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# Effects of dietary protein and phosphorus restriction on the progression of early renal failure

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**Effects of dietary protein and phosphorus restriction on the progression of early renal failure.** Three groups of patients with chronic renal failure were studied. Group 1 comprised 25 patients with a mean serum creatinine of 2.18 mg/dl and a mean arterial pressure of 117 mm Hg. Group 2 had 20 patients with a mean serum creatinine of 4.24 mg/dl and a mean arterial pressure of 119 mm Hg. All these patients were kept for 18 to 76 months on a diet containing about 40 kcal/kg, 0.6 g/kg of protein, 700 mg of phosphorus, and 1,000 to 1,500 mg of calcium (orally supplemented). Group 3 comprised 30 patients with a mean serum creatinine of 2.28 mg/dl and a mean arterial pressure of 116 mm Hg. They had followed no specific dietary regimen for 3 to 72 months, and their dietary calorie, protein, phosphorus, and calcium intakes averaged 35 kcal/kg, 70 g, 900 mg, and 800 mg, respectively. The plots of reciprocal creatinine against time gave slopes of −0.0008 and −0.0010 in patients in groups 1 and 2, and a slope of −0.020 in group 3 patients. The slopes of both groups 1 and 2 were statistically different (analysis of variance and "F" test, $P < 0.01$) from that of group 3. No evidence of progressive protein and phosphorus depletion was observed in groups 1 and 2 patients. We conclude that a moderate dietary restriction of protein and phosphorus is an acceptable and effective regimen for delaying progression of functional deterioration in early renal failure.

**Effet de la restriction protéique et phosphorée alimentaire sur la progression de l'insuffisance rénale débutante.** Trois groupes de malades ayant une insuffisance rénale chronique ont été étudiés. Le groupe 1 comprenait 25 malades ayant une créatinine sérique moyenne de 2,18 mg/dl et une pression artérielle moyenne de 117 mm Hg. Le groupe 2 comportait 20 malades ayant une créatinine sérique moyenne de 4,24 mg/dl et une pression artérielle moyenne de 119 mm Hg. Tous ces malades ont été soumis pendant 18 à 76 mois à un régime contenant environ 40 kcal/kg, 0,6 kg de protéines, 700 mg de phosphore, et 1000 à 1500 mg de calcium (par supplémentation orale). Le groupe 3 comprenait 30 malades ayant une créatinine sérique moyenne de 2,28 mg/dl et une pression artérielle moyenne de 116 mm Hg. Ils n'avaient pas suivi de régime alimentaire spécifique pendant 3 à 72 mois, et leurs apports alimentaires caloriques, protéiques, phosphorés et calciques étaient en moyenne de 35 kcal/kg, 70 g, 900 mg, et 800 mg, respectivement. Les courbes de créatinine en fonction du temps ont donné des pentes de −0,0008 et de −0,0010 chez les malades des groupes 1 et 2, et une pente de −0,020 chez ceux de groupe 3. Des pentes des groupes 1 et 2 différaient statistiquement (analyse de variance et test de "F", $P <$ 0,01) de ceux du groupe 3. Il n'a pas été observé de preuve de déplétion progressive en protéines et en phosphore chez les malades des groupes 1 et 2. Nous concluons qu'une restriction alimentaire modérée en protéines et en phosphore est un régime acceptable et efficace pour retarder la progression de la détérioration fonctionnelle au cours de l'insuffisance rénale précoce.

In the last few years, accumulating experimental evidence reports that dietary protein and phosphorus restriction may have beneficial effects on the structure and function of the remnant kidney in animals with surgically induced reduction of renal mass.

In rats, dietary phosphorus restriction has prevented hyperphosphatemia, increased phosphaturia per nephron, parenchymal calcification, fibrosis in the remnant kidney, functional deterioration, and death in uremia [1, 2]. In addition, low-phosphate diets may prevent severe glomerular and tubular-interstitial damage and functional deterioration in rats with established nephrotoxic serum nephritis [3].

