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Is There a Role for Protein Restriction in the Treatment of Chronic Renal Failure?

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Traditional Views

Rationale for Protein Restriction in Renal Failure

The rationale for protein restriction is very simple: since the kidneys have the major responsibility for removing the waste products of protein metabolism, these products accumulate in patients with chronic renal failure and are the direct cause of most of the signs and symptoms, even though the quantitative relationship between these signs and symptoms and the level of these accumulated metabolites is variable. Obviously a high protein intake will thus aggravate these signs and symptoms, while a low protein diet will ameliorate them. But protein restriction can clearly be overdone. If the intake of essential amino acids is less than the subject's requirements, progressive protein malnutrition will slowly develop. It follows logically that a diet completely free of whole protein, but supplemented by essential amino acids as such, will be optimal for reducing signs and symptoms. Rose and associates, in their classic studies, had established that normal subjects need no protein at all and only small amounts of nonessential N to maintain N balance on a diet supplemented by essential amino acids [1].

Historical Aspects

Restriction of dietary protein has been the mainstay of the treatment of chronic renal failure for at least 80 years. To quote Volhard [2] in 1918, 'in patients with chronic renal failure it is possible to postpone the increase of serum urea concentration for a long time, reducing the nitrogen intake to 3–5 g. Sometimes we have succeeded in reducing considerably high serum urea concentrations. Consequently, the first uremic symptoms disappeared.' However, if the intake of essential amino acids is less than the subject's requirements, progressive protein malnutrition will slowly develop.

This concept was first put into practice in chronic renal failure by Giordano [3] nearly 40 years ago. He found that a protein-free diet was impractical, and allowed small amounts. However, the resulting diet was still quite unpalatable and had few followers, not because it was inefficacious but because it was hard to follow. When patients did follow these diets, however, they exhibited dramatic clinical improvement and maintained their nutrition very well. Many subsequent studies have documented the benefits of a less restrictive diet supplemented by essential amino acids or ketoacids. For example, Giovannetti [4] presented the results of 6–23 months of treatment with a diet containing only 0.24 g/kg of protein, supplemented by essential amino acids or amino plus ketoacids, in 38 patients with an average creatinine clearance of 7.8 ml/min. Despite this severe level of renal insufficiency, all nutritional indices, including serum albumin concentration (3.8 g/dl) as well as N balance, were entirely normal. Signs and symptoms decreased, with the exception of anemia (this work was conducted before erythropoietin became available).

Every US textbook of nephrology that I have been able to identify confirms the importance of protein restriction in the treatment of chronic renal failure. Clearly, the fact that this issue is now up for debate here today signifies a radical departure from traditional views. Before review-

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ing the pertinent literature, it should be noted that the quality of the evidence supporting one approach or another to the treatment of chronic renal failure, before or during renal replacement, is almost uniformly low. Prospective, randomized, double-blind studies do not exist, and many studies have no controls at all. One reason for this state of affairs is the dire consequences, for the patient, of choosing the wrong option. Also, blinding is often impossible. When prospective studies are done, they are frequently simple crossover trials, i.e. results are compared before and after instituting a change in treatment. Such studies leave open the question of what would have happened if no change in treatment had been instituted. Another problem is the selective nature of the patient population studied. Patients who are willing to enter a study, in general, are likely to be more intelligent, more cooperative, and wealthier than those who decline. Clinical results in such subjects are likely to be better than can be expected in the population as a whole.

Symptomatology in Chronic Renal Failure

Role of Urea

At moderate levels of accumulation, urea is apparently nontoxic. But when patients are dialyzed against a bath containing urea at high levels, typical uremic symptoms appear, including nausea and vomiting [5]. Thus it is clear that urea contributes to the symptoms of renal failure, but it is also clear that there must also be other substances that contribute.

SUN as a Function of N Intake

Excretion of waste N in forms other than urea is minimally affected by N intake. It follows that the fall in SUN, when protein intake is restricted, will be greater, proportionately, than the fall in N intake – provided that N balance is maintained. This relationship has often been overlooked. An extreme example is shown in figure 1 [6]. These patients were fed, by nasogastric tube, a mixture of ketoanalogues and amino acids, plus glucose, while they awaited the start of dialysis. Despite very low levels of residual renal function, their SUNs decreased to low levels. Their N intake was only 2–5 g/day, and yet they were in neutral or positive N balance. Less extreme examples are shown in table 1, in which SUNs are listed for a number of patients placed on supplemented very low protein diets [7]. Again, despite severe renal insufficiency, these patients exhibit nearly normal SUNs.

