Occasional Survey

DIETARY TREATMENT OF CHRONIC RENAL FAILURE: TEN UNANSWERED QUESTIONS

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DIETARY protein restriction has long been used for the symptomatic management of patients with advanced chronic renal failure (CRF) and there have lately been suggestions that low-protein diets may slow or halt the progression of renal disease.[1] The survival rate of laboratory animals with CRF can be greatly improved by administration of a low-protein diet.[2] In many trials a beneficial action in human disease is claimed,[1] and wider treatment with low-protein diet is being advocated[3]—even for patients with a plasma creatinine of 200 μmol/l or less.[4] We review here the evidence for the efficacy and safety of low-protein diets by asking ten questions.

DOES CHRONIC RENAL FAILURE ALWAYS PROGRESS?

Implicit in the use of a low-protein diet is the assumption that, without treatment, renal function will continue to deteriorate; this is not always so. The MRC Glomerulonephritis Registry (Davison A. M., personal communication) has analysed the outcome for patients with biopsy-proven glomerulonephritis (membranous nephropathy and crescentic nephritis excluded). Of 70 patients who had a plasma creatinine of 150–249 μmol/l at presentation, 32% had unchanged or improved function two years later. Of the 40 patients whose creatinine was 250–500 μmol/l at presentation, 22% had stable or improved renal function over the same period. In a multicentre study of the natural history of membranous nephropathy, 6 of 20 patients with chronic renal failure did not show progressive impairment of renal function.[5] In chronic pyelonephritis, 39·8% of the patients showed stable renal function over 6–240 months.[6] We too have observed many patients with stable CRF over several years. Fig 1A shows results from 2 patients whose creatinine measurements did not change over five years.

Maschio et al[4] concluded that a low-protein diet was more effective in preventing progressive CRF if started early—i.e. when plasma creatinine was about 200 μmol/l. However, they did not establish the rate of progression in different subgroups before the introduction of the diet, and thus the results could reflect the variable natural history of mild compared with severe CRF.

Whether CRF progresses could depend on the type of the underlying nephropathy, on the degree of renal functional impairment and hypertension at presentation, as well as on the severity of proteinuria.[7] Age and sex could also be prognostic factors: in membranous nephropathy, older-age and male patients seem to have a particularly poor outlook.[5] However, proteinuria may well be the most important.[7,8,9] In the design of most trials these factors have not been considered. The only randomly allocated study of low-protein diet in CRF took into consideration patients' age, sex, and degree of renal failure, but not proteinuria at the start of the treatment;[10] in this study proteinuria decreased during the low-protein diet. We have shown that a decrease in proteinuria indicates an improved prognosis in patients with chronic glomerulonephritis.[11]

HOW SHOULD WE ASSESS THE PROGRESSION OF CHRONIC RENAL FAILURE?

The effect of low-protein diets on CRF can be assessed only if the rate of failure of renal function follows a predictable pattern, and this seems to be so in most patients with CRF. A widely used method of assessing progression is to plot the reciprocal or the logarithm of plasma creatinine against time.[12,13] The reciprocal method is based on the notion of a constant decline; the logarithm method on that of a constant fractional loss. Linear regression analysis often reveals close fit of the calculated line to the measured values, but, not all patients with CRF show a predictable pattern. In one study the results of 15% of patients did not fit any mathematical model,[13] while Ledingham and Hart[14] found that in up to 30% of patients the calculated slopes changed with time, including 12% who showed a spontaneous improvement; one common cause for the variation is the onset of hypertension.[15]

In most studies reciprocal creatinine concentrations before and after the introduction of the low-protein diet have been compared. Unfortunately, once the patient is on the diet the plasma creatinine ceases to be a valid measure of renal function,[16] since it is mostly derived from creatine in the diet and in muscle. All low-protein diets entail a reduction in creatine intake which is the source of up to 15% of plasma creatinine.[17,18] Fig 2 shows the fall of plasma creatinine in 2 patients on a low-protein diet (0·2 g/kg body weight per day) supplemented by essential aminoacids and their keto-analogues—i.e. no exogenous creatine.[19] Glomerular filtration rate, as judged by combined urea and creatinine clearance, was not improved. This example emphasises the unreliability of plasma creatinine measurements as a marker of renal function in patients on a low-protein diet.[20]