On the other hand, restriction of dietary protein intake has been effective in preventing both hyperfiltration and histologic lesions in remnant glomeruli of rats with reduced renal mass [4] as well as functional renal deterioration in the same experimental model [5–7].

The clinical applicability of these experimental results is still under evaluation. There is no agreement on what stage of chronic renal failure dietary protein restriction should be started and the degree to which protein and phosphorus should be limited. We report in this study the results obtained in the last few years, during which a dietary protocol—originally intended for preventing renal osteodystrophy [8, 9]—was followed specifically for delaying progression of chronic renal failure in two groups of patients with different degrees of functional deterioration. A comparison has been made with a third group of patients, whose evolution has been assumed to represent the clinical course of chronic renal failure when dietary protein and phosphorus restriction were not prescribed.

## Methods

Three groups of patients with chronic renal failure were studied:

*Group 1.* This group comprised 25 patients, aged 25 to 68 years, with serum creatinine concentrations of 1.55 to 2.70 mg/dl (mean, 2.18). The underlying renal disease was established by means of renal biopsy in eight patients and by history,

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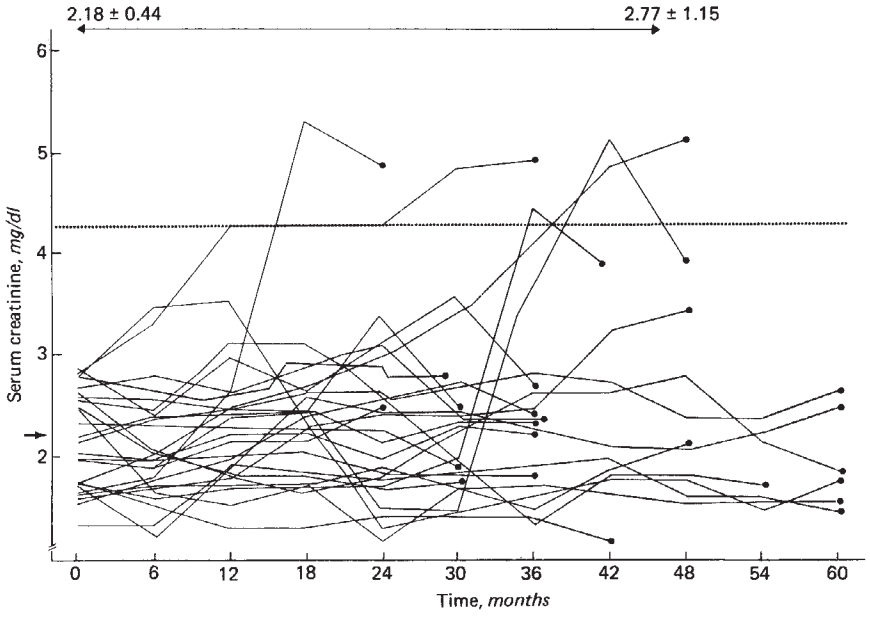


**Fig. 1.** *The follow-up of group 1 patients with chronic renal failure on a protein-restricted diet.* The *dotted line* represents the doubling of initial mean values of serum creatinine in the 25 patients.

