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with essential amino acids (EAA) or nitrogen-free keto-analogues of the EAA [3,4,6,7]. The supplement enhances re-utilization of amino acid in urea for generation of protein.

In the developing countries chronic renal failure is prevalent, and the financial burden of management of end-stage renal disease can hardly be accommodated within the lean resources of these countries. It is therefore mandatory that the applicability of dietary therapy in chronic renal failure be vigorously explored.

However, in view of the relatively low protein/high calorie intake pattern in the developing countries, there have not been any significant efforts to explore the applicability of this form of therapy in the management of patients with CRF. In a study of dietary intake among adult Nigerians in the low to middle socio-economic class, Smith & Oluwoye [8] have shown the average daily protein intake to range between 40 and 60 g. This is well above the level needed to maintain a balanced protein metabolism in patients with CRF [5]. But, of greater implication is the low biological value of the dietary protein consumed, being mainly of vegetable origin. This is of little benefit, and indeed may be deleterious to the patients with chronic renal failure.

The appropriate dietary regimen should therefore consist of low protein of high biological value, and a high calorie content in addition to vitamin supplementation and salt and fluid regulation.

We have therefore evaluated the clinical usefulness of this form of dietary therapy in seven of our patients with chronic renal failure, followed up for between 18 and 28 months. Five other patients similarly followed-up on unrestricted protein intake served as controls.

Patients and methods

Twelve patients with chronic renal failure who had been followed-up for a period ranging from 9 to 28 months were selected from our records. None of the patients had uncontrollable hypertension, chronic congestive cardiac failure, or correctable cause of CRF such as obstructive uropathy, or abuse of nephrotoxic drugs.

Seven of these patients, forming the study group, had been strictly followed up on restricted protein/high calorie diets. These comprised five males and two females with ages ranging from 30 to 40 years, mean 38.2 years. Their serum creatinine values were consistently above 2 mg% (range 2.3 to 7.3 mg%, mean 4.17 ± 0.69) at the point of entry into the study. The underlying renal disease was glomerulonephritis in four, while three had hypertensive nephrosclerosis. The diagnosis was mainly clinical in four but supported by histology in three.

The dietary regimen consisted of (1) protein, 20–30 g per day, of high biological value made up of fish, egg-protein and/or cray-fish; and (2) high calorie intake (3000 kcal/day) derived from locally available food items — cassava, yam, corn, etc. (Tables 1 and 2). Serial serum biochemical estimations of albumin, globulin, electrolytes, urea, creatinine, phosphate, and calcium were performed. Protein intake was assessed by a 2-day dietary recall by one of us (F.S.) and by serial weight and serum albumin determination.

Good blood pressure control was achieved by the use of one or a combination of antihypertensive drugs, namely: methyldopa, brinerdin, hydralazine and labetalol, when necessary. Haematinics, such as iron, folic acid and multivitamins, were administered generously. The daily dietary intake of sodium and potassium

Table 1. Composition of low protein/high calorie diet used in the study

1.	Contains 20–30 g protein per day.
2.	Protein of relatively high biological value.
3.	Essential amino acids provided by egg, meat, fish, crayfish, and occasionally milk.
4.	Intake of meat, fish, crayfish, egg and milk permitted within protein restriction and constituting 70–80% of total daily protein intake.
5.	Legumes, pulses and seeds (watermelon seeds) either excluded or permitted very occasionally within protein restriction.
6.	All local fruits and leafy vegetables permitted.
7.	Bread and local cereals (rice, corn, guinea corn and sorghum) permitted.
8.	Fats (palm oil, groundnut oil), local roots and tubers, and plantains used as major sources of calories.

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Low protein/high calorie dietary regimen in the management of chronic renal failure. A preliminary study of Nigerian patients

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Summary

The progression of renal failure was evaluated in seven patients with established chronic renal failure (mean serum creatinine 4.17 mg%), while on a supervised dietary regimen consisting of low protein of high biological value (20–30 g/day), and a high calorie content (3000 kcal/day) for a period of between 18 and 28 months. Five other patients with a comparable degree of chronic renal failure whose protein intake was unrestricted (evaluated to vary between 40 and 60 g per day) served as controls. In the study group, serum creatinine levels stabilized or improved in five, while a moderate rise was observed in two. In contrast, a considerable and significant rise in serum creatinine values was observed in all the controls. Two significantly different slopes ($P < 0.01$) were also obtained from the linear regression analysis of the reciprocal of serum creatinine values against time, for the two groups. Our preliminary observation of a beneficial effect of this regimen in our patients is particularly relevant to the developing countries because of the high prevalence of chronic renal failure against the background of grossly inadequate facilities for maintenance dialysis or renal transplantation.

