

THREE YEARS EXPERIENCE WITH A VERY LOW NITROGEN DIET SUPPLEMENTED WITH ESSENTIAL AMINO ACIDS AND KETO-ANALOGUES IN THE TREATMENT OF CHRONIC URAEMIA

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Summary

A low nitrogen, low phosphorus diet, supplemented with essential amino acids and keto-analogues, was administered to 48 chronic uraemics for a maximum of 36 months. In 10 cases renal function deteriorated and dialysis was started; eight patients changed to the dialytic therapy having difficulties in complying to the diet and three died for reasons not directly related to renal failure. The remaining twenty-seven patients are still on dietetic treatment and their renal function has not changed significantly. Their serum inorganic phosphorus and their circulating iPTH decreased significantly. Their subjective and objective conditions are satisfactory and no manifestation of protein malnutrition or other unwanted effects are detectable.

Introduction

Low nitrogen, low phosphorus diets supplemented with essential amino acids (EAAs) and keto-analogues (KAs) have been found to slow the progression of renal failure and to cause a fall of hyperphosphataemia and of the circulating iPTH levels in chronic uraemia [1-5]. Such studies were performed on few patients followed for short periods of time. The present trial investigated 48 patients with chronic uraemia, followed for an average of 11 months (from four to 36 months), while on a very low nitrogen and phosphorus diet supplemented with EAAs and KAs (artificial diet - AD).

Patients and methods

Forty-eight chronic uraemic patients (38 male and 10 female) aged 25 to 70 years (mean 42) were studied. The mean of serum creatinine concentration (sCr) was 8.3 ± 1.5 mg/dl and of creatinine clearance (CrCl) 8.2 ± 2.4 ml/min, when they started the AD. Patients with a daily urinary protein loss of greater than 0.5g were excluded from the trial, as well as those with severe diabetes

and with systemic diseases. The cause of renal failure was glomerulonephritis in 21 cases, pyelonephritis in 13, polycystic kidney disease in four and was unknown in the remaining 10 cases.

All patients had previously followed a conventional low nitrogen diet (CLND), for a mean period of 12 months, before starting the AD. The CLND supplies daily, per Kg of body weight, 0.4 – 0.6g of protein, mostly of high biological value, 11 – 12 mg of phosphorus and 30 – 40Kcal, from starch-made foods (bread, biscuits, spaghetti, etc) [6], and by sugar, jam, honey, and fats, of both animal and vegetable nature. Selected fruits and vegetables are given liberally and small amounts of alcohol are permitted.

Before starting the AD all patients were informed that such treatment was just an attempt to defer dialysis and that dialysis is the therapy usually employed in their condition. All of them accepted the dietetic restrictions of the AD described. We included patients in the study of AD only after a Cimino-Brescia A.V. fistula had been formed. We regarded such a precaution as mandatory in order to be ready to start dialysis promptly, if needed.

The AD consists of the basal 'protein-deficient diet' [6] supplemented with EAAs and KAs in the daily amounts employed by Zimmermann et al [7] as previously described [3]. The 'basal protein-deficient diet' supplies, per Kg of body weight, 0.15 – 0.20g of protein of vegetable origin, 3 – 4mg of phosphorus and 30 – 40Kcal daily, provided by the same foods of the CLND. A daily supplement of approximately 1g of calcium is also given in the form of a mixture of carbonate, lactate and gluconate.

Hypertension was present in 43 of the 48 patients studied and both in the period of the CLND and in that of the AD, the sodium intake was restricted to 20 – 30mEq/day. Hypotensive drugs (methyldopa, clonidine, captopril) were required in many cases. High doses of frusemide (0.5–1.0g) were given occasionally and even repeatedly when water and sodium retention occurred.

The measurement of sCr and urine creatinine was performed by a standard autoanalyser procedure, serum inorganic phosphorus (sPi) by the method of Ziverson and Davis [8], serum calcium (sCa), with the Corning 940 calcium analyser [9,10] and alkaline phosphatase (sAP), by Melani's method [11]. The N-terminal and the C-terminal fragments of PTH were measured in duplicate, with the RIA kits of the Immuno Nuclear Corporation (Stillwater Minn.).

The statistical analysis was by Student's t test.

