PAPERS AND SHORT REPORTS

Selective effect of low protein diets in chronic renal diseases

A M EL NAHAS, A MASTERS-THOMAS, S A BRADY, K FARRINGTON, V WILKINSON,
A J W HILSON, Z VARGHESE, J F MOORHEAD

Abstract

It has recently been established that the rate of progression of chronic renal failure in man can be slowed by restricting dietary protein. Consequently, the short term and long term effects of a low protein diet on the course of different chronic nephropathies were studied in an attempt to delineate the factors that determine the response to such a diet. When a low protein diet was given for six months renal function improved significantly in nine patients with chronic tubulointerstitial nephritis ($p < 0.025$); the diet had a marginally beneficial effect in 12 patients with chronic glomerulonephritis ($p < 0.05$) and no effect in nine with hypertensive nephrosclerosis. The heterogeneous functional response in the patients with chronic glomerulonephritis correlated closely with the effect of the diet on these patients' proteinuria ($r = 0.76$, $p < 0.01$). In a short term study (four weeks) of 12 patients with chronic renal failure changes in renal plasma flow were proportional to dietary protein intake. Renal vascular resistance fell during a high protein diet and increased when dietary protein was restricted. The changes in renal plasma flow during the low protein diet correlated well with the patients' long term functional response to the diet ($r = 0.76$, $p < 0.01$).

It is concluded that the response to a low protein diet in chronic renal failure is determined, firstly, by the nature of the underlying nephropathy, with maximal benefit being observed in non-glomerular disorders;

secondly, by the effect of the diet on the proteinuria in chronic glomerulonephritis; and, thirdly, by the haemodynamic response to the diet, with patients with a reactive renal vascular bed improving with a low protein diet.

Introduction

Chronic renal diseases often progress relentlessly to end stage renal failure. The rate of progression of nephropathies, though variable between individual patients, does not seem to be influenced by the nature of the underlying disease.^{1,2} In most patients the decline in renal function seems to occur at a constant rate, allowing an often accurate prediction of the date when end stage renal failure will be reached.¹

In man the precise mechanism of such progressive renal failure remains poorly understood. In animals, on the other hand, recent progress has been achieved in defining the pathophysiology of progressive renal scarring in experimental models of chronic renal failure. Two glomerular haemodynamic patterns have emerged as likely contributors to the chronic changes of glomerulosclerosis after an acute renal injury. The first is of glomerular hyperperfusion and hyperfiltration, whereby glomeruli compensate for the loss of adjacent functional renal mass by increasing their blood flow and filtration rate.³ These adaptive changes, though functionally beneficial in the short term, might be morphologically harmful, leading in the long term to further glomerular structural damage.⁴ This haemodynamic pathway to renal failure was described in experimental models when the initial glomerular injury was mild⁵ or absent such as the remnant kidney,⁶ diabetic nephropathy,⁷ and pyelonephritis.⁸

The second pattern of response to injury by the glomerular vascular bed was observed in conditions in which the glomeruli were predominantly and severely affected at the onset of the nephritis.⁹ In animals with such conditions severe glomerular vasoconstriction occurred with subsequent glomerular ischaemia and underfiltration.⁹ Apparently, therefore, glomeruli in animals exhibit a wide range of haemodynamic adjustments to renal injury. Whether similar changes occur in man remains to be determined.

The understanding of the pathophysiology of chronic renal failure in animals has led to some therapeutic advances. A low

Departments of Nephrology and Transplantation and Nuclear Medicine, Royal Free Hospital, London NW3 2QG

A M EL NAHAS, MRCP, registrar
A MASTERS-THOMAS, SRD, senior dietitian
S A BRADY, MB, MRCP, senior house officer
K FARRINGTON, MRCP, MD, senior registrar
V WILKINSON, PHD, medical physicist
A J W HILSON, MRCP, consultant in nuclear medicine
Z VARGHESE, PHD, consultant biochemist
J F MOORHEAD, FRCP, consultant nephrologist

Correspondence to: Dr A M El Nahas, KRUF Institute of Kidney Diseases, University of Wales College of Medicine, Cardiff Royal Infirmary, Cardiff CF2 1SZ.