Résumé

Pendant une période de 18 à 28 mois, nous avons suivi la progression du défaut rénal chronique chez sept malades (taux moyen de créatinine sérique 4.17 mg%), nourri d'un régime à basse protéine de haute valeur biologique (20 à 30 g/jour), et à haute valeur calorifique (3000 kcal/jour). Cinq autres malades atteint au même degré du défaut rénal chronique et dont l'ingestion journalière de protéine, estimée de 40 à 60 g/jour, n'était pas limitée, ont servi comme témoins. Le taux de créatinine sérique s'est stabilisé ou s'est amélioré chez 5 des 7 malades d'essai, et on a constaté une légère hausse chez les deux autres. Au contraire, le taux s'est élevé d'une manière significative chez les témoins. Une analyse de la régression linéaire entre la réciproque du taux de créatinine sérique et le temps chez les deux groupes, nous a donné deux courbes différentes, et la différence était significative ($P < 0.01$). Le régime semble donc bien salutaire et apte dans les pays en voie de développement, où malgré la haute prédominance du défaut rénal chronique, les conditions ne sont pas favorables pour la dialyse ou la transplantation rénale.

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Introduction

Chronic renal failure (CRF), once established, normally runs an inexorably progressive course. There is, however, abundant evidence that protein restriction alleviates the symptoms of uraemia in patients [1]; it slows down the rate of progression of the CRF, and in some cases it may actually improve renal function [2–4]. The ultimate goal of dietary therapy is delay of the time of institution of specific therapy such as dialysis or renal transplantation, thereby considerably reducing the overall cost of treatment.

Hitherto the major constraint to institution of a protein-restricted diet has been depletion of body protein [5] but this can be eliminated by supplementing the low protein/high calorie diet

equations and were tested against a null hypothesis of a zero slope (i.e. a slope that is horizontal to the x axis). The two slopes were further compared with each other using Student's t-test.

The mean initial and terminal serum albumin values and weight were compared for the study group, to determine the effect of protein restriction on the protein balance of the patients.

Serum creatinine values are stated as means ± s.e.m.

Results

The various serum creatinine values at the beginning and the end of study, and the duration of the observation for both the study and the control groups are shown in Table 3. In the study group, serum creatinine levels stabilized or improved in five, while a moderate rise was observed in two. In contrast, a considerable rise in serum creatinine values was observed in all the five controls. Three of the latter died in hospital while two were lost to follow-up.

The mean initial serum creatinine values were comparably similar for both the study and control groups, the values being 4.17 ± 0.69 mg% and 4.38 ± 0.48 mg% respectively ($P > 0.10$). At the end of the study the mean serum creatinine values for the study and control groups were 4.36 ± 0.76 mg% and 6.5 ± 0.47 mg% respectively. There was no significant difference between the mean serum creatinine values at the beginning and the end of the study for the treated patients. In contrast, the mean serum creatinine value rose significantly in the control patients from 4.38 ± 0.48 mg% to 6.5 ± 0.47 mg% ($P < 0.001$) (Table 4).

The linear regression equation for the study group was $y = 0.2947 - 0.000922\,x$; s.e. was 0.0024; the slope was not significantly different from zero, t being −0.38, and $P = 0.71$. The linear regression equation for the control group was $y = 0.25 - 0.0056\,x$; s.e. 0.0015; and the slope was significantly different from zero, t being −3.7, $P < 0.01$ (Table 5, Fig. 1).

Comparing the two slopes of the regression equation, a t-value of 2.8, with a statistically significant difference $P < 0.01$ (Table 5), was obtained.

The mean weights and serum albumin levels at the beginning and the end of the study did not differ significantly for the treated patients.

Table 4. Comparison of mean serum creatinine values

Patients	Mean serum creatinine values (mg%) ± s.e.m. Initial	Terminal	P value
Study group	4.17 ± 0.69	4.36 ± 0.76	0.10
Control group	4.38 ± 0.48	6.5 ± 0.47	< 0.01
Difference (P)	> 0.10	< 0.01	

Table 3. Table of patients and parameters

Patient no.	Study group: Serum creatinine (mg%) Initial	Follow-up	Duration of observation (months)	Controls: Serum creatinine (mg%) Initial	Follow-up	Duration of observation (months)
1.	5.0	5.8	16	4.1	5.3	9
2.	7.3	6.7	24	4.1	5.8	16
3.	4.5	4.2	22	4.8	7.8	16
4.	5.0	6.6	28	3.0	7.3	18
5.	2.3	2.2	16	5.9	6.3	16
6.	2.4	2.3	28			
7.	2.7	2.7	18			