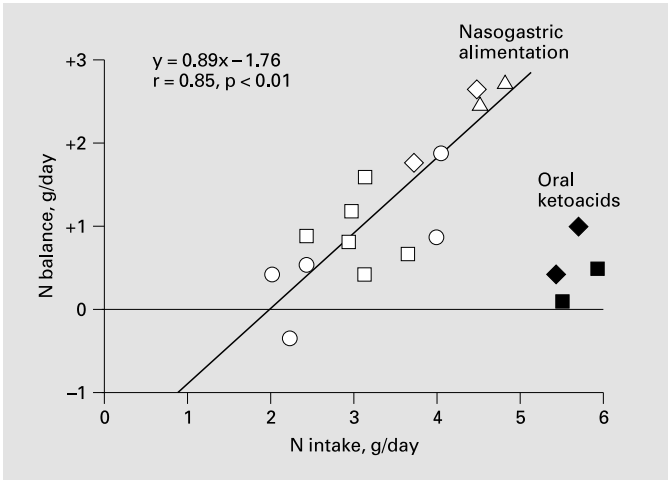


Fig. 1. Nitrogen balance as a function of nitrogen intake in patients awaiting dialysis who were fed by continuous nasogastric infusion a mixture of amino acids, keto acids, and glucose. The intersection of the diagonal line with zero balance line shows that the nitrogen intake requirement for balance on this regimen was about 2.5 g/day. On oral intake of ketoacids, as shown, nitrogen requirement for balance was higher. Reprinted by permission from Abras and Walser [6].

Table 1. Examples of low serum urea N concentration in patients with severe chronic renal failure receiving nutritional therapy [from ref. 7]

Gender	Age years	Dx	GFR, ml/(min · 70 kg IBW)	SUN mg/dl	UNA g/day
M	38	G	9.0	26.0	2.2
F	47	H	13.3	26.2	3.0
M	65	D	10.4	25.2	2.4
M	31	D	8.2	28.8	2.9
M	50	P	14.8	27.8	4.5
F	42	P	13.3	27.3	4.8
M	33	I	14.4	23.0	2.6

Dx = Diagnosis; GRF = glomerular filtration rate; SUN = serum urea N; UNA = urinary urea N appearance; IBW = ideal body weight. Each value is the average of four or more observations over a period of four or more months. G = Chronic glomerulonephritis; H = arteriolar nephrosclerosis; D = diabetic nephropathy; P = polycystic kidney disease; I = interstitial nephritis.

Level of Severity at which Symptoms Appear

Recently, we reviewed the charts of 175 patients in two ways: first, we recorded their symptoms and lab values on presentation, and, second, noted the lab values at which each of the four most common symptoms appeared (or