Results

The 27 patients who are still on the AD (Group 1) had a decline of renal function while on the CLND: sCR changed from 5.4 ± 1.8 to 8.3 ± 1.5 mg/dl and CrCl from 14.6 ± 6.5 to 8.2 ± 2.4 ml/min (Figure 1). During the study period, while they were on the AD, sCR changed from 8.3 ± 1.5 to 7.6 ± 2.4 mg/dl, and CrCl from 8.2 ± 2.4 to 8.8 ± 3.5 ml/min (Figure 1). The rate of decline of CrCl, expressed as ml/min/month, was -0.65 ± 0.9 during CLND, and $+0.15 \pm 0.48$ during AD (Table I).

The mean sPi fell from 6.3 ± 1.6 to 4.1 ± 0.8 mg/dl, while sCa increased from 8.7 ± 0.8 to 9.4 ± 0.7 mg/dl and sAP decreased from 148 ± 73 to 100 ± 33 U/L (Table I).

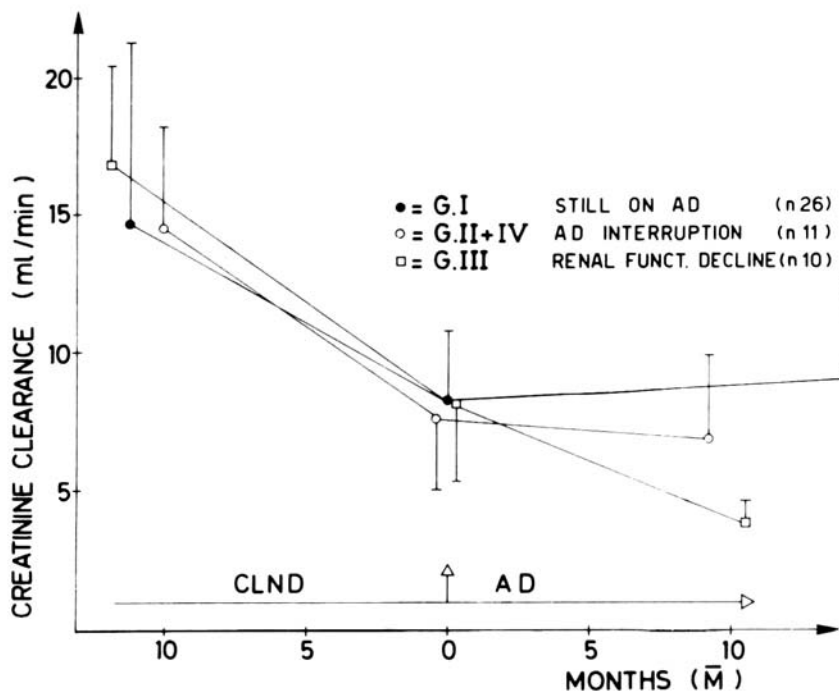


Figure 1. Changes of creatinine clearance during conventional low-nitrogen diet (CLND) and during the artificial diet (AD) in the four groups of patients studied (first and last measurements): group 1 still on treatment, group 2 and 4 interruption of treatment, group 3 with renal function decline

TABLE I. The changes of serum creatinine (in mg/dl/month) and those of creatinine clearance (in ml/min/month) that occurred during the period of conventional low nitrogen diet and during that of the artificial diet, and the changes of serum calcium (mg/dl) and of alkaline phosphatase (mU/ml) that occurred during the artificial diet in the patients of the various groups

Groups	CrCl changes		sCr changes		sCa changes (AD)		sAP (AD)	
	Mean	(ml/min/	Mean	(mg/dl/	Mean	(mg/dl)	Mean	(mU/ml)
	± SD	month)	± SD	month)	± SD		± SD	
	CLND	AD	CLND	AD	Start	End	Start	End
I Still on AD (n = 27)	-0.65 ±0.93	+0.15 ±0.48	+0.26 ±0.16	-0.15 ±0.35	8.75 ±0.8	9.45 ±0.7	148.3 ±72.9	100.1 ±33.4
II + IV AD interruption (n = 11)	-0.58 ±0.27	-0.06 ±0.37	+0.28 ±0.15	+0.07 ±0.38	8.80 ±0.9	9.60 ±0.9	127.9 ±42.7	91.9 ±21.4
III Renal function decline on AD (n = 10)	-0.96 ±0.52	-0.49 ±0.33	+0.47 ±0.20	+0.50 ±0.34	8.46 ±0.8	9.58 ±0.7	134.0 ±41.7	95.2 ±25.5

The circulating iPTH levels (C-terminal fragment) changed from 5.2 ± 3.4 to 2.2 ± 0.9 ng/ml and the N-terminal fragment from 0.36 ± 0.24 to 0.15 ± 0.14 ng/ml (Figure 2).