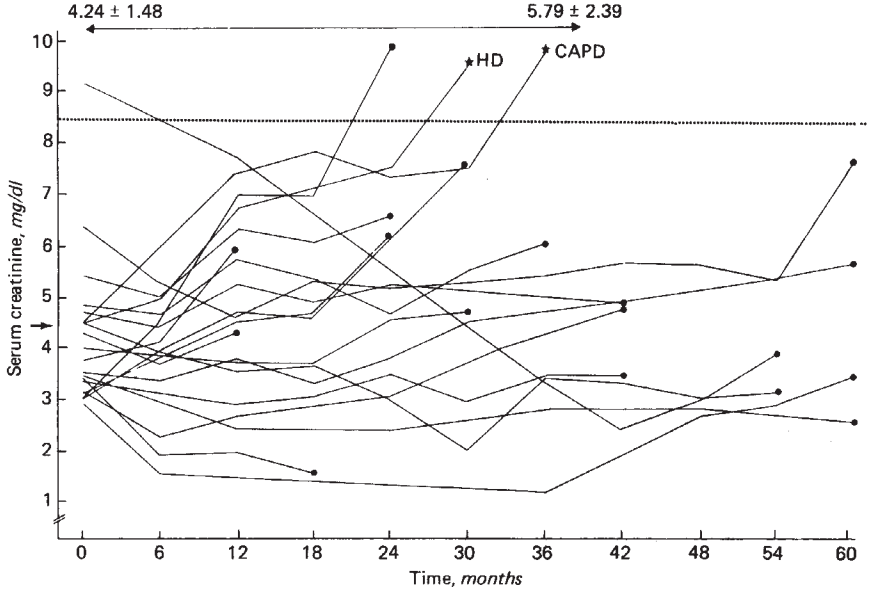


**Fig. 2.** *The follow-up of the 20 patients in group 2 with chronic renal failure on a protein-restricted diet.*

clinical, and radiological data in 17 patients. Eight patients had chronic pyelonephritis; seven, chronic glomerulonephritis; two, benign nephrosclerosis; one, renal tuberculosis; one, diabetic renal disease; one, Alport syndrome; and in five of them the underlying renal disease was unknown. Their mean arterial pressure was 117 mm Hg, and 60% of them were hypertensive. All patients were kept for 28 to 76 months (mean, 48.2) on a diet containing about 40 kcal/kg, 0.6 g/kg of protein (75% of which had high biological value), 600 to 750 mg of phosphorus, about 75 mEq of sodium and chloride, and 1,000 to 1,500 mg of calcium (orally supplemented). Additional treatment with vitamin D or its analogues was given for only short periods to some patients, and conventional antihypertensives (alpha-methyldopa, clonidine, propranolol) or allopurinol was only prescribed when needed.

*Group 2.* This group comprised 20 patients, aged 35 to 68 years, with serum creatinines of 2.90 to 5.40 mg/dl (mean, 4.2). The underlying renal diseases, established by means of renal biopsy in five patients and by history, clinical, and radiological data in the remaining 15, were chronic pyelonephritis in five patients, polycystic renal disease in five, chronic glomerulonephritis in four, diabetic renal disease in two, and were unknown in four patients. Their mean arterial pressure was 119 mm Hg, and 80% of them were hypertensive. All patients were kept for 18 to 76 months (mean, 42.3) on the same diet as those in group 1. The extent to which patients in groups 1 and 2 followed their prescribed diets was checked carefully by the members of the staff by means of the following procedures every 2 to 3 months: *(1)* dietary interviews with each patient and those members of the family who were taking care of food preparation. Written

