NUTRITION IN RENAL FAILURE

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INTRODUCTION

The present review will consider nutritional support problems in acute renal failure (ARF) and chronic renal failure (CRF) patients, chronic ambulatory peritoneal dialysis (CAPD) and those receiving regular haemodialysis (HD) treatment. For many years little advance had been made in the nutritional management of ARF until it was understood that such patients should receive protein and adequate energy input. Nevertheless, there is still a very high mortality rate in hypercatabolic ARF patients and this is partly related to their poor nutritional support. Studies have shown (Lee & Talbot, 1989) that relying on oral or enteral nutrition for such patients is bound to lead to inadequate intake, and there is a growing move afoot to suggest that all ARF patients, irrespective of gut function, should have their complete nutrition given intravenously.

With respect to CRF the pendulum has swung from considering low-protein diets simply as palliative treatment in advanced CRF to the now more cautious approach suggesting that low-protein diets given early in progressive renal failure, i.e. serum creatinine between 150 and 200 μmol/l, might considerably delay end-stage renal failure. Many problems remain in this area with respect to (*a*) the mechanisms by which low-protein diets work, (*b*) the patients who can best benefit from this treatment, (*c*) the effects of treatment of other intercurrent problems and (*d*) ensuring that diets are palatable and patients are given adequate dietary instruction.

By and large, with respect to haemodialysis patients, there are few nutritional problems compared with earlier years, though nutritional problems are a continuing source of concern in CAPD patients, particularly in the elderly.

ACUTE RENAL FAILURE

ARF is associated with a wide variety of serious and potentially lethal disorders but is one of the few diseases from which complete recovery is possible.

There have been considerable improvements in ARF mortality rates over the last 50 years.

In the Korean war the overall mortality of sixty-one patients with post-trauma ARF treated by HD was 65%, which was significantly lower than the 91% mortality in oliguric ARF in World War II without HD (Teschan *et al.* 1960).

The first comparative study of the beneficial effect of HD by Kleinknecht *et al.* (1972) found a significant reduction in morbidity and mortality between early and late HD. The respective mortality rates for these two groups were 29 and 42%. This effect of HD was confirmed by Conger (1975) in a prospective study of eighteen patients from the Vietnam war to exclude the possibility of time-related effects.

Nutritional support is specifically aimed at providing nutrients capable of influencing the net loss of body cell mass that accompanies ARF and the commonly associated injury and sepsis. The optimal conditions of composition, quantity and administration have been the subject of much investigation; advances in the understanding of the catabolic process have led to regimens which have demonstrably reduced the degree of catabolism and improved mortality rates.

ARF patients often have associated injury and infection and it is known that sepsis, burn injury and trauma cause a loss of cellular protein. In patients with sepsis or accidental injury negative nitrogen balance occurs (Cuthbertson & Tilstone, 1969; Beisel *et al.* 1967), and the magnitude of the N loss indicates the size of the catabolic response. The high N losses result from the increased catabolism of muscle protein, and there is an increased production of 3-methylhistidine, a non-metabolizable amino acid (AA) arising primarily during degradation of skeletal muscle (Long *et al.* 1975). Although it is difficult to differentiate the effects on protein metabolism of ARF from those of associated injury or infection, it has been possible to show that ARF *per se* is a catabolic event. Persike & Addis (1949) showed in rats that 24 h after bilateral nephrectomy (BNX) the urea appearance rate (UAR) was higher than in rats with only 25% of normal kidney tissue or normal rats, and Fröhlich *et al.* (1974) found an increased rate of hepatic gluconeogenesis and ureagenesis after BNX in rats compared to sham-operated or normal rats.

