, the uremic state of the enrolled patients was actually minimized by preexisting multiple pharmacologic and dietetic interventions. Further benefits of a more severe protein restriction became manifest even in this setting of adequate management of CRF. VLPD, in fact, was not coupled with the relentless decline of measured creatinine clearance, that, on the contrary, was detected in the group randomized at LPD; this phenomenon certainly contributed to postponing the initiation of hemodialysis treatment in this small group of patients. Of note, the MDRD Study, that is, the largest trial addressing this issue, led to a similar conclusion only in the secondary analysis of the data [29]; this was possibly due to the slight difference (less than 0.1 g/kg body weight/day) in the mean achieved protein intake in LPD and VLPD groups. Conversely, in our study, such a difference was on average of 0.3 g/kg body weight/day. On this regard, it is important to underline that since protein restricted diets represent a major change in lifestyle, patients often show an imperfect compliance [30]. Nevertheless, on the basis of MDRD findings [29], other previous studies [14, 16], and the present work as well, it is reasonable to recommend a well-designed protein-restricted diet even if the compliance will be not optimal because of the favorable effects on dialysis requirement, nutritional status, anemia management, and hyperparathyroidism.

Of note, our study also suggests a role of salt intake on CRF progression. At variance with the previous works on this issue, in fact, we measured urinary sodium excretion; this index of sodium intake significantly decreased during VLPD, while it remained unchanged in controls. Experimental studies have shown that salt restriction slows the progression of renal failure by directly inhibiting glomerular hypertrophy [31, 32]. Our group has previously suggested, by means of a retrospective long-term study, a beneficial effect of low salt diet on the rate of glomerular filtration rate (GFR) decline in CRF patients [33]. Furthermore, a reduced salt intake allows an improved control of blood pressure in CRF [34]. Overall, the previous and the present findings may indicate that a lower salt intake, which is invariably coupled with protein restriction [33], may contribute to slowing CRF progression by antihypertrophic and antihypertensive effects.

CONCLUSION

This study provides first-time evidence that in patients with advanced CRF and without recognized conditions of EPO resistance, an effective decrease of dietary protein intake of 0.3 g/kg body weight/day, obtained by means of supplemented VLPD, induces a progressive reduction of about 35% of the EPO dose required to maintain the target hemoglobin levels. This effect appears dependent on the correction of the moderate secondary hyperparathyroidism rather than on the reduction of plasma urea levels. The increase of responsiveness to EPO, together with the delayed beginning of hemodialysis treatment, undoubtedly represent a money-saving feature of dietary protein restriction.

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