Review Article

Management of progressive renal failure: the role of dietary manipulations

A.M. El Nahas

Northern General Hospital, Herries Road, Sheffield S5 7AU, UK.

In the majority of patients with chronic renal failure (CRF), the underlying nephropathy continues to progress well after the initiating events have subsided.¹ As a result, renal function in these patients declines relentlessly with time as functional renal tissue is progressively destroyed. Such progressive decline in renal function occurs in most patients at a constant and predictable rate.² This should allow for the testing of the efficacy of therapeutic interventions aimed at slowing the progression of CRF. Unfortunately, the development of such therapies has been hampered in the past by our limited knowledge of the pathophysiology of the underlying renal and glomerular scarring processes. Recently, major advances have been achieved in this field which might suggest more rational and successful therapies.

The progression of CRF is known to be affected by factors such as patients' age and sex,³ underlying disease,⁴ genetic profile and immune environment.⁵ Similarly, in individual patients the severity of proteinuria and systemic hypertension⁴ can influence the rate of progression of their nephropathy. So far the management of CRF has been confined to the symptomatic relief of uraemic symptoms, treatment of renal osteodystrophy and control of hypertension.

Recent observations by Brenner and his colleagues in experimental animals suggest that renal haemodynamic factors play a preponderant role in the initiation and progression of CRF; following an initial reduction in functional renal mass, compensatory haemodynamic changes take place in the remnant glomeruli. These are brought about by changes in glomerular arteriolar resistances. They are characterized by glomerular vasodilatation, hyperperfusion and hyperfiltration when the initial glomerular lesion is mild or absent⁶ and by glomerular vasoconstriction with subsequent ischaemia when the vessels or glomeruli are severely damaged at the onset.⁷ Both an increase in glomerular blood flow or in glomerular vascular resistances could lead to a compensatory increase in

filtration rate secondary to intra-glomerular hydrostatic hypertension (Figure 1). Glomerular hypertension and hyperfiltration would damage the endothelium layer which in turn would stimulate platelet aggregation and glomerular capillary thrombosis. Such glomerular micro-atherosis, combined with subsequent ischaemic tubulo-interstitial atrophy and calcification, would lead to end stage renal failure.

The relevance of these experimental observations to CRF in man remains to be determined. However, they shed some light on the mechanisms of action of some dietary interventions aimed at slowing the progression of CRF. Such therapies could be directed at reversing the early compensatory glomerular haemodynamic adjustments and/or the prevention of the late glomerular cellular damage and subsequent glomerular thrombosis. Finally, interventions could also aim at preventing the destruction of the renal tubules and their calcification. Dietary manipulations designed to achieve some of these goals are currently being evaluated.

Low protein diets

As early as 1939, Farr & Smadel showed that a low protein diet (LPD) can considerably reduce the severity of experimental CRF.⁸ Since then, their observations have been confirmed by many workers in a variety of models of CRF in the rat.^{9,10} In these animals, LPD reduces proteinuria, slows the progression of the underlying nephropathy and delays death from uraemia.⁹ Such diet reverses the early compensatory glomerular hyperperfusion and hyperfiltration.¹¹

In man, up to the late sixties, low protein diets were confined to the symptomatic management of terminal uraemic symptoms. More recently, Johnson *et al.* observed that such diet delays the progression of CRF and postpones the requirement for dialysis therapy.¹² This was later confirmed by others who showed that diets low in protein and supplemented with essential amino acids¹³ or their keto-analogues¹⁴ were equally

Correspondence: A.M. El Nahas, M.R.C.P., Ph.D.
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Figure 1 Compensatory glomerular haemodynamic alterations. G: normal glomerulus; G': hypertrophied, hyperperfused and hyperfiltrating glomerulus; G'': atrophic, ischaemic and hyperfiltrating glomerulus; A = afferent arteriolar resistance; E = efferent arteriolar resistance. G': In chronic tubulo-interstitial nephritides; afferent > efferent vasodilatation leading to compensatory intra-glomerular hydrostatic hypertension with subsequent hyperfiltration ($\Downarrow$). G'': In chronic glomerulonephritides; efferent > afferent vasoconstriction, leading to compensatory intra-glomerular hydrostatic hypertension with subsequent hyperfiltration ($\Downarrow$).

beneficial. It was also claimed that the early introduction of a LPD enhanced its efficacy; initiation of such dietary therapy was recommended when serum creatinine levels did not exceed $200 \mu\text{mol/l}$.¹⁵ We noted that the beneficial effect of LPD was maximum in chronic tubulo-interstitial nephritides where the remnant glomeruli, as in their experimental counterparts, are relatively spared and capable of reversible hyperperfusion and hyperfiltration. Finally, we also observed that LPD reduces the magnitude of proteinuria in chronic glomerulonephritis.¹⁶ This was later confirmed by others in patients with nephrotic syndrome.¹⁷