In ARF the catabolic hormones, plasma glucagon (Bilbrey *et al.* 1974) and plasma cortisol concentrations (Englert *et al.* 1958) are raised and partly explain the increased catabolism. Glucagon infused into normal subjects caused an increased urea production from increased gluconeogenesis from glucogenic AA (Marliss *et al.* 1970). Raised corticosteroids increase protein degradation (Nishizawa *et al.* 1978) and stimulate interleukin-1 (IL-1) production (Dinarello, 1979), whereas serum urea is decreased after adrenalectomy in acutely uraemic BNX rats (Bondy *et al.* 1949; Schaefer *et al.* 1988). Schaefer *et al.* (1989) showed that in BNX rats the infusion of a glucocorticoid antagonist lowered myofibrillar proteinase activity, decreased plasma 3-methylhistidine concentration and reduced serum glucose and urea concentrations.

It has been suspected for some time that a substance released from injured tissue may induce catabolism in initially normal organs. It has been suggested that IL-1 is the initiating factor in the proteolysis seen with sepsis, fever and injury (Baracos *et al.* 1983; Dinarello, 1984). Endotoxins cause monocytes to release IL-1, which stimulates prostaglandin E_2 production in muscle. This in turn leads to the release of lysosomal proteases, which catabolize proteins in this tissue. Giving IL-1 to healthy animals induces fever, raises serum insulin and glucose concentrations, increases skeletal and collagen protein degradation, AA mobilization and oxidation, and hepatic protein synthesis (Yang *et al.* 1981; Dinarello, 1985).

HD is known to increase protein catabolism in CRF patients. Ward *et al.* (1979) found that HD increased urea-N appearance (UNA) by 27% in CRF patients. This increase in protein catabolism has recently been related to IL-1 induction and release. Monocytes can

be stimulated to release IL-1 by blood–HD membrane contact, especially cuprophane membranes (Port *et al.* 1987), microbial product contamination of dialysate (Bingel *et al.* 1986) and sodium acetate (Bingel *et al.* 1987; Port *et al.* 1987).

Arisi *et al.* (1989) studied the effect of the prostaglandin inhibitor indomethacin before and during HD on UNA 2–3 h after HD in six CRF patients. The indomethacin group had a significantly reduced UNA (116 mg N/h) post HD when compared with the indomethacin-free group (216 mg N/h). This suggests that the increased catabolism on HD in CRF is at least partially stimulated by prostaglandins and that indomethacin might reduce catabolism and improve N balance. This may be the case in ARF patients as they also have an increased protein catabolism on HD, as demonstrated by an increased UNA (Talbot *et al.* 1989*b*).

The acute nature of the disease influences the nutritional status of ARF patients and is largely determined by previous health, the nature of the insult, and the presence of associated complications and injuries. It is the associated complications and injuries that largely determine the degree and rate of catabolism.

Bull *et al.* (1949) and Borst (1948) demonstrated that the provision of large amounts of exogenous energy could reduce UAR. Berlyne *et al.* (1967) used an ARF diet (9·21 MJ (2200 kcals) and 2·6 g N/d as high-quality protein) with a high intake of non-protein energy and a protein intake lower than that required for normal subjects. This diet reduced the UAR and patients looked less emaciated.

Abel *et al.* (1973) reported a double-blind trial. Twenty-eight patients were daily given approximately 13·8 g essential AA (EAA) with 6·0 MJ (1424 kcal) of D-glucose as a 50% solution. At the same time twenty-five patients received, on average, 6·9 MJ (1641 kcal) of D-glucose as a 50% solution but no EAA. The EAA supplement improved survival, the overall mortality for the D-glucose-receiving patients was 56%, whilst in the AA group it was 25% (non-controlled study).

Baek *et al.* (1975) studied the effect of a fibrin hydrolysate on survival. They gave fibrin (5·2 g N/d) and glucose (4·2 MJ; 1000 kcal) or glucose alone intravenously to 129 post-operative ARF patients in an uncontrolled trial. There was 70% mortality in the glucose group whilst in the AA group it was 46%. However, the blood urea rise did not stabilize, as had been previously reported when only EAA and glucose was given (Dudrick *et al.* 1970; Abel *et al.* 1973), possibly because of the addition of non-essential N.