protein diet has been shown to be beneficial in some models of chronic renal failure in which hyperfiltration occurred.^{10 11} Such a diet, by preventing the compensatory increase in blood flow to remnant glomeruli, protected them from further sclerotic changes and delayed the onset of renal failure.⁶ Similarly, in man dietary management of chronic renal failure has proved beneficial: a low protein diet not only alleviates the symptoms of uraemia but also slows the progression of the underlying nephropathy.¹² Maschio *et al* suggested that the effect was optimal when the diet was introduced early in the course of the disease,¹³ but the response of individual patients is quite variable, with some patients improving dramatically while others remain unaffected.

We undertook this study to determine some of the factors that might influence the response of patients with chronic renal diseases to a low protein diet. From the patients' responses to the diet we were able to make extrapolations about the underlying pathophysiology of their nephropathies.

Patients and methods

The study was divided into two parts.

LONG TERM STUDY

In this first phase we aimed at determining the long term response of different nephropathies to a low protein diet.

Patients—We studied 39 patients (22 men and 17 women). Their mean age at the beginning of the study was 59 (range 18 to 71). At the onset of the study the mean (SEM) serum creatinine concentration was 241 (28) $\mu\text{mol/l}$ (2.7 (0.3) mg/100 ml). The patients comprised 14 with chronic glomerulonephritis, 10 with chronic tubulointerstitial nephritis (predominantly chronic pyelonephritis), nine with hypertensive nephrosclerosis, four with polycystic kidney disease, and two with diabetic nephropathy.

Protocol—Patients were studied for six months while taking a normal diet and then for another six months while taking a low protein diet.

Diet—The dietary protein intake prescribed during the low protein period was 0.5 g/kg body weight/day. The diet was also low in phosphate (700 mg/day) and calcium (350 mg/day). Patients with hypocalcaemia were given supplements of calcium carbonate 1.5 g/24 hours. A high energy intake (10.5–12.5 MJ (2500–3000 kcal)/day) was achieved through supplementation with carbohydrate and polyunsaturated fats. The patients' dietary intake was reviewed once a month by one of us (AM-T) and assessed at interviews as well as by dietary questionnaires. Nitrogen balance and dietary protein intake were estimated by calculating the urea nitrogen appearance.¹⁴

Assessment of progression of chronic renal failure—Patients were seen as outpatients at monthly intervals, when their weight and blood pressure were checked. Plasma urea, electrolyte, creatinine, and urate concentrations, fasting serum lipid concentrations, and 24 hour urine excretion of creatinine, urea, electrolytes, and protein were also measured at each visit. The rate of progression of renal failure was assessed from the slopes of the reciprocal of serum creatinine concentration against time.¹ Using this mathematical conversion of serum creatinine concentration other workers have documented a linear progression of renal failure with time, implying that loss of renal function occurs at a constant rate.^{1 2 15} Accordingly, persistent changes in such slopes after dietary interventions are likely to reflect the influence of diet on chronic renal failure.

SHORT TERM STUDY

The second part of the study explored the short term effects of dietary protein loading and restriction on the renal function of patients with chronic renal failure.

Patients—We studied the first 12 patients who volunteered to participate. Eleven had completed the previous study, and most of them had subsequently elected to continue taking a low protein diet. The patients comprised seven men and five women with a mean age of 52 (range 45 to 65). Four had chronic pyelonephritis, four chronic glomerulonephritis, and four hypertensive nephrosclerosis. Renal function was severely impaired in this group at the beginning of the study (mean creatinine clearance 27 (3.6) ml/min).

Protocol—All the patients were receiving a low protein intake (0.5 g/kg body weight/day) when they entered the study. They were given a high protein diet for two weeks and then switched to a low protein diet for another two weeks.