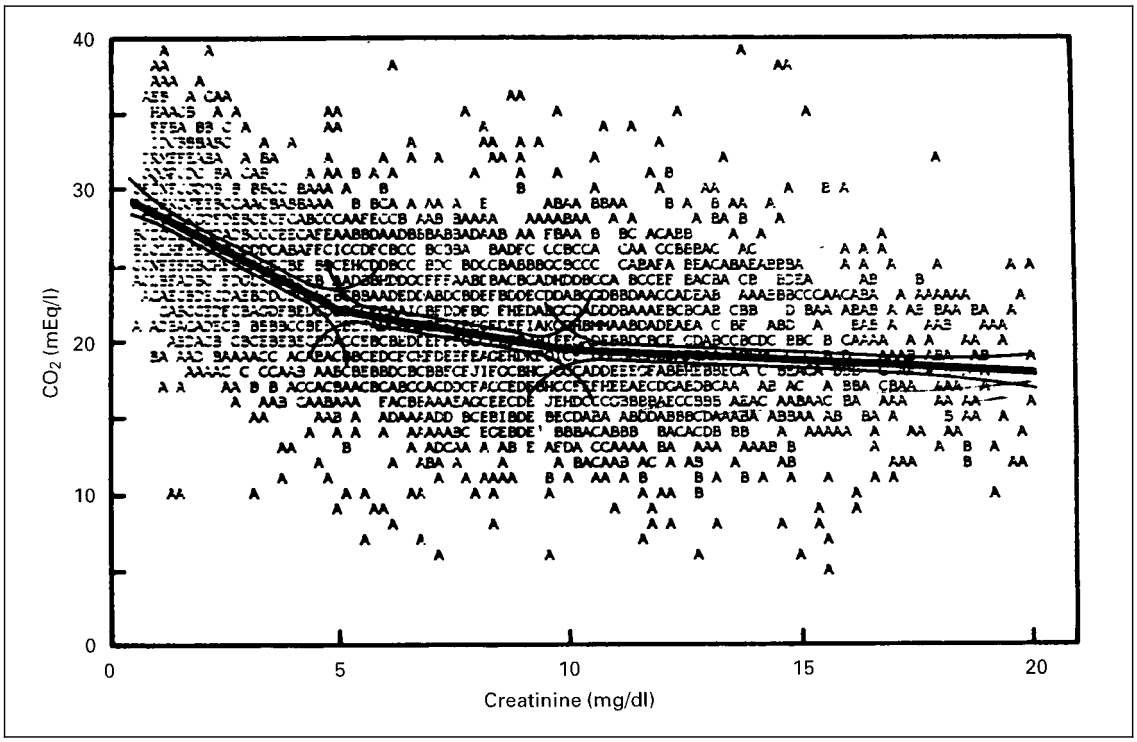


Fig. 2. Serum CO_2 concentrations in relation to serum creatinine concentrations in patients with chronic renal failure, predialysis, according to Hakim and Lazarus. Reprinted by permission from Hakim [10].

reappeared) during follow-up [8]. The four symptoms documented were fatigue, nausea and vomiting, itching, and muscle cramps. The median levels at which these symptoms appeared were quite similar in the two analyses, lending credence to their validity. In general, SUN and CO_2 were the best predictors of symptoms. The median SUN at the onset of symptoms was generally about 50 mg/dl. Since this is far below the level at which symptoms are induced by adding urea to the dialysis bath, it is again clear that urea is only one of the accumulated metabolites causing symptoms.

Uremia in the Absence of Renal Insufficiency

Subjects who have normal renal function, but who eat enormous amounts of protein, develop a form of uremia: their SUN levels become abnormal and they may develop 'meat intoxication'. Eskimos learned centuries ago that they needed to eat some whale blubber along with their whale meat to avoid these same symptoms. Again, these observations underscore the importance of protein intake in mediating the symptoms of renal failure.

Essential Amino Acid and Protein Requirements in Normal vs. Uremic Subjects

It was formerly stated that renal insufficiency is a protein-wasting state, as it is in rats. More recently it has become clear that the protein-wasting often observed is usually caused by negligence on the part of the physician or noncompliance on the part of the patient. When patients with renal failure are studied on protein-restricted diets under carefully controlled conditions, they are seen to conserve N as well as normal subjects [9]. Acidosis used to be a common feature of predialysis patients (fig. 2) [10]; now that the role of acidosis in accelerating protein breakdown has been emphasized [11], acidosis is generally corrected by sodium bicarbonate administration and protein-wasting from that cause should be eliminated. Specific abnormalities of circulating amino acid concentrations are often seen in patients with renal failure, such as high levels of cysteine and 3-methylhistidine and low levels of tyrosine. It is not known to what extent these abnormalities may contribute to protein-wasting, but their impact must be minor.

Consequences of Inadequate Intake of Protein or Essential Amino Acids

When even one essential amino acid is supplied in inadequate amounts, serum levels of albumin and transferrin fall. A woman with polycystic kidney disease and chronic renal failure was maintained on a diet containing 0.3 g/kg of protein supplemented by a mixture of amino acids that was devoid of tryptophan. This was the only such mixture then available because tryptophan had been taken off the market. This ruling by the FDA was based on the occurrence of eosinophilic myodystrophy, found to be caused by a contaminant of tryptophan from one source. Other patients on this regimen exhibited progressively decreasing levels of free tryptophan in the serum [12], but none as profound as this woman. Her serum levels of albumin and transferrin fell below normal as her free tryptophan level decreased to 4 μM, which I believe is the lowest ever recorded. Tryptophan was then supplied, with no change in diet, at 200 mg/day. As tryptophan levels increased, serum transferrin and later serum albumin rose to normal. Incidentally, we were unable to detect any other clinical abnormalities in this women when she was tryptophan deficient. In particular, cognitive function did not change as she improved.

Limitations of Protein Restriction

Does Protein Restriction Predialysis Lead to Protein Deficiency at the Start of Dialysis?

Nationwide surveys of serum albumin levels in patients starting dialysis have reported that more than half of such patients are hypoalbuminemic [13]. It is well known that most patients, nationally, do not receive instruction on a low protein diet before reaching the end stage [14]. The relationship between previous dietary history and final serum albumin has apparently not been studied.

Since serum albumin level predicts survival on dialysis [15], any increase in this alarming incidence of hypoalbuminemia caused by dietary protein restriction would be a major concern. We have therefore reviewed the final serum albumin levels, in 46 patients we have treated for at least 6 months with a very low protein diet supplemented by amino acids or ketoacids, just before they began renal replacement. As shown in figure 3, hypoalbuminemia was rare in this group of subjects [16]. Aparicio et al. [17] have recently reported similar observations.

This paradoxical response of protein nutrition to protein intake will be a recurring theme of my presentation. It is now clear that high protein intake, in a subject with renal failure, increases symptoms and therefore promotes anorexia, leading to protein malnutriton, while a supplemented very low protein diet supplemented by essential amino acids, on the contrary, decreases symptoms and increases appetite, leading to improved protein nutrition.