Table 2. Sample day's menu providing 25–30 g protein, 3000 kcal, 60 mEq (1380 mg) Na^+, 40–60 mEq (1560–2340 mg) K^+

	Protein (g)	Na^+ (mEq)	K^+ (mg)	Kcal
Breakfast				
Moderately thick pap (2½ large teacups = 750 g)	—	—	950.0	164.0
One (20 k worth) salt-free akara ball (approx. 60 g)	4.36	Neg.	87.1	199.0
Lunch				
Eba (2½ kitchen spoon scoop = approx. 400 g)	1.73	10.0	710.0	573.6
Okro (five large, approx. 50 g)	0.9	1.5	142.5	15.5
Stew (small onion/tomato/two kitchen spoon scoop oil)	Neg.	Neg.	72.9	720.0
One (50 k worth) piece meat or fish (30 g)	7.6	16.8	111.0	86.5
Supper				
Three heaped kitchen spoons plain boiled rice (approx. 300 g)	5.28	15.0	225.0	550.0
Stew (small onion/tomato/two kitchen spoon scoop oil)	Neg.	Neg.	72.9	720.0
One (50 k worth) piece meat or fish (30 g)	7.6	16.8	111.0	86.5
Total	27.47	59.8	2482.4	3115.0

See reference [8].

was regulated according to results of repeated 24-h urinary excretion tests.

The control group comprised three males and two females, with ages ranging from 27 to 40 years, mean 33.6 years. Three of them had chronic glomerulonephritis, while two had hypertensive nephrosclerosis. Histological diagnosis was obtained in four of them.

These patients attended the clinic at least once every month; they had reliable biochemical flow charts, and the serum creatinine values at the point of entry into the study ranged between 3 and 5.9, mean 4.38 ± 0.4 mg%. This was similar to that of the study group ($P > 0.10$). These patients were on unrestricted protein intake but had antihypertensive therapy and low salt diet when necessary. Careful evaluation of their 2-day dietary recall history revealed an average daily protein intake of between 40 and 60 g and high calories (at least 3000 kcal).

Statistical method and evaluation of progression of renal failure

Both the mean initial and terminal serum creatinine values were compared for each group using Student's *t*-test, and the level of significance checked from standard statistical tables. The evaluation of the rate of functional progression was calculated with the least-squares regression analysis of the relationship between the reciprocal of serum creatinine concentration and time on the computer.

Regression equations were thus estimated for the study and control groups. The estimates of the slopes were obtained from the regression

clinical and biochemical features of azotaemia, but it was usually accompanied by negative protein balance [5].

The dietary management of CRF was, however, further improved with the observation of Giordano [19] that uraemic patients could be brought into positive protein balance on low protein diets, supplemented with essential amino acids. Essential amino acids enhance the recycling of urea nitrogen into the protein pool. These findings were then utilized in a successful clinical trial by Giovanette & Maggiore [3] who treated uraemic patients with a calorie-rich, protein-poor diet supplemented with essential amino acids.

Sitprija & Suvanpha [20] also observed that renal functions stabilized for more than 3 years in five Buddhist monks in CRF with a low protein intake of 15–19 g per day, and during the period no malnutrition was reported.

In more recent studies, a complementary role has been established for the inclusion of amino acids or their nitrogen-free keto-analogues in an artificial diet containing markedly low protein (about 0.3 g/kg body-weight) and high calories. With this artificial diet, nitrogen balance has been positively enhanced [15,21,22]. Utilizing this strategy, Alvestrand, Ahlbergh & Bergstrom [2] were able to treat patients with advanced azotaemia with favourable results. Gretz, Korb & Strauch [7] observed that the rate of progression of serum creatinine from a value of 6 mg% to 10 mg% was significantly lower in patients treated with a protein-poor diet supplemented by keto-acids, than those without dietary restriction.

In spite of these foregoing intriguing observations, it is still generally agreed that dietary regimen should ideally be recommended only for patients with mild to moderate azotaemia (serum creatinine < 5 mg%), as it is in these cases that optimum benefit can usually be guaranteed [23]. Unfortunately, most of our patients with CRF present in the terminal stage when dietary regimen may not be effective. This may explain the limited number of patients with moderate renal failure available for this study; it may also be responsible for the paucity of literature in this aspect of CRF from our environment.