Diet—The low protein diet in this short term study differed from the one used in the long term study: although the protein content was comparable, it was supplemented with sodium chloride, calcium carbonate, and phosphate to match the content of the high protein diet. Therefore the two experimental diets differed only in their protein content. With the low protein diet the mean intakes were: protein 46 (3) g/day, sodium 126 (11) mmol(mEq)/day, calcium 1343 (62) mg/day, and phosphorus 1453 (55) mg/day. The high protein diet provided 129 (56) g protein/day. Both diets provided 10.7 (0.5) MJ (2553 (128) kcal)/day. The dietary intake and the ratio of serum urea to creatinine concentrations were assessed at interviews and by dietary questionnaires.

Assessment of changes in renal function—Patients were tested on days 0 (low protein diet), 14 (high protein diet), and 28 (low protein diet). Their weight and blood pressure were checked on each occasion. Plasma urea, electrolyte, and creatinine concentrations and 24 hour urine excretion of creatinine, electrolytes, urea, and protein were measured fortnightly. Glomerular filtration rate was measured as endogenous creatinine clearance and as clearance of edetic acid labelled with chromium-51 by the single injection method.¹⁶ Effective renal plasma flow was estimated by the single shot method of clearance of Hippuran labelled with iodine-131.¹⁷ Renal vascular resistance was calculated for individual patients by dividing their mean arterial blood pressure by the effective renal plasma flow.

STATISTICAL ANALYSIS OF RESULTS

Results were expressed as means (SEM). The reciprocals of serum creatinine concentrations were plotted against time for individual patients; a negative value for the slope of the linear regression curve implied declining renal function. The Mann-Whitney U test was used to estimate the significance of differences between groups of patients. Paired Student's *t* test was used to compare results in the short and long term studies for individual patients. The relation between variables was estimated by linear regression analysis. A probability of 5% was used as the criterion of significance.

Results

LONG TERM STUDY

General observations—Compliance with the low protein diet was good, and the mean protein intake was 0.52 (0.25) g/kg/day. Only three patients withdrew from the study, at an early stage, as they had difficulties adhering to the diet. The results in these three patients were not included in the analysis. Blood pressure was controlled satisfactorily in most hypertensive patients, with diastolic readings between 90 and 100 mm Hg. No significant difference in blood pressure was observed between the nephropathies. The low protein diet reduced plasma urea concentrations but had no significant effect on serum phosphorus concentrations. Patients' weight was stable throughout the year of the study. Their nitrogen balance, as judged by the urea nitrogen appearance (+4 (0.4) g/24 h), was positive (+1 (0.3) g/24 h), and no reduction in serum albumin concentration was observed.

Effect of low protein diet on progression of chronic renal failure—Renal function as judged by serum creatinine concentration and creatinine clearance was comparable between the four major nephropathies at the onset of the study. The rate of decline in renal function in all the patients was constant, with a high correlation coefficient (0.82 (0.06)) between the reciprocal of serum creatinine concentration and time. The rate of decline was comparable between the nephropathies. We observed an improvement in renal function with the low protein diet; after its introduction the overall rate of decline in renal function in the 36 patients studied over six months decreased significantly ($p < 0.05$). The response to the dietary protein restriction varied considerably between the nephropathies. Patients with chronic tubular disorders (tubulointerstitial nephritis and polycystic kidney disease) responded well to the diet, showing a significant difference in the slope of the reciprocal of serum creatinine concentration over time before and during the diet ($p < 0.025$), while patients with chronic glomerulonephritis and hypertensive nephrosclerosis had a poor response. Within these two major groups patients with chronic pyelonephritis had the best response with an appreciable slowing of the rate

of decline of their renal function ($p < 0.025$). On the other hand, patients with hypertensive nephrosclerosis had a poor response to the diet with only one out of nine patients improving. Interestingly, this patient had only one kidney after unilateral nephrectomy for nephrolithiasis. He improved dramatically while taking the diet, the slope increasing from -2 to $+0.72$. Blood pressure control in this patient was unchanged throughout the observation period. Patients with chronic glomerulonephritis showed a heterogeneous functional response to the diet ($p < 0.05$), improving considerably in some patients but continuing to deteriorate in others (fig 1).