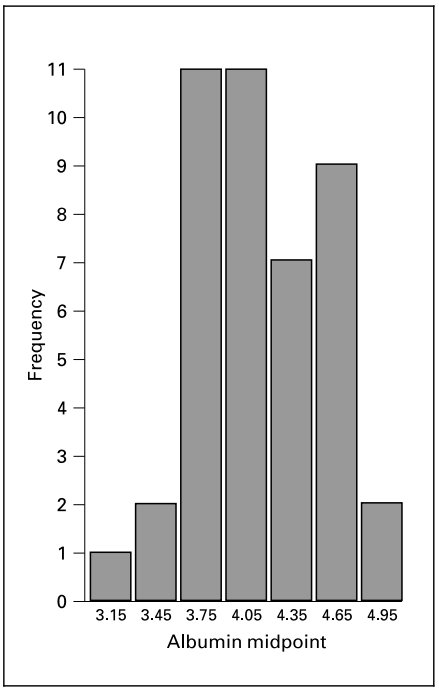
The common observation that patients avoid meat as their renal failure becomes more severe testifies to the 'wisdom of the body' in this regard. The response to a progressively falling protein intake should be to restrict protein intake further, rather than trying to encourage greater intake, and to add a supplement of essential amino acids.

Should Dietary Protein Intake Be Increased in Patients with Nephrotic Range Proteinuria?

For decades, nephrotic syndrome was treated by a high-protein diet. In 1985 and 1986, several authors reported that dietary protein restriction reduces proteinuria [18, 19] and may, in some nephrotic patients, increase serum albumin concentration [20]. Only one group of workers [21] tried a supplemented very low protein diet. We extended these observations to 16 nephrotic patients [22], prescribing a diet containing only 0.3 g/kg of protein, supplemented by essential amino acids (or in some cases, ketoacids). Proteinuria decreased in all and serum albumin tended to rise. Nevertheless, patients with more advanced renal insufficiency progressed to dialysis. But in 5 patients with GFRs >30 ml/min, proteinuria decreased progressively over the ensuing months (fig. 4); serum albumin rose to normal (fig. 5), and GFR improved in most (fig. 6). Long-term follow-up of these patients has confirmed that they have entered into prolonged remission. Again, since this study lacked controls, it cannot be said to show cause and effect. But clearly, severe protein restriction, rather than aggravating the nephrotic syndrome, is worth trying as treatment. In contrast with steroids or immunosuppressive agents, dietary treatment has essentially zero side effects when properly applied.

Contraindications to Dietary Therapy

Since nephrotic range proteinuria is not a contraindication, under what if any circumstances should a supplemented very low protein diet not be recommended? Patients on steroids are unable to conserve protein and should not be placed on severely protein-restricted diets. One of the mechanisms, in fact, for protein conservation is suppression of cortisol production. Apart from this group, there appear to be no contraindications to dietary therapy of chronic renal failure.



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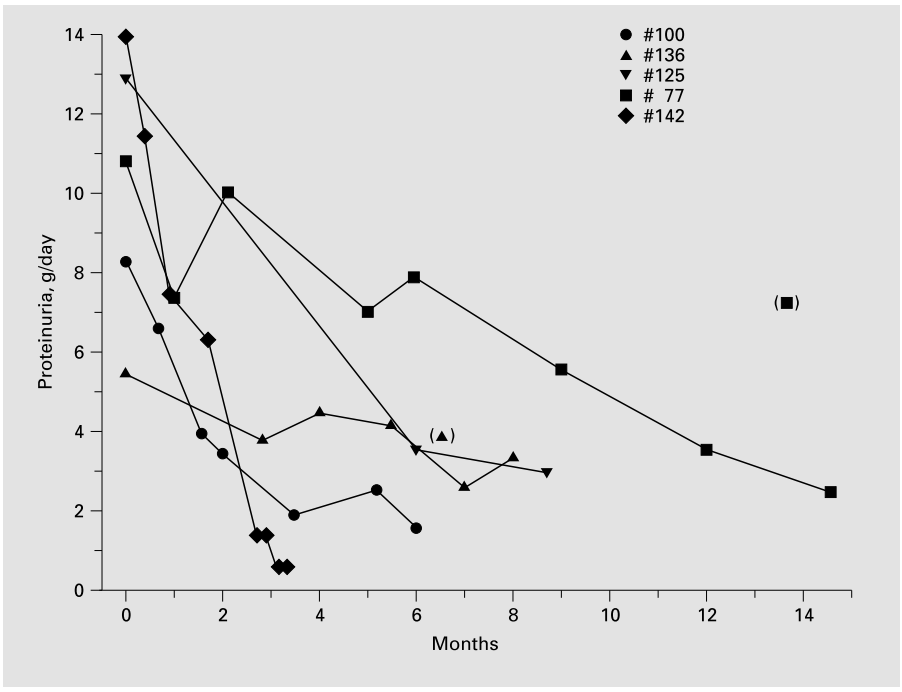