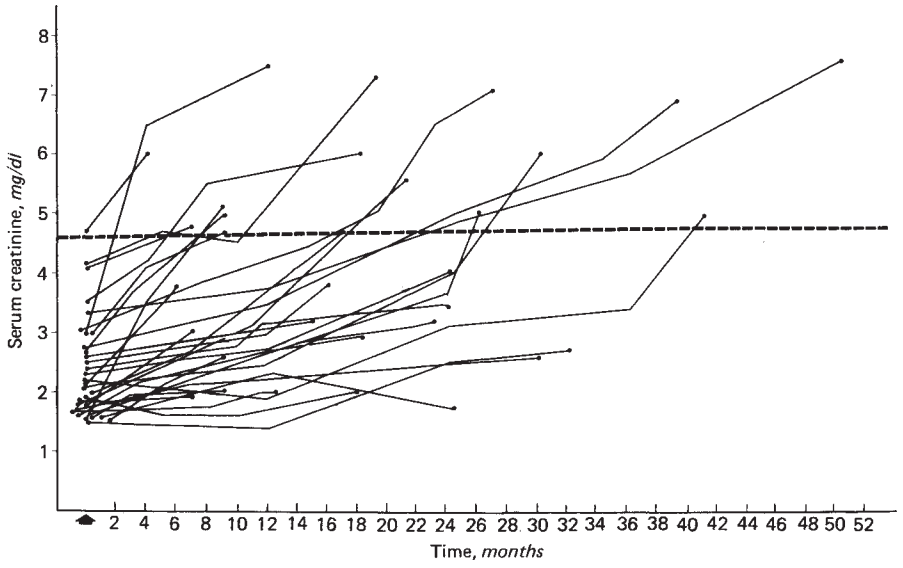


**Fig. 3.** *The follow-up of patients in group 3.*

dietary diaries at 2-month intervals also were obtained from each patient; *(2)* control of blood urea nitrogen, simultaneously to that of creatinine; *(3)* control of urine phosphate and urea excretions. Additional treatment with vitamin D analogues was only given for short periods to some patients, and conventional antihypertensive drugs or allopurinol was only prescribed when needed.

*Group 3.* This group had 30 patients, aged 13 to 73 years, with serum creatinines of 1.60 to 4.70 mg/dl (mean, 2.28). The underlying renal diseases, established by means of renal biopsy in 11 patients and by history, clinical, and radiological data in the remaining 19, were chronic glomerulonephritis in 11 patients, chronic pyelonephritis in 6, polycystic renal disease in 5, benign nephrosclerosis in 2, diabetic renal disease in 1, and in 5 patients the disease was unknown. Their mean arterial pressure was 116 mm Hg, and 50% were hypertensive. All these patients were referred to our units by other colleagues. Since the discovery of renal failure in the patients, no attempt to control serum phosphorus and calcium levels by means of dietary restriction, calcium supplementation, or vitamin D administration had been done for 3 to 72 months (mean, 23.4). A good control of blood pressure and serum uric acid levels, however, had been obtained in nearly all patients with conventional antihypertensives or allopurinol. A careful survey of dietary intakes was done in all patients and in those members of their family who prepared the food. The estimated dietary calorie, protein, phosphorus, sodium, and calcium intakes averaged 35 kcal/kg, 70 g, 900 mg, 70 mEq, and 800 mg, respectively. After the first visit in our units, group 3 patients were given the same diet as those in groups 1 and 2, and the prospective follow-up then ranged from 1 month to 2 years.

Serum concentrations of total protein, albumin, urea nitrogen, creatinine, phosphate, and calcium, and urine phosphate and urea nitrogen were determined with a Technicon Autoanalyzer. Skeletal muscle biopsy specimens were taken from muscle quadriceps femoris according to the technique of Bergström [10]. The fat-free solid tissue was chosen as the base of

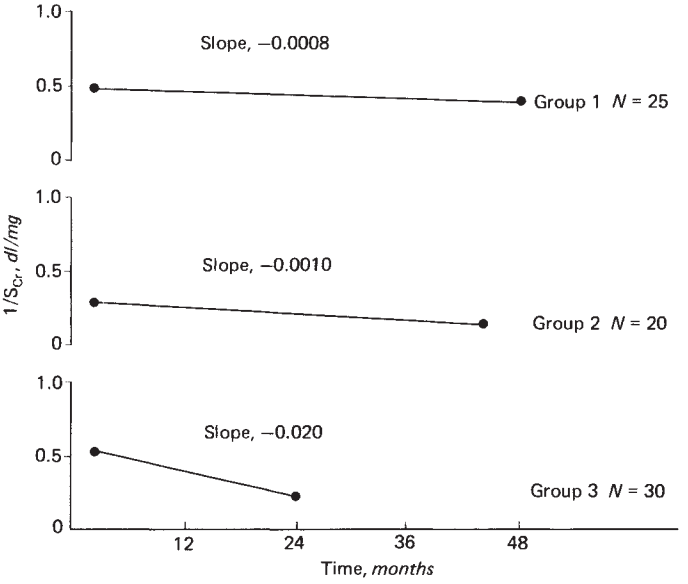


**Fig. 4.** *Relationship of the reciprocal of serum-creatinine concentration, plotted against time, in the three groups of patients.* Statistical comparison (analysis of variance and "F" test): Group 1 vs. group 3, F = 17.2, $P < 0.01$; group 2 vs. group 3, F = 11.9, $P < 0.01$.

reference for the inorganic phosphate and protein nitrogen contents [11]. The evaluation of the rate of functional renal deterioration was calculated using linear regression analysis from the relationship between time and the reciprocal of serum-creatinine concentration [12, 13]. In this analysis, the slope represents the fraction of initial renal function lost per month (in milligrams per deciliter), assuming that serum creatinine before the onset of renal failure was 1 mg/dl.