FIG 1—Effect of low protein diet on course of chronic renal failure in different nephropathies (chronic glomerulonephritis ($n=12$, $\bullet$); chronic tubulointerstitial nephritis ($n=9$, $\blacksquare$); hypertensive nephrosclerosis ($n=9$, $\blacktriangle$); polycystic kidney disease ($n=4$, $\blacklozenge$)). Top: Changes in reciprocal of serum creatinine concentration during low protein diet (mean (SEM)). Bottom: Changes in slopes of reciprocal of serum creatinine concentration against time (six months) before and after low protein diet. Negative values (slopes) indicate decline in renal function.

Effect of low protein diet on proteinuria—In an attempt to determine the reason behind the heterogeneous response of patients with chronic glomerular diseases we looked at the effect of the diet on proteinuria. A significant reduction in proteinuria was observed in all patients with proteinuria ($n=17$) receiving the low protein diet ($p < 0.025$). In addition, in patients with chronic glomerulonephritis the response of proteinuria to dietary restriction seemed to discriminate between patients whose renal function did or did not improve. There was a good correlation between the extent of reduction in urine protein excretion during the low protein diet and the improvement in creatinine slopes of individual patients ($r = 0.76$, $p < 0.01$) (fig 2). It seemed, therefore, that the patients with chronic glomerulonephritis whose proteinuria was reversed by dietary protein restriction had the better chance of a favourable overall response to the diet.

SHORT TERM STUDY

General observations—The patients' dietary compliance through this phase was remarkable. Many patients developed symptoms (anorexia, nausea, and vomiting) during the period of high protein intake, and some developed gastrointestinal intolerance to the oral phosphate supplements. Despite these side effects, however, they remained compliant, although two stopped the phosphate supplementation. The ratio of plasma urea to creatinine concentration accurately reflected the dietary protein intake: it rose to 110 (10) during the high protein diet and subsequently fell to 40 (3) during the low protein diet ($p < 0.025$).

Effect of variations in dietary protein on renal plasma flow—Protein loading led to a significant increase in effective renal plasma flow ($p < 0.025$). Similarly, the reduction in dietary protein intake led to a

FIG 2—Effect of low protein diet on proteinuria in chronic glomerulonephritis. Top: Correlation between decrease in proteinuria (mean value during normal diet minus mean value during low protein diet) and changes in slopes of reciprocal of serum creatinine concentration against time (slope during normal diet minus slope during low protein diet) in individual patients with chronic glomerulonephritis. Negative values indicate further decline in renal function. Bottom: Each point represents mean proteinuria over six months in individual patients during normal and low protein diets. The six patients whose proteinuria decreased significantly during the low protein diet had a significant concomitant improvement in renal function.

decrease in renal plasma flow, though of a smaller magnitude ($p < 0.05$). The magnitude of the changes in renal plasma flow, however, varied between the nephropathies; all four patients with chronic pyelonephritis responded to the diet while only two of the four in each of the two other groups did. Renal vascular resistance fell significantly during the high protein diet ($p < 0.05$) and increased during the low protein diet (table).

Effect of dietary protein variations on glomerular filtration rate—None of the 12 patients showed a significant change in glomerular filtration

Effect of changes in dietary protein on renal function (values are means (SEM)). Values were obtained on day 0 (low protein diet), day 14 of high protein diet, and day 28, after two weeks of low protein diet

	Low protein diet	High protein diet	Low protein diet
Glomerular filtration rate (ml/min)	27 (3.6)	24 (2)	24 (3)
Effective renal plasma flow (ml/min)	154 (28)	224 (28)**	180 (19)**
Filtration fraction	0.17 (0.02)	0.11 (0.11)**	0.13 (0.01)*
Renal vascular resistance (mm Hg/ml/min)	0.89 (0.09)	0.60 (0.07)**	0.67 (0.07)

Significance of difference between test value and value during preceding dietary period: * $p < 0.05$, ** $p < 0.025$.

rate during the two diets. Changes in filtration fraction were, therefore, inversely related to changes in renal plasma flow. Finally, we observed good correlations in individual patients between their short term (two weeks) changes in renal plasma flow, and in renal vascular resistance, during the low protein diet and their long term (six months) changes in renal function with a similarly restricted diet ($r = 0.76$, $p < 0.01$) (fig 3). It seemed, therefore, that acute changes in clearance of Hippuran during a low protein diet predicted the long term functional response to a similar dietary restriction.