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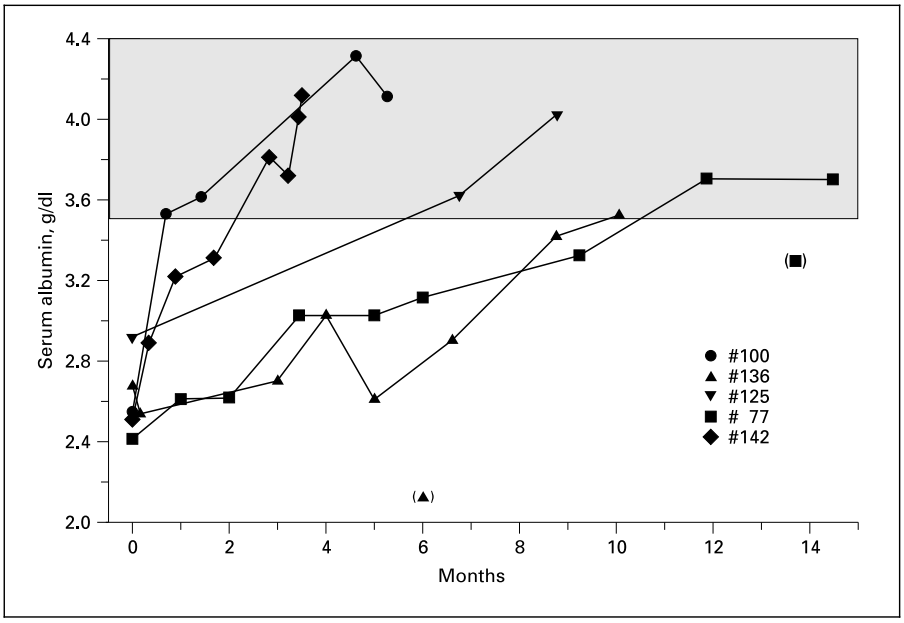

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Fig. 3. Final serum albumin concentrations in 46 patients, just before starting dialysis, who had followed a supplemented very low protein diet for at least 6 months. Hypoalbuminemia was rare. Reprinted by permission from Walser [16].

Fig. 4. Effect on proteinuria of a supplemented very low protein diet in five nephrotic patients with GFRs >30 ml/min. Reprinted by permission from Walser et al. [22].

Fig. 5. Effect on serum albumin levels in the same subjects as in figure 4.

Does Protein Restriction Predialysis Increase Mortality on Dialysis?

Even though protein restriction predialysis seems to prevent hypoalbuminemia at the start of dialysis, it could in some way make dialysis patients more vulnerable. We therefore determined the mortality on dialysis of 75 patients who had been treated by a supplemented very low protein diet predialysis (including the subjects reported in the preceding studies) [16]. To our surprise, survival on dialysis of these patients was substantially improved, in comparison with the national experience, as reported in the USRDS, after correcting for gender, age, and diagnosis [23] (fig. 7). Again, the control group, not being randomized, is probably different in many ways, and the comparison is therefore statistically invalid. How-

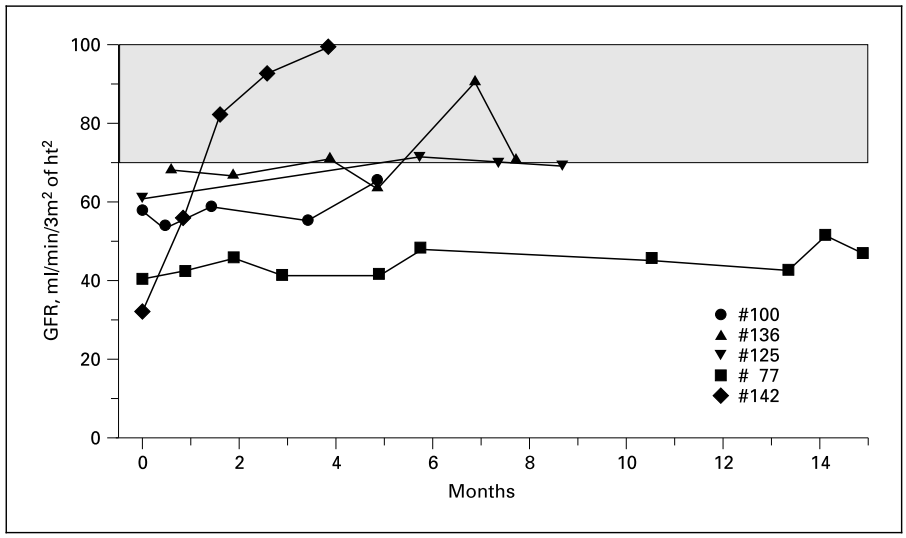

Fig. 6. Effects on glomerular filtration rate in the same subjects as in figure 4.

ever, Aparicio et al. [17] have also observed very low mortality on dialysis of 165 patients who entered dialysis after prolonged treatment with a similar regimen. It seems safe to conclude that severe protein restriction predialysis does not increase mortality on dialysis, and may in fact decrease mortality.

