Occasional Survey

ANSWERS TO TEN QUESTIONS ON THE DIETARY TREATMENT OF CHRONIC RENAL FAILURE

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THIS paper is an attempt to answer concisely the ten questions posed by El Nahas and Coles earlier this year[1] and to comment on some of the points they make. Most of the opinions are shared by the steering committee of the European Study Group for the Conservative Treatment of Chronic Renal Failure. Where opinions are held only by the Pisa group, this is indicated.

DOES CHRONIC RENAL FAILURE ALWAYS PROGRESS?

In some patients with chronic renal failure the residual function remains stable, even for many years, as stated by El Nahas and Coles,[1] but when renal failure is severe, stability of renal function while the patient takes a free diet is exceptional. Of 143 chronic uraemic patients with serum creatinine (SCr) ≥ 5 mg/dl who remained on a free diet (52 with pyelonephritis, 40 with glomerulonephritis, 24 with diabetes, 11 with polycystic kidney disease, 8 with nephrosclerosis, and 8 with amyloidosis) 130 went into end-stage renal failure in less than 2 years.[2] In our experience stabilisation occurs in severe chronic uraemics only if they stick to a low-protein low-phosphorus diet; the longest duration of stability recorded is 7 years, in a man with chronic glomerulonephritis whose SCr has remained at 9 mg/dl since 1979.

The Pisa experience with proteinuria accords with that of El Nahas and Coles that low-protein diets reduce proteinuria in several patients. I also believe that the fall in proteinuria obtained with dietary treatment may be one mechanism by which the residual renal function is protected, as suggested by experimental findings.[3-5]

To conclude from trials lasting 2 years that chronic renal failure need not necessarily progress could be misleading. Animal experiments show that glomerulosclerosis, but not terminal renal failure, can be induced in uninephrectomised rats but several experimental studies suggest that the progression of renal impairment is only a function of time.

HOW SHOULD WE ASSESS PROGRESSION OF CHRONIC RENAL FAILURE?

Change in glomerular filtration rate (GFR) is regarded as the most reliable and precise indicator of alteration in renal function and the Swedish nephrologists in our Group measure it with external markers (Cr-labelled edetic acid or diethylene triamine penta-acetic acid) in samples obtained hourly for several hours. This procedure is the best if the bladder can be emptied completely and if the GFR in the few hours during which the clearance is measured is assumed to reflect GFR during the rest of the day.

The "creatininase" activity of the aerobic gut flora from uraemic patients is much higher than that of gut flora from healthy subjects,[6] which explains why creatinine excretion (Cr) is lower in the former than in the latter. A low-protein diet with little or no creatine and creatinine (little or no meat) would reduce urinary excretion of Cr further. It is clear then that the SCr gives an optimistic assessment of renal function, especially when patients are on a low-protein diet. The same considerations apply to assessment of renal function on the basis of the reciprocal of SCr.

Different considerations must be given to Cr clearance (CrCl)—whatever the changes in the metabolic production of Cr, they affect equally both its urinary output and its serum level, so their ratio (the clearance) does not change.

It has been well known for many decades that the clearance of creatinine is higher than GFR because of tubular secretion and, since the secretion of creatinine rises as GFR falls,[7,8] the ratio of CrCl/GFR increases as the renal function declines. Clearly the extent of a drop in renal function is blunted if CrCl is taken as a marker of GFR. Despite these drawbacks, I think that the relevant changes in renal function can be satisfactorily assessed by the measurement of CrCl provided the urine collection is complete during the clearance period (24 h). However, it must be remembered that the CrCl is greater than GFR and that the changes in renal function are not indicated to the same extent by CrCl as they are by the GFR.

My opinion thus is that long periods of follow-up and repeated measurements of creatinine clearance will give an adequate assessment of renal function and will indicate satisfactorily the rate of decline and of the possible improvement.

IS THERE A PLACEBO EFFECT IN DIET TRIALS?

In so-called placebo groups care may have been taken to reduce blood pressure to $<150/95$ mm Hg and correct, for example, fluid balance, acidosis,[9] or to prevent or give early treatment for urinary tract infections. These measures may retard the progression of chronic renal failure and should not be accepted as placebo treatment. The two patients whom El Nahas and Coles followed up and whose renal function stabilised after transfer to a renal clinic "without any great change in treatment" also cannot be said to have received placebo treatment. Thus it is difficult to accept conclusions that frequent clinical check-ups without any therapeutic measure can retard the progression of chronic renal failure.

HAVE THERE BEEN ANY CONTROLLED STUDIES?