Mitch[16] has noted that it takes several months for a new steady state to be achieved, and has recommended a wait of up to 4 months before creatinine values are used to assess renal function. So far, all published trials have used creatinine values to assess the effect of dietary treatment from the start of low-protein diets. If early changes in creatinine values are included, this may give a falsely encouraging impression of renal function improvement. Since several of the research groups have examined only the effect of 6 months' dietary treatment, their results may well represent changes in creatinine metabolism rather than in renal function. In advanced renal failure a substantial proportion of the creatinine is not excreted in the urine but is lost extra-renally, possibly being degraded in the gut;[18] this fact has also been ignored.

Clearly, direct measurement of glomerular filtration is more reliable than measurement of plasma creatinine. Creatinine clearance testing is subject to error, and glomerular filtration can be overestimated where there is poor renal function due to glomerular disease.[21] Changes in creatinine clearance may result from variations in dietary protein intake;[22,23] these could be secondary to changes in renal tubular handling of creatinine associated with low-protein or high-protein diets[24] and are not necessarily due to changes in glomerular filtration. Combined urea and creatinine clearances correlate better with values obtained with inulin.[25]

Only one group of investigators has consistently provided data on changes in creatinine clearance before and after various diets: in this study dietary protein restriction did not significantly improve renal function; only when severe phosphorus restriction was combined with nitrogen restriction was the slower rate of decline in renal function significant.[26]

Isotope measurements might be the best way to assess renal function, but reliance on plasma measurements alone after a single dose might lead to an overestimate of glomerlular filtration rate.[27] Paired urine collections and plasma samples are therefore essential. None of the groups who have claimed benefit from a low-protein diet measured renal function isotopically.

IS THERE A PLACEBO EFFECT IN DIET TRIALS?

Bergström et al[28] have shown that frequent clinic visits have a beneficial effect on the rate of decline of renal function. It is likely that regular monitoring of calcium and phosphate metabolism, hypertension, and urinary tract infections will lead to improved renal function. In some of our patients renal function has apparently stabilised after transfer to a special renal clinic, without any great change in treatment (fig 1B). In very few published trials have patients been monitored at comparable intervals or for the same observation period before and after treatment with low-protein diet.

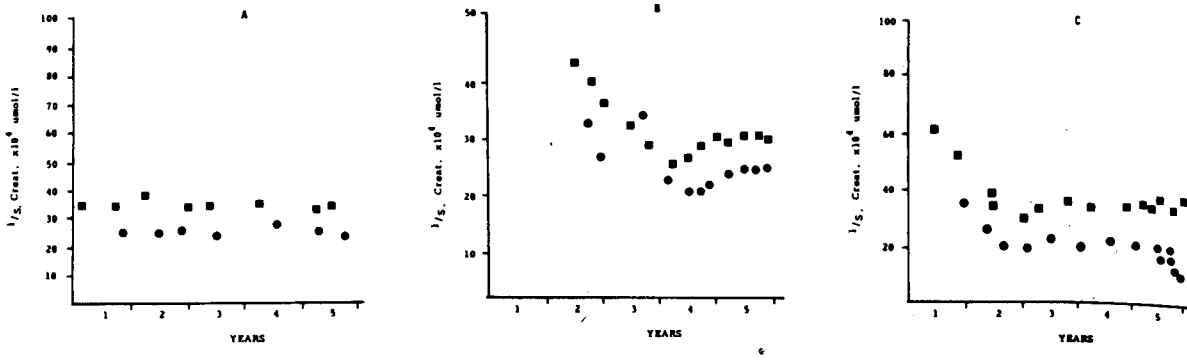

Fig 1—Long-term indices in patients with renal failure.

(A) Reciprocal of serum creatinine plot against time of 2 patients with non-progressive chronic renal failure. (B) 2 patients whose rates of decline in renal function changed upon more frequent outpatient follow-ups. (C) 2 patients whose rates of decline in renal function changed spontaneously. Creat = creatinine.