Rainford (1981, 1987) compared the effect of dialysis and total parenteral nutrition (TPN) on survival over a 25-year period. He divided his patients into three groups: (1) 1958–1964 patients had a mean predialysis blood urea of 71 mmol/l and an energy intake of less than 4·2 MJ (1000 kcal); of 221 patients, 48% survived: (2) 1965–1975 mean predialysis blood urea 33 mmol/l and an energy intake of less than 8·37 MJ (2000 kcal); of 246 patients, 58% survived: (3) 1976–1980 predialysis blood urea of less than 33 mmol/l and an energy intake of 12·6 MJ (3000 kcal), 9 g N and continuous insulin infusion; of eighty-five patients, 71% survived.

All groups were significantly different from each other with respect to survival rates. The major difference between groups 1 and 2 was one of early dialysis, although partial parenteral nutrition was given. The main difference between groups 2 and 3 was the introduction of TPN.

Spreiter *et al.* (1980) reported on fourteen hypercatabolic ARF patients given varying intakes of AA (14–224 (mean 74) mg N/kg per d) and hypertonic glucose (25–297 (mean 128) KJ (6–71 (mean 30) kcal)/kg per d. Increased nutrient intake correlated significantly with improved N balance for both glucose and AA.

Feinstein *et al.* (1983) compared five patients given 2·3 (SD 0·1) g N/d in the form of

EAA with six patients infused with 11·3 (SD 1·9) g N/d in the form of non-essential amino acids (NEAA). Both groups received similar energy intakes but no significant improvement in N balance was found with the higher N intake.

Pelosi et al. (1981) studied forty-six post-traumatic ARF patients, treated with HD at 24–48 h intervals. All patients were in negative N balance, but eleven patients given a full profile AA glucose solution (42 mg EAA-N + 114 mg NEAA-N/kg per d, glucose 126–167 kJ (30–40 kcal)/kg per d) were less negative than the five who were given an isoenergetic EAA-glucose solution (28 mg EAA-N/kg per d). Thirty patients given glucose alone (126–167 kJ (30–40 kcal)/kg per d) were in greater negative N balance than the other two groups.

Proietti et al. (1983) studied forty patients who were assigned to one of three groups. Group 1 received 80–100 mg N/kg per d with EAA:total N 4·13 and branched-chain AA (BCAA):EAA 0·424. Group 2 received 80–120 mg N/kg per d with EAA:total N 4·17 and BCAA:EAA 0·754. Group 3 received 85–150 mg N/kg per d with EAA:total N 3·79, and BCAA:EAA 0·6. All groups were given an energy:N ratio of 350–400:1. Group 3 received enteral nutrition with parenteral BCAA, whilst the other groups were given TPN. Group 3 patients who received the highest BCAA:EAA ratio had a significantly lower negative N balance. The authors recommended the combined use of parenteral BCAA and enteral nutrition and that a balanced AA intake should be given with an EAA (g AA):total N ratio of > 4 and a BCAA:EAA ratio of > 0·5.

To determine the degree of N loss found in patients with ARF and the effects of increasing N intakes twenty-four patients were recently studied with ARF of differing aetiology and N intakes varying from 31 to 200 mg N/kg per d (Talbot et al. 1989a). Uraemia was managed by intraperitoneal dialysis (three patients), HD (three patients), continuous arterio-venous haemofiltration (CAVH; eight patients), combined therapy (nine patients) or no treatment (one patient). They received either TPN with fat, carbohydrate, a full-profile AA solution and vitamin and mineral supplements (fourteen patients), or a commercial enteral feed (six patients), or both (four patients). The energy: N ratio was 200:1. All output (urine, vomitus, faeces, aspirate and drainage), HD effluents and CAVH filtrates were collected and the total N and urea content measured. The excretion of 3-methylhistidine was used as an index of endogenous protein catabolism. N-balance study periods varied between 3 and 8 d and each patient contributed one observation period.