Can Protein Restriction Predialysis Safely Defer Dialysis?

Recently, we determined from our patient records the date on which each patient being followed on a supplemented very low protein diet reached the level of severity at which reimbursement is authorized by Medicare, namely, a GFR of 10 ml/min in nondiabetics or 15 ml/min in diabetics [24]. The interval between this date and the date on which renal replacement actually started was then taken as renal survival. The start of renal replacement in these patients was decided by their chosen dialysis/transplant team, with no input from us. Renal survival in these 75 patients is depicted in figure 8. Median survival is nearly 1 year. During this interval, average serum chemical values were as shown in table 2. Clearly, these subjects were in good condition biochemically during this interval. We conclude that this form of nutritional therapy can safely defer dialysis for a median of one year.

Two mechanisms are doubtless involved here: first, nutritional therapy, by reducing the accumulation of nitrogenous products of metabolism, enables the patient to reach a substantially lower level of renal function before dialysis becomes necessary; and secondly, progression may be slowed. Time does not permit a review of the extensive literature devoted to the question of whether protein restriction slows progression; suffice it to say that the preponderance of evidence supports this possibility. It is important to emphasize, however, that protein restriction, particularly when accompanied by a supplement of essential amino acids, has many benefits other than slowing progression.

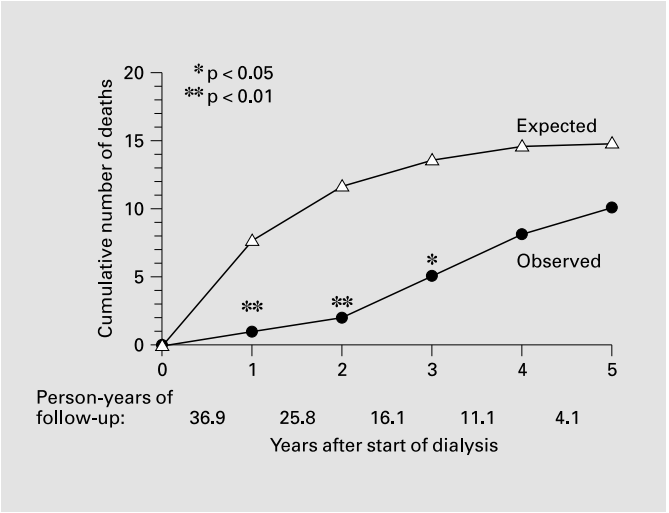

Fig. 7. Death rates observed during dialysis in patients treated with a supplemented very low protein diet before dialysis, as compared with death rates expected from the national experience, as reported in the USRDS, corrected for age, gender, and diagnosis. Reprinted by permission from Coresh et al. [23].

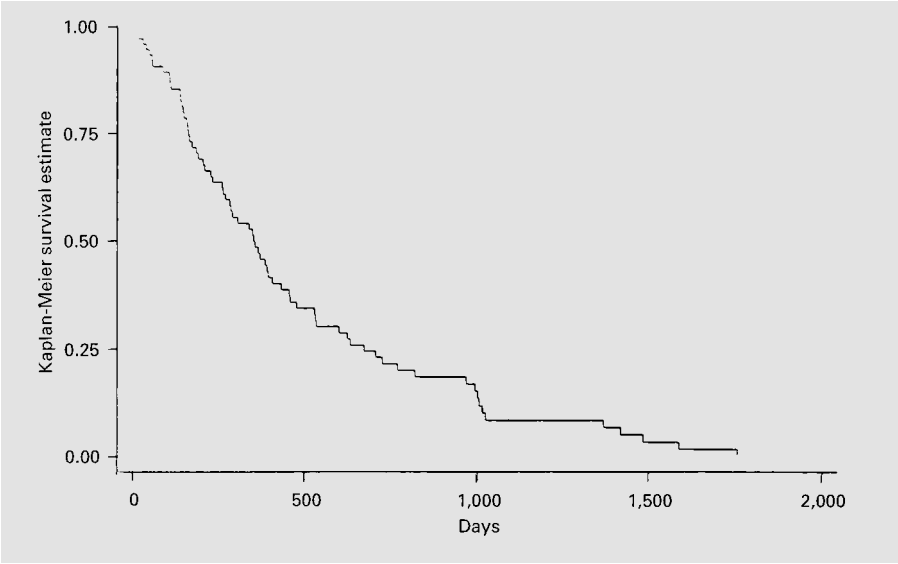

Fig. 8. Renal survival of patients treated with a supplemented very low protein diet, defined as the interval between their reaching a level of severity that would qualify them for ESRD support from Medicare (GFR <10 ml/min for nondiabetics and <15 ml/min for diabetics) and the actual start of dialysis. Reprinted by permission from Walser et al. [22].