For statistical comparison of the slopes in the three groups of patients, the methods of analysis of variance and the "F" test were used.

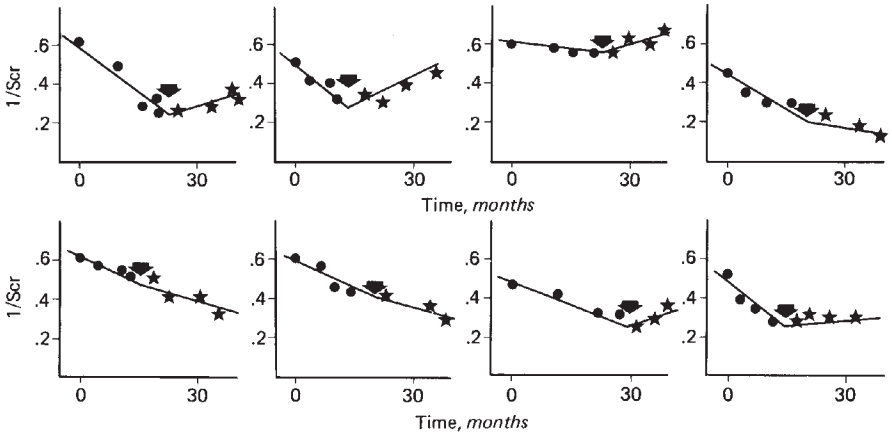


**Fig. 5.** *The regression lines for the changes in renal function before* (closed circles) *and after* (stars) *dietary treatment in eight patients from group 3.* Difference between the mean values of the slopes equals: F = 6.57, $P < 0.01$.

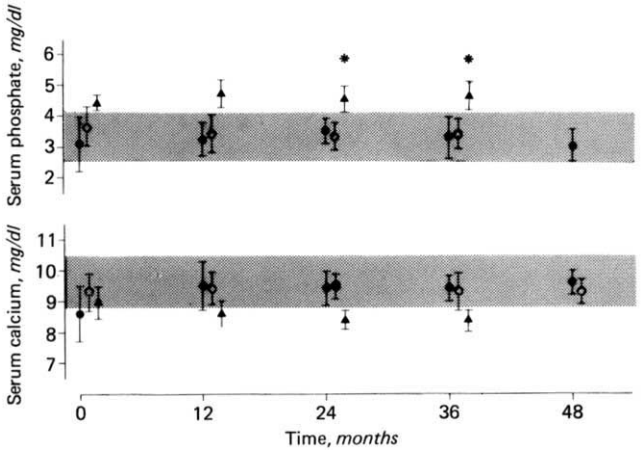


**Fig. 6.** *Mean values of serum phosphate significantly higher in patients in group 3 than in those in groups 1 and 2.* Symbols: ●, group 1; ○, group 2; ▲, group 3; *, $P < 0.005$; ▨, normal range.

## Results

The follow-up of group 1 showed remarkably stable renal function in most patients. In only three of them was there evidence of significant deterioration of renal function, expressed by a rise of serum creatinine above the doubling of initial mean values (Fig. 1). In group 2, two patients had to start hemodialysis or peritoneal dialysis during the follow-up (Fig. 2). In group 3, about 40% of the patients had a rise of their serum-creatinine concentration above the doubling of initial mean values during the clinical course of their disease before prescription of the diet (Fig. 3). Since, in most of our patients, the relation of the reciprocal of serum-creatinine concentration plotted against time was linear, the data were analyzed by linear regression. We obtained slopes of −0.0008 and −0.0010 in the two groups of patients on the protein-restricted diet, and a slope of −0.020 in that of patients on a free diet (Fig. 4). The differences between the slopes in patients in groups 1 and 2 versus that in patients in group 3 are statistically significant: group 1 vs. group 3, F = 17.2, $P < 0.01$; group 2 vs. group 3, F = 11.9, $P < 0.01$. After the diet was prescribed, we obtained a follow-up sufficient to make a reliable comparison with the pretreatment period in eight patients, whose regression lines for the changes in renal function before and after the treatment are reported in Figure 5. The difference between the mean values of the slopes before (−0.0132) and after (−0.0013) the dietary treatment is statistically significant (F = 6.57, $P < 0.01$).