FIG 3—Correlation between changes (improvement) in slopes of reciprocal of serum creatinine concentration against time (six months) (slope during normal diet minus slope during low protein diet) and percentage decrease in effective renal plasma flow after two weeks of low protein diet.

Discussion

Preventing renal diseases from progressing to end stage renal failure continues to be a challenge to medical science as well as a growing social and economic problem in many countries. In Britain the number of patients with end stage renal failure requiring dialysis is increasing every year while available facilities remain limited.¹⁸ Therefore medical interventions that might delay the onset of terminal uraemia and, perhaps, one day prevent it are of paramount importance. The slow progression of chronic renal failure offers the ideal opportunity for such treatment, but our limited knowledge of the mechanisms that have a role in progressive renal scarring make such a task more difficult. Recently, research has focused on the factors affecting the progression of nephropathies.³ Brenner *et al* advocated that glomerular compensatory hyperperfusion and hyperfiltration were the common pathway of most nephropathies to end stage renal failure.³ This interesting and challenging concept is based on observations made in the remnant kidney⁶ and, to a lesser extent, in the diabetic nephropathy⁷ models of experimental renal failure. Similar observations were made as early as 1966 by Lubovitz *et al*, who noted the presence of hyperperfused supernephrons in experimental pyelonephritis.⁸ These authors and others,¹⁹ however, failed to detect such supernephrons in experimental glomerulonephritis. Blantz and Wilson observed

glomerular hypoperfusion and decreased filtration in severe progressive experimental glomerulonephritis. Glomerular vasoconstriction has since been shown to be mediated by both the α adrenergic system²⁰ and synthesis of thromboxane.²¹

From these experimental data it appears that the glomerular response to injury is to some extent determined by the nature of the original renal insult; glomeruli when spared at the onset or when mildly damaged are capable of compensatory adaptive changes. On the other hand, when the glomeruli are severely affected at the onset of the nephropathy they become ischaemic with little scope for functional adaptation. Both these pathways lead to end stage renal failure in animals.

In man progression of chronic renal failure occurs at a constant rate with little deviation from a straight line until end stage failure occurs.¹⁵ This observation allowed us to study the effect of a low protein diet on the course of the nephropathies without a crossover therapeutic trial. A low protein diet, known to improve the outcome of chronic renal failure in man,¹² was shown for the first time in our study to have a selective, variable effect on different nephropathies. Patients with predominantly non-glomerular disorders responded well, while patients with chronic glomerulonephritis or with hypertension nephrosclerosis failed to improve significantly with the same diet.

In hypertensive nephrosclerosis, in which the vascular arteriolar lesions are diffuse with resulting glomerular ischaemia, a low protein diet had no beneficial influence on the rate of decline of the renal function. Interestingly, the only patient with this disease who improved had only one kidney. This observation is in keeping with the known haemodynamic pattern of glomeruli in experimental hypertension; Azar *et al* showed that glomerular vasoconstriction and ischaemia predominated in the two kidney hypertension models,²² while in the one kidney model Bank *et al* observed that compensatory vasodilatation overcame the hypertensive ischaemic tendency.²³

In patients with chronic glomerulonephritis the response to restriction of dietary protein varied and might have reflected the heterogeneity of remnant glomerular morphology and function. In these patients focal and segmental glomerular hyperperfusion and hyperfiltration could occur with a favourable response to a low protein diet. On the other hand, when the lesions are diffuse and severe with concomitant vascular sclerosis such a diet has little chance of success.

The good response to the diet of patients with chronic pyelonephritis suggests that progressive scarring in man, as in experimental animals, is mediated by a massive increase in glomerular perfusion with subsequent glomerulosclerosis. In this disease progressive renal failure is likely to be haemodynamically mediated, as urinary reflux²⁴ as well as recurrent infections²⁵ do not seem to affect the late course of the disease.