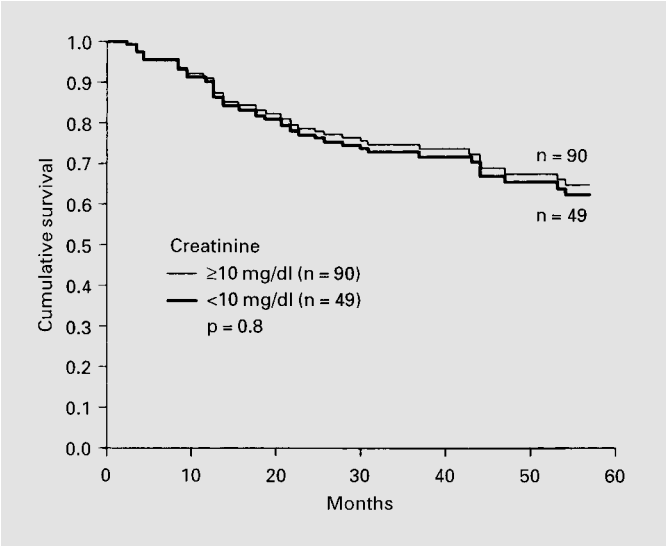

Fig. 9. Survival on dialysis of patients started at a serum creatinine concentration <10 mg/dl compared with those started at a serum creatinine concentration of <10 mg/dl. No difference is seen (note that this was not a randomized study). Reprinted by permission from Ifudu et al. [27].

Does Protein Nutrition Improve in Patients with Chronic Renal Failure when Protein Intake Is Increased?

Curiously, there seem to be no data on this point, either in predialysis patients or in dialysis patients. Perhaps I have overlooked some publications. There are several studies that demonstrate some improvement in hypoalbuminemia during the first months of dialysis, but obviously there are other possible explanations of these findings.

How Does Mortality on Dialysis Compare with Predialysis Mortality?

Mortality on dialysis in the US is reported in detail in the annual USRDS publications [25]. According to the most recent volume, the mortality rate, expressed as deaths per year at risk, is approximately 23%. Predialysis mortality is more difficult to calculate and has been little studied. Obviously, it increases as renal failure progresses towards the end stage. A few reports have appeared that provide at least preliminary estimates of pre-dialysis mortality. One is the MDRD Study [26]. This study did not follow all patients until renal replacement, and therefore may give a lower estimate of mortality than would have been observed in these same subjects if followed longer. Total deaths, in 'study B' of the MDRD Study, divided by years at risk, gives 2.5% as the annual mortality. Another estimate can be obtained from our study in 76 predialysis patients followed until renal replacement [24]. Again, total deaths divided by patient-years at risk yields 2.5% mortality. A third estimate can be obtained from the work of Aparicio et al. [17]. During their follow-up of 175 patients, deaths divided by patient-years at risk again produces an estimate of 2.5% mortality.

Table 2. Parameters before, during, and at end of treatment [from ref. 24]