A good control of serum calcium and phosphorus concentrations was obtained regularly in both groups of patients on the protein-restricted diet, whereas the mean values of serum phosphate were significantly higher in those without dietary treatment (Fig. 6). The serum concentrations of total protein and albumin did not change significantly during the treatment. The serum concentrations of urea nitrogen were always found to be adequate to those of serum creatinine and hence to reflect the prescribed protein intake at all levels of renal function. The relative figures were as follows: BUN 25.8 ± 4.5 mg/dl (mean ± SD) at $S_{cr}$ of 2.0 mg/dl; BUN 41.0 ± 10.0 at $S_{cr}$ of 3.0; BUN 44.0 ± 9.9 at $S_{cr}$ of 4.0; BUN 60.0 ± 12 at $S_{cr}$ of 5.0; BUN 69.0 ± 10.0 at $S_{cr}$ of 6.0 mg/dl.

The urinary excretion of phosphate, whether expressed per 24 hr or factored per deciliter of GFR (creatinine clearance), was significantly smaller in patients in group 1 than in those in group 3, at comparable levels of renal function (Table 1). A biochemical analysis of muscle tissue was available in 20 patients and showed normal mean values of phosphate and cell protein contents, without correlation to the duration of dietary treatment (Fig. 7).

## Discussion

During the first 5 years (1970 to 1974) of administration of protein-restricted diets to prevent renal osteodystrophy, we did not look specifically at the survival of renal function in our patients. However, a retrospective analysis of 18 patients with chronic renal failure of varying etiology, followed for 5 to 13 years, showed that their serum creatinine concentrations had increased from the mean values of 4.3 to only 8.2 mg/dl over a mean period of 7 years, during which good control of the serum concentrations of calcium and phosphate also was obtained [14]. Our present data suggest that dietary protein restriction, with emphasis on control of serum calcium and phosphate, is effective in preventing secondary hyperparathyroidism and bone disease [19], as well as in delaying the progression of chronic renal failure.

In our opinion, the degree of functional renal deterioration is critical in modulating the effects of dietary protein and phospho-

**Table 1**[a]

| | Average $PO_4$ intake *mg/24 hr* | Urinary $PO_4$ *mg/24 hr* | Urinary $PO_4$ per deciliter of GFR $C_{Cr}$ |
|---|---|---|---|
| Normal subjects (41) | 900 ±230 | 594 201 | 495 179 |
| Patients with chronic renal failure on free diet (group 3) (30) | 900 ±135 | 558 160 | 1992 440 |
| Patients with chronic renal failure on diet (group 1) (25) | 650 ±75 | 377[b] 109 | 1450[b] 375 |

[a] The values are expressed as mean ± SD. The numbers in parentheses refer to the number of patients.
[b] $P < 0.01$ (Student's $t$ test) when compared with group 3.