Fig. 1 shows N intake, loss and balance in three catabolic rate groups and demonstrates the N deficit in these patients. All groups received a similar mean N intake.

Table 1 presents the percentage of prescribed intake received. Patients fed enterally received a significantly lower percentage of the prescribed intake than those fed intravenously. TPN resulted in 84% of the prescribed intake. This supports Rainford's (1981) view that in ARF TPN is essential to ensure an adequate supply of nutrients.

In the work of Talbot et al. (1989a), using multiple linear regression analysis it was shown that only 50% of an increased N intake was wasted as urea, up to an intake of 200 mg N/kg per d. This value is similar to those obtained in other studies. A 47% wastage was shown in five oliguric ARF patients given TPN when urea appearance was measured on days between dialyses (Mirtallo & Fabri, 1984). Radrizzani et al. (1986) gave TPN to malnourished patients and found an improvement in N balance of 56% (approximately 44% urea appearance). The Talbot et al. (1989a) value is also similar to the 45% N intake contributing to N output in critically injured patients given TPN for 6 d post trauma (Iapichino et al. 1984). The urea generated from N intake did not increase dialysis requirements, which confirms Mirtallo & Fabri's (1984) findings. The results do not support findings of Feinstein et al. (1981, 1983), who carried out a double-blind controlled
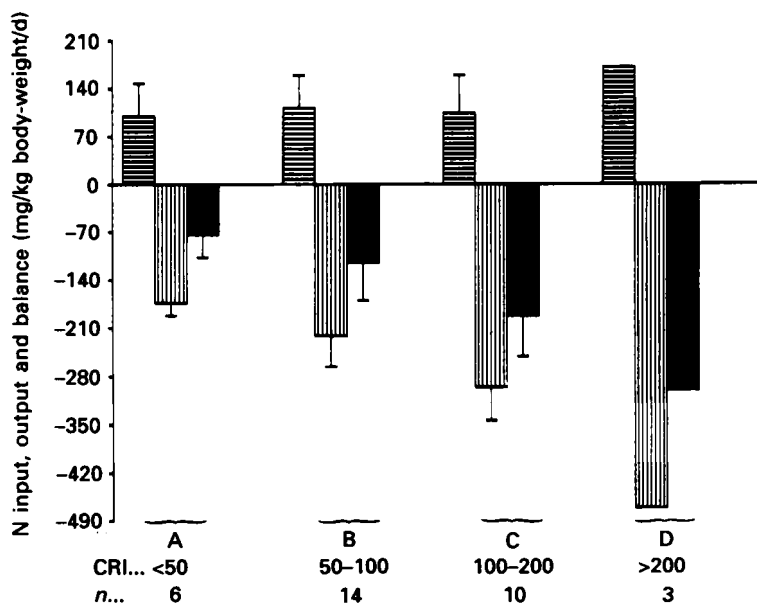
Fig. 1. Nitrogen-balance studies on twenty-four acute renal failure patients. Note deteriorating N balance with increasing catabolic rate index (CRI); also little change in N input in spite of increasing CRI. (▤), N input; (▥), N output; (■), N balance (mg N/kg body-weight (BW) per d). Values are means and standard deviations represented by vertical bars. The CRI was modified from Bistrian (1979) and calculated as follows

$$CRI = UNA - (0.5 \times NI) + 43 \text{ mg N/kg per d},$$

where UNA = urea nitrogen appearance; NI = nitrogen intake; 43 represents 43 mg N obligatory nitrogen loss.

Table 1. *Percentage of prescribed nitrogen intake received with different feeding methods*

(Mean values with their standard errors)

	Mean	SEM	No. of patients
Enteral			
Oral	52·4	6·1	5
NG	53·7	15·6	5
All enteral	53·0	7·9	10
Intravenous			
IV only	84·0	3·0	19
IV and NG	97·1	18·2	3
All intravenous	85·8	3·5	22

NG, nasogastric; IV, intravenous.
There were no significant differences between means for oral and NG groups in the enteral group or between means for IV only and IV and NG groups in the intravenous group. The mean for 'all enteral' group was, however, significantly different from that for the 'all intravenous' group ($P < 0.001$).

study with two different N intakes and concluded that the higher N intake only resulted in an increased urea appearance and not an improved N balance.