There have been several controlled studies,[10-21] but the adequacy of the controls has to be examined. It may be impossible to have ideal controls if a trial is to be realistic. We agree, however, with El Nahas and Coles that sufficient numbers of patients can be obtained only in multicentre trials, such as those being conducted by our Group and the National Institutes of Health.

It must be recognised, however, that a slowing of the rate of progression of renal failure (and even its stabilisation for several years) in large numbers of patients with very low CrCl after a low-protein diet is very strong evidence that such a diet protects renal function. Also, absence of symptoms and the correction of several hormonal and metabolic derangements (see below) after a low-protein diet indicate the detoxifying, not mere symptom-relieving, effect of the diet.

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WHEN SHOULD A LOW-PROTEIN DIET START?

First, a low-protein diet should be defined, since there is much confusion on this point. For instance, a diet supplying 1 g/kg/day of protein is regarded as a moderately low protein diet in many industrialised countries, where a daily intake of 2 g/kg/day or more is quite common. In Italy most healthy adults take 1 g/kg, whereas in some Asian countries, where rice and fat are the greatest sources of calories, the protein intake is approximately 0·55 g/kg/day.[22] An acceptable definition of a very moderately restricted protein diet is 0·5–0·6 g/kg/day of protein (mostly of high biological value), since the minimum recommended dietary daily allowance for protein is approximately 0·5 g/kg for adult persons.[23] such a diet should be applied from the early stages of renal failure, together with a restriction of inorganic phosphorus intake (400–500 mg/day) and calcium (calcium-carbonate) supplementation, to prevent or reverse secondary hyperparathyroidism, hyperphosphataemia, and acidosis.

A more severe protein restriction to approximately 0·3 g/kg/day of unselected protein, together with a more severe restriction of phosphorus intake (200–250 mg/day), should be recommended for patients with severe renal failure. these patients would require supplements of essential aminoacids (EAAs) or of EAAs plus ketoanalogues (KAs), to prevent protein malnutrition. Such a regimen has been followed by 300 patients in the department of nephrology at Göteborg university[18] and 200 in the Clinica Medica of Pisa, and results have definitely been positive.

In the protocol of the European Study Group such regimens are accepted.

WHICH LOW-PROTEIN DIET?

One reason for the existence of many low-protein diets is the attempt to adjust the degree of restriction to severity of the renal failure. Another reason is the attempt to adapt the low-protein diet to local dietary habits. Whatever the diet, the principles remain the same. The first is to reduce the protein intake to the minimum required to maintain nitrogen balance; with severe protein restriction, EAA supplements are required to prevent protein malnutrition. The second is to reduce the phosphorus intake to obtain normal serum phosphate levels. The third is to satisfy caloric needs—at least 35 kcal/kg/day, furnished mainly (60–65%) by carbohydrates (mostly polysaccharides) and by lipids (25–30%), mostly of vegetable origin and rich in polyunsaturated fatty acids; small amounts of ethyl alcohol may be used to increase the caloric supply. The final principle is to give calcium, iron, and multivitamin supplements.

In Italy, where the main source of calories is bread and pasta, it is easy to apply these principles by the use of protein-free and phosphorus-free starch. The liberal use of vegetable oil in the normal diet and the availability of fresh vegetables and fruits throughout the year facilitate the preparation of acceptable dishes, which obviously help patients to comply with the diet and ingest sufficient calories. In countries where meat intake is higher the preparation of palatable dishes is more difficult than in Italy.

HOW SHOULD COMPLIANCE BE ASSESSED?

Assessment of compliance with a low-protein diet plus EAA and KA supplements should take into account (1) compliance with restriction in protein intake; (2) compliance with recommended caloric intake; (3) compliance with ingestion of EAA and KA supplements.

There is general agreement that urea levels in serum and urine are adequate for monitoring restriction of protein intake; they are being used in protocols of the European Study Group. Either serum or urinary urea needs to be measured since they drop in parallel if compliance is good.

Adequacy of calorie intake to prevent protein breakdown (with consequent azotaemia) is indicated by constancy or increase of body weight or middle arm skinfold thickness. In our experience both skinfold thickness and body weight increase moderately but significantly when patients in severe uraemia change from a conventional to a supplemented low-protein diet.

Ingestion of EAA and KA supplements may be assessed by testing for allo-isoleucine in the blood.

In assessing compliance account should be taken of the gastric discomfort caused by large amounts of oligosaccharides given to raise caloric intake, as well as by EAAs and KAs when given in powder form (they should be given in gastric-coated tablets), and of the anorexia and vomiting caused by severe renal failure (such as in patients 2, 4, and 7 described by Lucas et al[24]).