Parameter	At entry	During treatment	Final
Group 1[a]			
Weight, kg	72.1 ± 13.9		69.1 ± 13.0
GFR, ml/min	7.4 ± 1.9		4.5 ± 1.8
Mean arterial pressure mm Hg		109 ± 12	
Hematocrit, %		28.4 ± 4.7	
Estimated protein intake g/kg		0.52 ± 0.15	
Serum values			
Creatinine, mg/dl	5.8 ± 1.4		9.1 ± 2.2
Urea N, mg/dl	64 ± 16	62 ± 18	82 ± 26
Calcium, mg/dl	9.0 ± 0.8	9.0 ± 0.8	8.8 ± 0.9
Phosphorus, mg/dl	5.0 ± 0.9	4.9 ± 0.8	5.6 ± 1.4
CO_2, mEq/l	21 ± 4	22 ± 4	22 ± 5
Albumin, g/dl	4.1 ± 0.5	4.1 ± 0.4	4.1 ± 0.6
Transferrin, mg/dl	233 ± 38	221 ± 28	223 ± 46
Cholesterol, mg/dl	204 ± 32	190 ± 38	184 ± 39
Triglycerides, mg/dl	158 ± 74	165 ± 85	158 ± 74
Renal survival, days (median): 530			
Group 2[b]			
Weight, kg	69.6 ± 13.0		71.5 ± 14.2
GFR, ml/min			6.2 ± 1.9
Mean arterial pressure mm Hg		108 ± 9	
Hematocrit, %		32.3 ± 4.6	
Estimated protein intake g/kg		0.51 ± 0.13	
Serum values			
Creatinine, mg/dl			8.3 ± 2.9
Urea N, mg/dl		60 ± 17	75 ± 26
Calcium, mg/dl		9.0 ± 0.5	9.0 ± 0.8
Phosphorus, mg/dl		4.8 ± 1.0	5.4 ± 1.4
CO_2, mEq/l		23 ± 3	23 ± 5
Albumin, g/dl		4.2 ± 0.4	4.1 ± 0.5
Transferrin, mg/dl		239 ± 48	239 ± 62
Cholesterol, mg/dl		201 ± 56	195 ± 59
Renal survival, days (median): 346			

[a] Patients presenting with GFR <10 ml/min (<15 ml/min in diabetic patients) (n = 23). Age: 57 ± 14. Gender: 8 women, 15 men.
[b] Patients presenting with GFR >10 ml/min (>15 ml/min in diabetic patients) who later reached <10 ml/min (<15 ml/min in diabetic patients) (n = 53). Age: 50 ± 14. Gender: 19 women, 34 men.

While these estimates will clearly need further refinement, it is clear that predialysis mortality is far lower than dialysis mortality.

Is Mortality on Dialysis Reduced by Starting Earlier?

The wrong question is being asked here. From the patient's point of view, the question of interest is whether mortality is reduced by starting dialysis earlier, including both predialysis and dialysis mortality. Unless patients started on dialysis earlier experience a much lower mortality than the figures given by USRDS, which is almost certainly not the case, there is no possibility that starting dialysis earlier can reduce overall mortality. On the contrary, early dialysis can only increase overall mortality.

There are a few studies that have compared mortality of patients started relatively early vs. those started relatively late. However, these studies cannot be said to answer the question posed here, because they are not randomized. Thus patients started earlier are liable to be those with more comorbid conditions, for example. One such analysis was reported by Ifudu et al. [27] (fig. 9). Survival on dialysis was not different between patients started at a serum creatinine concentration of greater than 10 mg/dl from those started at a lower serum creatinine.

The performance of a randomized study of this question would be desirable. However, there is no possibility that mortality on dialysis, no matter how early it is started, could be lower than predialysis mortality. The conclusion seems inescapable that dialysis should be postponed as long as possible.

Compliance with Protein-Restricted Diets

In general, two separate aspects of compliance can be recorded: (1) the fraction of potential subjects who decline to attempt a certain treatment, and (2) the level of adherence to the treatment by those who do participate.

It is often stated that patients' compliance with these low-protein diets is so poor that their applicability is very limited. Few reports of dietary treatment have documented the fraction of patients who have declined to consume a low-protein diet. In one report from Johns Hopkins [24], we noted that 5% of patients who were asked to enter a diet study refused to participate. But this estimate cannot be said to answer the question as to what fraction of patients with chronic renal failure, nationwide, would

be willing to follow a restrictive diet. Obviously, the answer will depend, among other things, on (1) the nature of the diet; (2) its cost; (3) the acceptability of the supplement (if any), and (4) the benefit to be anticipated. But predictions of widespread refusal should not be cited as an objection to trying a new treatment. Clearly, many patients will accept these restrictions, and the fraction that will not can only be determined by a trial.

The second question, the level of adherence achieved, is easier to answer. Almost every study of protein-restricted diets that has been published has recorded compliance, measured as the ratio of protein consumed (from measurements of 24-hour urea excretion) to protein prescribed. This ratio is usually close to 1.5. Thus, patients generally consume approximately 50% more protein than prescribed on these diets. This does not mean that such diets are useless; on the contrary, this level of compliance still represents a substantial reduction in protein intake for almost all patients, and the benefits have been thoroughly documented.

Conclusions

All patients with symptomatic renal failure, unless on steroids, should be offered a very low protein diet, designed by a skilled dietician, and supplemented by a mixture of essential amino acids, at a dose of approximately 10 g/day, taken with meals. They should be closely followed to control acidosis, hypertension, edema, anemia, and hyperkaliemia.

Renal replacement should be postponed as long as possible. It should only be started when it is certain to reduce symptoms, because it will undoubtedly be associated with an increase in mortality compared with predialysis mortality, even though it makes long-term survival possible in most patients despite little or no renal function.

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