There was, in the findings of Talbot *et al.* (1989a), a close relationship between the regression slopes of N intake with both urea appearance and N balance (both slopes being 0·5). This is understandable as urea appearance is the main determinant of N balance. The

variation in N losses other than urea did not, therefore, have a significant effect on the regression slope, since non-urea-N was not related to either N intake or catabolism. The significant improvement in N balance ($P < 0.02$) with an increase in N intake supports other clinical studies (Spreiter et al. 1980; Mirtallo & Fabri, 1984). Mean N loss was twice the mean N intake (N loss 223 mg N/kg per d, N intake 113 mg N/kg per d). Consequently, most patients had a markedly negative N balance, and no patients were in positive balance. If all patients had received a N intake of 200 mg N/kg per d, and allowing for 50% N wastage, only one patient would have been in positive N balance.

In attempts to control protein catabolism it has been found that leucine or its analogue α-ketoisocaproate can affect protein synthesis and degradation.

Goldberg & Tischler (1981) incubated rat diaphragm with leucine and found that protein synthesis was increased, whilst degradation was decreased. They concluded from other studies on incubated rat diaphragm that leucine had a direct stimulatory effect on protein synthesis, and its metabolites decreased protein degradation.

Further, the addition of keto-acid analogues of BCAA to the infusion fluid for the liver of normal rats led to an increased protein synthesis. The infusion of branched-chain keto acids in starving, obese human subjects decreased N wasting (Sapir & Walser, 1977). This effect was also found when only α-ketoisocaproate was given to starving obese subjects (Mitch et al. 1981).

There are few studies of BCAA or keto acids in ARF. Proietti et al. (1983), showed that a high BCAA:EAA ratio given to ARF patients resulted in a less negative N balance. However, the infusion of keto acids showed no beneficial effect on plasma urea concentration or survival when compared with EAA in dogs made acutely uraemic by BNX (Brissac et al. 1981). It remains to be shown if α-ketoisocaproate decreases protein degradation in ARF.

There is also evidence that the infusion of glutamine can improve N balance in catabolic patients. After surgery (Kapadia et al. 1982), injury (Askanazi et al. 1980b), sepsis (Roth et al. 1982), and glucocorticoid administration (Muhlbacher et al. 1984) intracellular glutamine concentration in skeletal muscle is halved and glutamine efflux from muscle increases by a factor of 3. There is a simultaneous decrease in the plasma glutamine concentration and an increased uptake of glutamine by the intestinal tract (Souba & Wilmore, 1983). The provision of exogenous glutamine might prevent this glutamine pool depletion, but glutamine is unstable in solution, hydrolysing to ammonia and pyrollidonecarboxylate which may be toxic. However, stable glutamine-containing dipeptides can be infused and these are rapidly hydrolysed to the constituent amino acids (Albers et al. 1988). Furst et al. (1989) gave catabolic patients a glutamine–alanine dipeptide solution or isonitrogenous isoenergetic TPN. The muscle glutamine pool was maintained in the dipeptide group whilst it was reduced in the control group, and N balance was better in the dipeptide group relative to the control group. Thus, in ARF, where patients are similarly catabolic, protein depleted and probably glutamine depleted (plasma glutamine concentration is decreased), there may be benefit by infusing glutamine-containing dipeptides.