HAVE THERE BEEN ANY CONTROLLED STUDIES?

The paper by Rosman et al[10] is the only published prospective, randomised trial of low-protein diet in CRF. Although their patient groups appeared comparable, there was no assessment of proteinuria or rate of progression at the outset. Moreover, the numbers of age and sex matched patients for each diagnosis were small, and there were no data on glomerular filtration rate. Rosman et al claimed benefit with dietary protein restriction, but their conclusion has been challenged.[29]

Many groups have claimed benefit on the basis of inadequate or non-existent controls. In some trials the effect of protein restriction was assessed prospectively in patients with varying degrees of renal failure, the control groups being recruited retrospectively.[4,7] In other studies results were compared before and after treatment,[11,26] but the frequency of observations and time before and after treatment have often been far from equal.[26] Other "controls" have been patients treated in different hospitals, by different physicians;[30] some workers have taken as controls the patients who refused or would not comply with low-protein diet.[31] In CRF, patient and control groups should be matched for age, sex, diagnosis, degree of renal failure and proteinuria, rate of progression, and presence or absence of other adverse factors such as uncontrolled hypertension. Sufficient numbers of adequately matched patients can be obtained only in multicentre trials.

WHEN SHOULD A LOW-PROTEIN DIET START?

It is often stated that low-protein diets are most beneficial when introduced early.[3] Some workers even recommend starting dietary protein restriction when serum creatinine exceeds 150 μmol/l.[4] There are no good data to substantiate these claims. The only study in which early and late protein restriction were compared had many of the shortcomings discussed earlier, including inadequate controls.[4] Linear regression analysis was used to assess progressive renal failure when plasma creatinine levels were between 150 and 200 μmol/l, but there is doubt about the method at this level of renal failure.[12,13] Finally, the rate of progression of CRF was not assessed before low-protein dietary treatment. The least affected group could have been progressing more slowly before the start of treatment.

WHICH LOW-PROTEIN DIET?

Unfortunately the number of different diets tried in CRF is nearly equal to the number of reported studies: protein intake has ranged from 0·6 to less then 0·2 g/kg per day.[1] The very low nitrogen intakes have usually been supplemented by essential aminoacids (EAA) alone or in combination with ketoacid analogues (KAA). Several different formulations of aminoacids and ketoacids have been proposed. All restricted protein diets have a low calcium content and below 0·5 g/kg per day deficiencies of other substances such as iron and zinc may occur. Moreover, once dietary protein is restricted it is essential to maintain an adequate calorie intake. As much as 50 kcal/kg per day may be required in patients on severely restricted diets.[1] In several trials the calories supplied are not specified[32] while in others, patients were not allowed enough calories for optimum use of the limited protein intake.[33]

Might phosphorus restriction contribute to the beneficial effect of a low-protein diet? In animals, phosphorus restriction was believed to have little effect on the progression of CRF and renal scarring; its influence seemed to be mediated by anorexia and the consequent reduction of protein intake.[34] However, recent data suggest that phosphorus restriction is synergistic with protein restriction in the prevention of severe renal scarring and CRF in animals[35] and in man.[26]

There is controversy also about supplementation of low-protein diets with EAA or KAA: in the very few studies in which supplemented diets have been compared with unsupplemented, nitrogen intakes differed, and the results are difficult to interpret.[36,37] Therefore, the claimed additional benefit from EAA could well be attributed to a reduction in nitrogen intake. Most studies of the effect of EAA supplementation on the progression of CRF were short-term, from a few weeks to 6 months[36,37]—ie, not long enough for assessment of changes in glomerular filtration.

There are similar shortcomings in the few published studies on the effect of KAA supplementation. In a long-term study Mitch et al[32] have reported beneficial effects of KAA supplementation on the progression of CRF, but their earlier studies with the same diet have been severely criticised.[38] Not only are there no data showing any advantage of such KAA supplements to the conventional low-protein diet, but also there is evidence that severe muscle wasting can occur in children[39] and in adults[19] on the supplemented diets. Changes in muscle mass and creatinine production and metabolism could explain the reported fall in plasma creatinine values. Mitch et al[32] did not provide anthropometric data on their patients, and serial plasma creatinine measurement alone is clearly an inadequate index of renal failure on such a restricted diet. Prospective, randomly allocated trials are needed to evaluate further the possible benefit of dietary aminoacids in the management of CRF.