Another potential beneficial effect of restriction of dietary protein was the observed reduction in proteinuria. The onset, severity, and persistence of proteinuria in chronic glomerular disorders have always been poor prognostic indicators.²⁶ Proteinuria in itself has been incriminated in the progression of glomerular scarring.²⁷ The reduction in proteinuria in our study may reflect the improvement of renal structural damage or, more probably, may represent the reversibility of glomerular overperfusion and filtration.

We showed in this study that renal vascular reactivity may be severely affected by renal diseases. We believe that the extent of the response of the renal vasculature to changes in dietary protein might hold the key to the overall response of individual patients to a reduction in their protein intake; regardless of the underlying nephropathy, in patients whose renal plasma flow decreased during a low protein diet, loss of renal function was slowed.

Finally, it would appear from our data that the loss of renal functional reserve is a universal finding in chronic renal disease; all our patients when challenged with a high protein diet failed to show an increase in their glomerular filtration rate.

Accordingly, patients with chronic renal failure could be divided into two groups; those with fixed filtration but reversible

perfusion, who responded to a low protein diet and had a good prognosis, and those with fixed filtration and perfusion resistant to dietary interventions, whose disease progressed relentlessly.

In conclusion, we believe that although a low protein diet is beneficial in slowing the progression of chronic renal failure, such a dietary effect depends on the underlying nephropathy and the nature of the glomerular perfusion pattern. Patients with increased or reversible glomerular perfusion are likely to be the ones with mild focal glomerular involvement. They are the most likely to benefit from dietary treatment. Patients with severe vascular and diffuse glomerular disease, as well as fixed renal perfusion, are unlikely to improve with such a diet. In the future the therapeutic approach to patients with chronic renal disease might have to be tailored to the underlying nephropathy once its haemodynamic profile has been established. Meanwhile, early introduction of dietary protein restriction should be seriously considered in patients with chronic renal failure.

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Regional variations in British alcohol morbidity rates: a myth uncovered? I: Clinical surveys

RICHARD W LATCHAM, NORMAN KREITMAN, MARTIN A PLANT, ALEX CRAWFORD

Abstract

Officially recorded rates of many alcohol related problems are much higher in the north than in the south of Britain. To try to shed some light on this the pattern and threshold for use of psychiatric and medical hospital services for alcohol dependence, abuse, and psychosis were studied in three areas differing greatly in official rates of alcohol related problems—namely, the Highland and Tayside regions in Scotland and part of the South East Thames region in England. The disparity in psychiatric admissions for alcohol dependence, abuse, and psychosis

were found to be largely explained by admission policies which reflected geographical factors.

The results of this study did not support the conventional view that rates of treated morbidity due to alcohol are appreciably higher in the north.

Introduction

Officially recorded rates of many alcohol related problems are substantially higher in the north of Britain than they are in the south.¹⁻⁴ The rate of first admissions to psychiatric hospitals for alcohol dependence, abuse, and psychosis is 12 times higher in the Highland region than it is in southern England. Information available about regional patterns of alcohol consumption has been very limited and is conflicting. While some evidence indicates that there is a decreasing gradient in heavy drinking from the north west to the south east,^{5,6} other data suggest that community alcohol consumption levels in Scotland are almost indistinguishable from those south of the border.⁷

We present data from one of two separate yet complementary studies. Both were related to the Highland and Tayside regions in Scotland and part of the South East Thames region in England. These three areas were selected because of their differences in official rates of alcohol related problems. In 1981

University Department of Psychiatry, Royal Edinburgh Hospital, Edinburgh EH10 5HF

RICHARD W LATCHAM, MB, MRCPsych, research psychiatrist, MRC unit for epidemiological studies in psychiatry

NORMAN KREITMAN, FRCP, FRCPsych, director, MRC unit for epidemiological studies in psychiatry

MARTIN A PLANT, BSc, PhD, senior research fellow, alcohol research group

ALEX CRAWFORD, BA, MSc, research fellow, alcohol research group

Correspondence to: Dr R W Latcham.