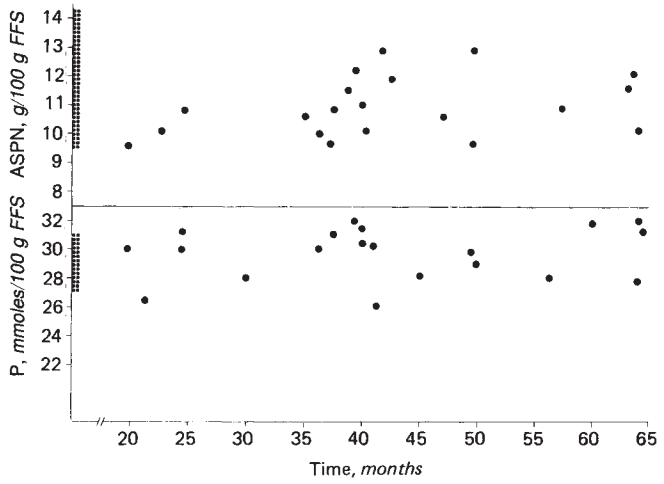


**Fig. 7.** *Mean values of muscle inorganic phosphate and cell protein contents normal in 20 patients on a low-protein diet.* There is no correlation to the duration of dietary treatment. Abbreviations: ASPN, alkali-soluble protein nitrogen; FFS, fat-free solid tissue. *Normal range* is ⁝⁝.

rus restriction; this therapeutic regimen produces better results in patients with only a moderate loss of renal function than in those with more advanced renal failure. Therefore, in agreement with Giordano [15], we prefer to restrict protein and phosphorus intakes early in the course of renal failure rather than in uremia, when the efficiency of protein utilization is reduced, tissue protein synthesis is diminished, catabolism is increased greatly, and signs of toxicity, including nausea and anorexia, are usually present [16].

For these reasons, our data are not comparable with those obtained by others [17, 18] in patients with advanced renal failure treated with low-protein diets supplemented with essential aminoacids and keto-analogues for a limited time. Furthermore, since only two of our patients began dialysis during the follow-up, we were unable to choose the deterioration time, that is, the value of elapsed survival time from early to endstage renal failure [15], as a measurable index in our population.

Some years ago, two groups of investigators showed that the average rate of decrease in reciprocal creatinine (in deciliters per milligram per month) was a reliable quantitative measure of the rate of progression of renal failure, regardless of the underlying renal disease [12, 13]. Since the relation of the reciprocal of serum creatinine concentration plotted against time was linear in most of our patients, the data were analyzed by linear regression. In patients with early renal failure on a protein-restricted diet (group 1), the average rate of decrease in reciprocal creatinine was nearly ten times lower than that observed by Mitch et al [12] and 20 to 40 times lower than those found by others [13, 19, 20] in patients who were not treated with dietary protein restriction.

Our results seem to be at variance with those reported in a recent paper [21] which states that a decrease in serum phosphate concentration, mainly obtained by administering large amounts of aluminum hydroxide, failed to significantly affect the rate of progression in a group of patients with moderate or advanced renal failure treated for a mean period of 10 months. Unfortunately, the authors gave no information on dietary protein, phosphate, calcium, and calorie intakes and on control of blood pressure in their patients. On the other hand, these apparently different data stress once again the importance of an earlier dietary protein and phosphorus restriction in patients with chronic renal failure.

The role of protein and phosphorus intakes has not been definitely separated as yet. The reduction in nitrogen load, the prevention of hyperfiltration and histologic lesions in surviving nephrons, the prevention of secondary hyperparathyroidism, the maintenance of a normal calcium times phosphate product, and the reduced phosphaturia per nephron might all contribute to the effectiveness of dietary treatment in patients with early renal failure. Since in our diet both the contents of protein and phosphorus were reduced in a comparable manner, the results of our study do not allow any conclusion on the relative role of protein or phosphorus restriction.

The patients' adherence to our diet has been very good, as is to be expected in a country where the average protein intake only recently has reached about 70 g/day.

Our results on tissue composition showed that dietary therapy, when properly applied, does not produce progressive protein and phosphorus depletion. On the other hand, metabolic studies of diets with a very similar composition showed that patients usually achieve neutral or positive nitrogen balance [22].

In conclusion, we believe that moderate dietary restriction of protein and phosphorus should begin early in patients with chronic renal failure to prevent renal osteodystrophy and to slow the progression of functional deterioration. Our dietary regimen is acceptable, and the maintenance of normal electrolyte and uric acid balances and blood pressure is obtained readily with conventional drugs (when needed).

Clearly, however, further studies along these lines are indicated before the conclusion can be reached that dietary management is a counteraction to the progression of chronic renal disease.

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