HOW SHOULD COMPLIANCE BE ASSESSED?

Strict adherence to a low-protein diet is demanding of the patient and his family, so the clinician must try to assess compliance. For the patient the most accurate method of controlling dietary intake is probably to weigh all meal portions for a few days every month, but this is tedious. Dietary questionnaires and interviews seem to be a satisfactory method of assessment, provided that they are conducted by an experienced dietitian.[40] Both patient and spouse should be interviewed. A four-day dietary history is usually adequate and correlates well with the true dietary intake.

In general, although dietary recalls and interviews are usually satisfactory, more objective ways of assessing patient compliance

should also be used. The plasma urea/creatinine ratio has been suggested[41] but is subject to the errors discussed earlier. Urea nitrogen appearance is probably the best guide to nitrogen intake,[42] but only one study of the progression of CRF has provided serial data for assessment of compliance.[11]

WHAT ARE THE RISKS OF A LOW-PROTEIN DIET?

The most serious hazard of dietary protein restriction is malnutrition. Therefore it is very important to avoid muscle-wasting in patients on a low-protein diet. In patients on dialysis, morbidity is largely related to physical fitness at the start of replacement therapy.[43] It would be a great disadvantage if the postponement of dialysis therapy secured by treatment with a low-protein diet was paid for by loss of fitness at the time dialysis is started.

In experimental CRF, the beneficial effect of a low-protein diet on progressive renal failure is often accompanied by some muscle-wasting and malnutrition.[44] However, we have shown that growth can be maintained if adequate calories, minerals, and vitamins are provided.[45] In children with CRF there is a similar dilemma because severe protein restriction can also retard growth[39]—an unacceptable price to pay for a few months' delay in the initiation of dialysis. In adults we have observed a serious depletion of protein stores in some patients treated with a very low-protein diet[19] (figs 2 and 3).

HOW SHOULD NUTRITIONAL STATUS BE ASSESSED?

Clinical and biochemical assessments of nutrition are mandatory for all patients on low-protein diets. Anthropometric measurements of muscle mass (protein stores) and skinfold thickness (fat stores) are accurate and reproducible,[46] but unfortunately such measurements have seldom been made on patients treated with low-protein diets.

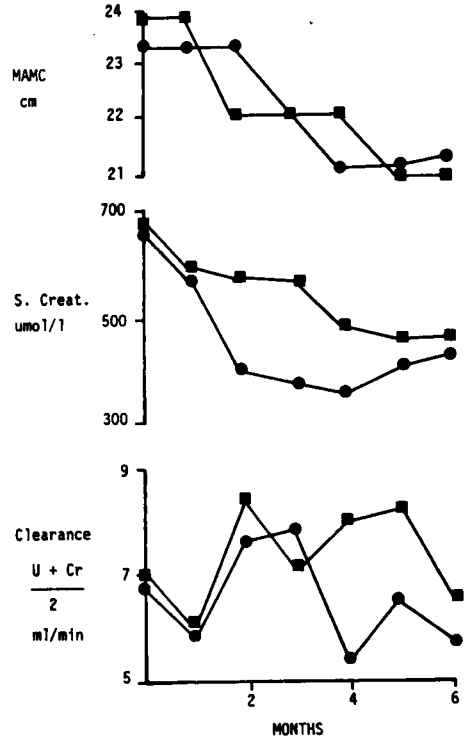

Fig 2—Effects of low-protein diet supplemented with EAA and KAA in two patients.

MAMC = mid-arm muscle circumference. S. creat = serum creatinine. Glomerular filtration rate = clearance of urea (U) and clearance of creatinine (Cr) ÷ 2.