While all these studies give reason for considerable hope and optimism, some doubts and controversy persist as to the potential benefit and side effects of LPD in the management of CRF. Briefly, a low protein intake decreases creatine and creatinine intake¹⁸ and might also interfere with their metabolism.¹⁹ Moreover, some degree of undernutrition²⁰ with loss of muscle mass could also contribute to a reduction in serum creatinine values. Unfortunately, the majority of studies conducted so far on the effects of LPD on progression of CRF have relied solely on serial estimations of serum creatinine as a marker of renal function. In view of the limitations of serum creatinine estimation on a low protein intake, these results and interpretations warrant some caution.²¹

Clearly, more studies are required where serial renal function assessments are made using isotopes. In the meanwhile, LPD (0.5 g/kg of body weight/day) should be restricted to the management of patients with advanced CRF (serum creatinine $> 600 \mu\text{mol}$). This should be done with careful monitoring of their nutritional status.²¹ Concomitantly, a high calorie intake should be encouraged ($> 35 \text{ kcal/kg/day}$) in order to prevent catabolism and maximize the utilization of the limited protein supply.²²

Low phosphate diets

In experimental animals, controversy has taken place over the actual benefit of low phosphate diets in CRF. While some authors reported a considerable improvement in renal function on such diets²³ others have attributed this effect to an overall reduction in food and protein consumption.²⁴ However, more recent data have confirmed that a reduction in phosphate absorption by aluminium-containing resins decreases proteinuria, and protects rats from severe glomerulosclerosis.²⁵ Similarly, the use of diphosphonates²⁶ as well as inhibitors of calcium phosphate precipitation and crystallization have proved beneficial in slowing progressive renal failure and preventing nephrocalcinosis.²⁷

In man, most low protein diets are equally restricted in phosphate. It is therefore difficult to determine the respective benefit of nitrogen and phosphate on chronic renal failure. However, in one study, severe phosphate restriction (< 500 mg/24 hours) was found to be synergistic with a low nitrogen diet in improving renal function.²⁸ A restricted phosphate intake (300 to 600 mg/24 hours) should be supplemented by an adequate (> 1 g/24 hours) intake of calcium. In this respect calcium carbonate supplementation should prove suitable to increase calcium consumption and simultaneously decrease phosphate absorption. This would negate the need for aluminium containing phosphate binders with their inherent toxicity in CRF.

Dietary lipids

It was postulated by Moorhead *et al.* that the hyperlipidaemia of CRF and of patients with nephrotic syndrome, could accelerate the underlying renal scarring process.²⁹ While confirmation of this hypothesis is awaited, many studies have examined the role of manipulations of dietary polyunsaturated fatty acids on the progression of experimental CRF; diets high in linoleic acid decrease experimental hypertension, reduce proteinuria and prevent severe renal histological damage.³⁰ Changes in the dietary fish oil (eicosapentenoic acid – EPA) content of animals with CRF has so far led to conflicting results; while some reported an improvement,³¹ others showed an acceleration of the course of a model of experimental CRF.³² Diets rich in polyunsaturated fatty acids are likely to have a dual effect on the glomerular scarring process; they could affect the early compensatory haemodynamic changes by modifying the levels of renal prostanooids,³³ and they are likely to have an inhibiting effect on platelet aggregation³⁴ and the late intra-glomerular thrombosis.

In man, diets supplemented with EPA have so far been shown to reduce the hyperlipidaemia and plasma viscosity of patients with CRF.³⁵ These diets also reduce systemic blood pressure in essential hypertension.³⁶ The role of such dietary manipulations on the progression of CRF in man is currently being evaluated.

Dietary carbohydrates

While most research has so far centred on the nephrotoxicity of dietary protein and phosphate, little attention has been paid to the effects of carbohydrates

on the failing kidney. Limited available experimental, data suggest that a high sucrose intake accelerates the nephropathy of ageing rats,³⁷ as well as the renal scarring in diabetic³⁸ and sub-total nephrectomized³⁹ animals. The relevance of these findings to the progression of CRF in man remains to be explored.

Dietary monovalent and divalent cations

In experimental models of CRF, restriction of dietary sodium intake has led to conflicting results; while some authors reported a reduction in proteinuria and a prevention of severe renal scarring in remnant kidneys and glomeruli upon dietary sodium restriction,⁴⁰ others failed to confirm these data using a sodium free diet.⁴¹ In man, it is likely that dietary salt restriction, by influencing systemic blood pressure, might favourably affect the progression of CRF.

Little is known about the effects of dietary potassium manipulations on renal scarring. A high potassium intake, like a salt restricted one, could reduce systemic hypertension.⁴² However, in advanced CRF, the risks of hyperkalaemia might preclude dietary potassium supplementation.

Finally, the modification of calcium intake, like that of sodium and potassium, could influence systemic hypertension.⁴² In experimental CRF, a low calcium diet has proved as detrimental to the progression of the renal scarring as a high phosphate diet.⁴³ In patients with CRF, calcium supplementation of their phosphate restricted diet is encouraged.

Conclusions

It is likely that, in the future, dietary manipulations in CRF will prove successful in slowing the progression of the underlying nephropathy. It is hoped that a better understanding of the pathophysiology of chronic renal scarring in man will lead to more rationalization of dietary therapy; dietary interventions might have to be tailored to the type and stage of the nephropathy treated. It is clear that more research and clinical trials are warranted before well defined and safe dietary guidelines could be drawn for patients with CRF.

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