In our limited study, we have observed that low protein of high biological value, and high calorie diet improved renal functions in our patients. The nutritional status, as evidenced by body weight and plasma albumin, remained stable. Patients also tolerated the diet, and were expressly convinced of the benefit derived from it. Achiardo *et al.* [24] reported an improvement of renal functions in six (40%) of 15 patients on low protein diet. They noted that the rate of progression of renal failure was lower in their treated patients than in the controls. Giovannetti [4] also reported a dramatic fall in the serum creatinine of eight patients following the change from a conventional low nitrogen diet to an artificial diet containing low protein supplemented by keto-analogues of EAA.

We observed that the average daily protein intake of our control patients is relatively low compared with recommended daily requirements. This may, in part, explain the moderate progression of the CRF as evidenced by the 'gentle' slope of the regression equation. However, the overall advantage that the relatively low protein intake might have conferred has conceivably been offset by the low biological value of these vegetable-derived proteins. Sources of high quality protein required by patients with CRF include egg-albumen, crayfish, milk, and a variety of other fish (not that expensive in the market) and beef.

While an intensive dietary regimen is mandatory in the management of patients with CRF, adequate control of other factors such as accelerated hypertension, intercurrent infections and fluid and electrolyte imbalance should be ensured, if optimum benefit is to be achieved.

Our preliminary observations thus far appear encouraging and therefore call for further intensive, collaborative, long-term studies.

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Table 5. Table of parameters of regression equation (study and controls)

Patients	Intercept	s.e.m.	Slope of regression equation	Comparison of slope with 'zero' slope		Comparison of slopes of regression equations (study and controls)	
				t value	*P* value	*t* value	*P* value
Study group	0.294	0.0024	−0.00092	−0.38	0.7 (n.s.)	2.8	0.01
Control group	0.2508	0.0015	−0.0056	−3.7	< 0.01		

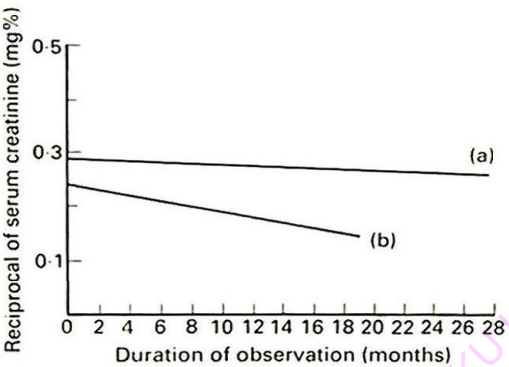

Fig. 1. Relationship of the reciprocal of serum creatinine concentration plotted against time in the study group (a) and control group (b). (a) $n = 7$; slope = −0.00092; duration of observation = 18–28 months. (b) $n = 5$; slope = −0.0056; duration of observation = 9–18 months.

The mean weights at the beginning and the end of the study were 59.3 ± 4.5 and 59.4 ± 4.0 kg respectively ($P > 0.1$). The initial mean serum albumin was 4.0 ± 0.1 g% while the terminal value was 3.9 ± 0.2 g% ($P > 0.1$).

Discussion

It is well established that CRF characteristically runs an inexorably progressive course, until end-stage at which time dialysis or kidney transplantation are the only possible therapies. There is strong evidence, based on observations made on renal ablation experiments, diabetic nephropathy and experimental mode of renal failure, that the progression of chronic renal failure is self-sustaining [9–13]; it is independent of the continued activity of the initiating injury or disease condition. These workers established that the mechanisms responsible for the progression of the renal failure are intimately related to the compensatory adaptive function of the intact nephrons.

Further evidence incriminating a common factor in the progression of CRF derives from the work of Oksa *et al.* [14] and Mitch & Walser [15]. These workers observed that the rate of decline of renal function in the majority of cases of CRF (irrespective of the cause) is characteristically linear with respect to time when the reciprocal of serum creatinine is plotted against time. The superiority of serum creatinine concentration over creatinine clearance measurements in the routine assessment of glomerular function or of changes in glomerular function in patients with CRF has been clearly established by Morgan, Dillon & Payne [16]. It thus becomes quite possible to chart the time course of CRF in most patients from serial serum creatinine concentration measurements.

The foregoing observations have led to experimental and clinical studies of factors that interfere with the adaptive functions such that the characteristic progression of CRF may be retarded. The factors that have been clearly established include low protein and low phosphorus intake [17,18].

Incidentally, long before this experimental evidence, protein restriction had been instituted in the treatment of uraemia [1]. It was successful to the extent that it ameliorated both

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