No side effects of the AD were noted, and particularly, no signs of protein malnutrition were detected, as has been reported elsewhere [6,12]. The symptoms that were present in some patients at the beginning of the AD (anorexia, vomiting, tremors, pruritus, subcutaneous purpura) disappeared completely after a few weeks, and all the patients of this group are in good condition, both subjectively and objectively.

Eight patients (Group 2) were unable to comply with the dietetic prescription of the AD and changed spontaneously, or following our suggestions, to dialysis after periods of time ranging from three to 25 months, in spite of good condition and constant renal function (Figure 1 and Table I).

Ten patients (Group 3) had a deterioration of renal function (Figure 1 and Table I), that reached (after 3 – 19 months) very low values ($\text{CrCl} < 5$ ml/min) and we believed it was not safe to continue conservative therapy. Dialysis treatment was then started, although their subjective condition was still satisfactory.

Group 4 includes two patients who died from myocardial infarction and one of a cerebral accident (Figure 1 and Table I).

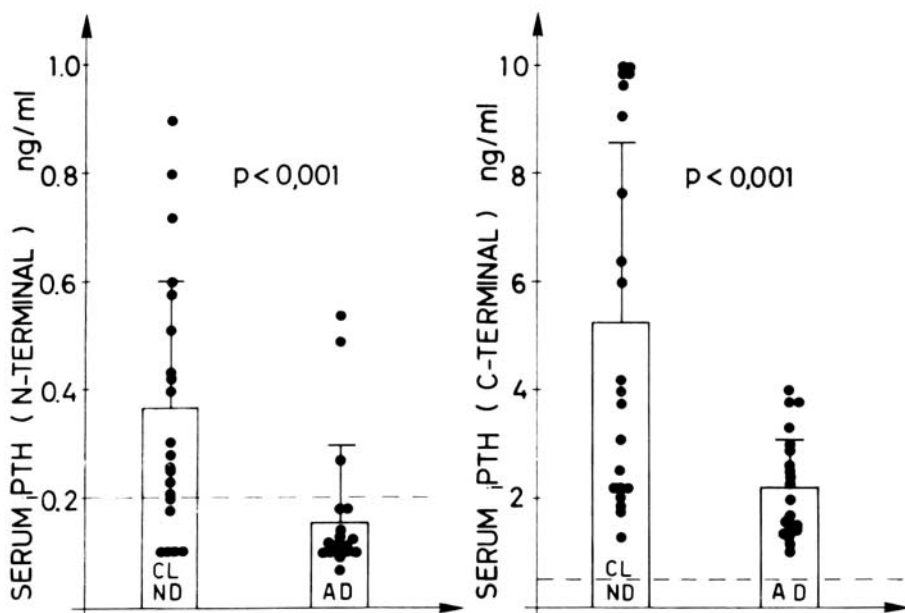


Figure 2. Changes of N-terminal and C-terminal fragments of iPTH that occurred during artificial diet (AD) (first and last measurements) in 21 patients still on diet with good compliance

Discussion

The conclusion we can draw from the present trial is that the employed AD is a safe treatment that may defer and even substitute regular dialysis therapy for considerable periods of time in patients with chronic uraemia. This is made possible by its symptomatic action but, mainly, by the preservation that it exerts on renal function.

This study also allows us to comment on the criticisms that are often made concerning low nitrogen diets in general. The first criticism is that the compliance to such diets is poor, but this is true for all dietary restrictions (the bad compliance to low calorie diets for obesity is a typical example) and does not justify a sceptical attitude 'a priori'. In the present trial only eight patients out of 48 refused to continue the dietetic treatment and some of them only after several months. The remaining 40 patients have had no serious problems, except some difficulties during the first days of AD.

The other common criticism is that low nitrogen diets cause protein malnutrition and this is true when certain conditions, never encountered in the present series, are present: wrong dietetic prescriptions, low caloric intake high proteinuria, and catabolic conditions. In such cases the dietetic treatment should never be started, but substituted with repeated dialysis. But, when these conditions are not present, no protein depletion is caused by the described AD [5,12].

Finally, another criticism of low nitrogen diets in general, is that patients who have followed such diets behave badly when they change to dialysis. Our experience based not only on the 17 patients of the present trial but also on hundreds of other patients, who changed to regular dialysis after periods of CLND in the course of many years, does not support such an impression. The only problems we have experienced when patients change from the conservative to the dialysis therapy are a rapid decline of residual renal function [3] and an increase of sPi, [3] which requires to be treated with phosphate binding drugs, due to the high phosphorus content of the free diet, which is started simultaneously with the beginning of the dialysis.

Acknowledgments

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