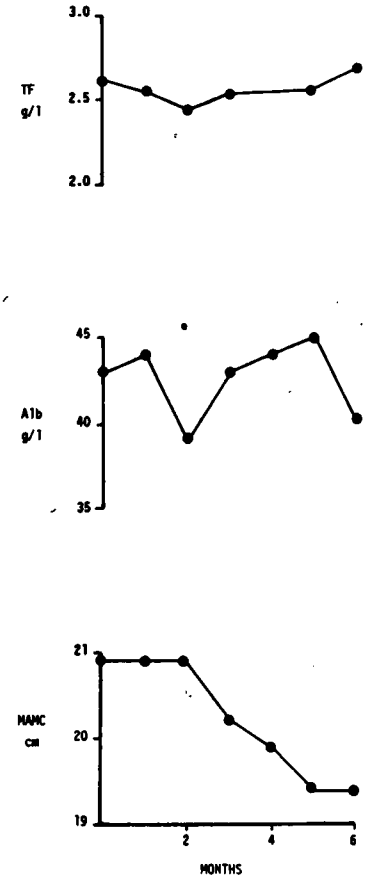

Fig 3—Results in a patient on a very low-protein diet supplemented with EAA and KAA

TF = transferrin. Alb = serum albumin.

Instead the patient's weight is recorded and monitored[32]—an unreliable means of assessing body solids in advanced ureamia.[47]

As to the biochemical indices, serum albumin, transferrin, complement, and retinol-binding protein have been used to monitor nutritional status;[46] unfortunately, most of these do not indicate early changes in nitrogen balance, and retinol-binding protein is raised in renal failure. We have observed substantial muscle loss without change in serum albumin and transferrin[19] (fig 3). Urinary excretion of 3-methylhistidine has been used as a measure of muscle protein breakdown,[48] but is dependent on the degree of renal failure[49] and the dietary protein intake.[20] Combined serial anthropometric and biochemical measurements probably offer the best approach.

WHAT IS THE COST OF A LOW-PROTEIN DIET?

If long-term dialysis is postponed by treatment with low-protein diets there will be a considerable cost saving. However, dietary restriction has its price. Firstly, it requires the skills of a renal dietitian. Secondly, dietary restrictions and adjustments require commitment from both patient and family. Exclusion of normal foods is difficult for the family because separate meals may have to be prepared, at extra expense. Finally, supplementation with EAA or KAA can cost up to £500/patient per year.

RECOMMENDATIONS FOR FUTURE STUDIES

The case for low-protein diets in CRF is not established in man. For further study we make the following recommendations. (1). Patients should be proven to have progressive renal failure with no obvious reversible factor before administration of a low-protein diet. (2). The rate of decline of renal function should be assessed over several months. This will allow for the placebo effect and ensure treatment of conditions such as hypertension. (3). Renal function should be monitored by isotopic clearances. (4). Assessment of nutrition should include anthropometric and biochemical measurements. (5). Patient compliance should be assessed by an experienced dietitian and also by the measurement of urea nitrogen appearance. (6). If a randomised trial is undertaken, groups of patients should be matched for age, sex, diagnosis, rate of progression, degree of renal failure, hypertension, and proteinuria. Control and experimental diet groups should be treated and followed up in the same way, and should be kept apart at clinics to prevent inadvertent "crossover" of diets. (7). In future trials we would favour the less restricted diets (standard 0·6 g/kg protein intake) since they are a more realistic option for large-scale use. (8). Follow-up should be for at least two years.

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References continued at foot of next column

Child Health

COST OF NEONATAL INTENSIVE CARE FOR VERY-LOW-BIRTHWEIGHT INFANTS

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Summary A detailed costing of the Mersey regional neonatal intensive care unit was made for 1983 (at 1984 prices) for three levels of care; costs per inpatient day were £297, £138, and £71 for intensive, special, and nursery care, respectively. Regression of ungrouped patient-specific costs against birthweight showed the explanatory power of birthweight to be negligible. The average cost per very-low-birthweight (<1500 g) infant was £4490 for a survivor and £3446 for a non-survivor. A similar study elsewhere showed an almost six-fold difference in cost between survivors and non-survivors. It is postulated that medical management policy largely determines this difference and is crucial to any investigation of cost-efficiency.

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