WHAT ARE THE RISKS OF A LOW-PROTEIN DIET?

A recurring criticism of low-protein diets is that they may cause protein malnutrition. However, protein malnutrition is not an acute condition. Its development follows weeks of negative nitrogen balance, which ought to be detected early by the regular checks to which patients on dietary therapy should be submitted.

The commonest cause of protein malnutrition in chronic uraemic patients on a low-protein diet is inadequacy of calorie supply which may often be recognised by means of a simple questionnaire. The other causes are intercurrent catabolic conditions, such as infections or neoplastic diseases, that are generally easily detectable or at least likely to be thought of. It should be noted that protein malnutrition is an absolute contraindication to a low-protein diet. If the cause of protein malnutrition cannot be recognised and rapidly removed, renal replacement therapy should be started immediately. In published reports severe malnutrition (resulting in cachexia) has always been attributed to the low-protein diets, when it should be attributed to inappropriate prescription of such diets or to inadequate monitoring of nitrogen balance. Similarly if patients are uraemic and malnourished when they are started on a haemodialysis programme after being treated for chronic uraemia with a low-protein diet, it is not the diet that should be blamed but the undue persistence with conservative therapy when it was no longer indicated. When correctly employed a low-protein diet, even when it has been given for several years, should enable a patient to start dialysis in a well-nourished state by correcting the metabolic and hormonal derangements.[25-34]

HOW SHOULD NUTRITIONAL STATUS BE ASSESSED?

"Combined serial anthropometric and biochemical measurements probably offer the best approach",[1] and this line is being followed by the European Study Group. The biochemical findings in patients followed up in our Clinic indicate that a supplemented diet giving the lowest protein intake, 0·3 g/kg/day, did not reduce serum levels of albumin, total proteins, transferrin, total indirect binding capacity, and complement. Instead, serum levels of albumin and of total protein often rise. Total body potassium in 53 chronic uraemic patients on a 20 g protein supplemented diet[34] did

not differ appreciably from those expected in healthy subjects or from those patients on maintenance haemodialysis and peritoneal dialysis.

The measurements of total body intake permits assessment of the body cell mass[34] and indicates that no protein or calorie malnutrition is induced by a supplemented diet providing 0·3 g protein/kg/day.

WHAT IS THE COST OF LOW-PROTEIN DIET?

In 7 years of regularly prescribing a supplemented diet for patients with severe chronic uraemia, we estimate that we have avoided approximately 175 years of haemodialysis in 151 patients. This result has been achieved by placing on supplemented diets patients without contraindications to low-protein diets and with a CrCl of 8 (SD 3) ml/min; these are the present criteria for starting patients on maintenance haemodialysis and a free diet. This CrCl level corresponds roughly to a GFR of 5 (SD 2) ml/min that is taken to indicate that conservative therapy should be terminated.[35]

Should the standard thrice-a-week dialysis schedule have been followed during these 175 years, 27 300 haemodialyses would have been done. In Italy these 27 300 procedures would have cost about £1 365 000. The cost of the protein-free foods and supplements plus salaries of dietitians and cost of additional clinic visits and various investigations would not add up to £100 000. This estimate does not take into account patients with CrCl higher than 8 (SD 3) ml/min, whose decline of renal function has been slowed by a low-protein, low-phosphorus diet with or without EAA and KA supplements, but who have not yet satisifed the criteria for haemodialysis.

RECOMMENDATIONS FOR FUTURE TRIALS

El Nahas and Coles' guidelines[1] on how to conduct trials should result in a perfect study, but they are unrealistic—for example, the enormous number of subgroups they suggest means that an adequate sample size (50–80 patients) is unlikely to be obtained.

El Nahas and Coles' recommendation that renal function be assessed by isotope clearance alone might be dangerous, since only a few data points per patient can be obtained and a clearance may occasionally go wrong. This may create difficulties in the statistical analysis. Thus we conclude that compromises concerning the study design are unavoidable.[36]

It is difficult to share El Nahas and Coles' preference for less restricted diets (0·6 g protein/kg/day), even on theoretical grounds. If it is accepted that protein and phosphorus restrictions are beneficial for chronic uraemic patients, then the degree of such restrictions should be directly proportional, within certain limits, to the severity of renal insufficiency. It is difficult to understand why a low-protein supplemented diet is not to be recommended once its efficacy and safety have been largely proved. We also think that researchers should be discouraged from applying time limits in their studies, since with some renal diseases 2 years represents a "short" period whereas in others this end point will never be reached.

I thank all members of the steering committee of the European Study Group for the Conservative Treatment of Chronic Renal Failure for their suggestions and criticisms.

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