Some studies in patients without acute renal failure suggest that there is a limit to the amount of N that can be utilized to improve a negative N balance. Ang et al. (1983) infused three different levels of N (7·9, 11·9 and 15·8 g N/d) as part of a TPN regimen into malnourished patients and found that protein synthesis plateaued at 11·9 g N/d. Shizgal & Forse (1980) gave TPN with different amounts of N to depleted hypercatabolic patients and found a positive correlation between N intake and N balance at intakes less than 204 mg N/kg per d. However, there was no improvement in N balance with higher intakes. Similarly, Wolfe et al. (1983) found that protein equilibrium was not improved with intakes

above 224 mg N/kg in patients with burns. Finally, Greig *et al.* (1987) fed septic patients with 191 or 366 mg N/kg and found no significant difference in N balance between the two levels of intake after 5 d.

Energy requirements are related more to associated catabolic events such as trauma or infection than the effects of uraemia. These requirements can be approximated from values derived from normal subjects (Wilmore, 1977*a*), and increased if sepsis or trauma are present, according to the degree of catabolism. In a study of post-operative and trauma patients with ARF the energy required to achieve N balance was 209 kJ (50 kcal)/kg per d (Feinstein *et al.* 1981), 50% greater than the recommended intake for healthy sedentary men.

There is no consensus on the most suitable energy substrate in the critically ill. In normal subjects the provision of exogenous non-protein energy decreases N excretion, and is related to the administration of both fat and carbohydrate (Wilmore, 1977*b*). In resting normal subjects, the provision of carbohydrate alone decreases urinary N excretion, but fat alone does not affect the rate of N loss of fasted subjects. When energy (fat or carbohydrate, or both) is given with N to normal human or animal subjects both energy sources improve N retention. This is also the situation in sepsis patients without malnutrition (Roulet *et al.* 1983). However, in hypercatabolic patients (Woolfson *et al.* 1979) a rapid decrease in N excretion was found with carbohydrate infusion. Similar energy as fat failed to exert the same effect (Wilmore, 1977*b*). These different responses may be due to the different neurohormonal signals between normo- and moderately catabolic, and hypercatabolic patients. In the latter the neurohormonal signals are to effect accelerated gluconeogenesis and override the ability of the body to adapt the metabolism to various energy sources. However, the administration of excess carbohydrate to energy requirements results in excessive carbon dioxide production, which may lead to respiratory problems in the critically ill (Askanazi *et al.* 1980*a*); thus both carbohydrate and fat should be used.

Hyperinsulinaemia with hyperglycaemia is a common finding in both experimental (Arnold & Holliday, 1979) and clinical (Kokot & Kuska, 1973) ARF and is also a frequent finding in hypercatabolic states (Wilmore, 1976). In patients with trauma or sepsis but normal renal function the hyperglycaemia is mainly due to increased hepatic glucose production (Wilmore *et al.* 1980), but there is also resistance of peripheral tissues to the hypoglycaemic effect of insulin (Brooks *et al.* 1984).

Glucose intolerance in ARF is primarily due to peripheral insulin resistance, because insulin-stimulated uptake of glucose by perfused hindquarters of ARF rats is reduced (Clark & Mitch, 1983) whilst hepatic glucose uptake is normal (Mondon *et al.* 1978).

It is unlikely that the reduced glucose uptake in muscle is the only factor responsible for reduced glycogen synthesis in muscle (Clark & Mitch, 1983) because glycolysis would also be reduced and this is not so (May *et al.* 1985). The reduced glycogen synthesis appears to be due to a lower glycogen synthase (EC 2.4.1.21) activity (May *et al.* 1985). Kahn (1978) found normal sensitivity to insulin for glucose uptake, glycogen synthesis, glycolysis and glucose oxidation in rats with ARF, which suggests that ARF causes post-receptor defects in insulin-mediated glucose metabolism (Kahn, 1978).

Although insulin is known to play an important part in AA metabolism, there is little information available on the effects of insulin on AA in uraemia. In normal man insulin is an anabolic hormone that enhances AA transport and stimulates protein synthesis (Wool, 1969; Fulks *et al.* 1975).

If the insulin resistance known to occur in CRF, ARF and post injury also included AA metabolism this could partly explain the increased net release of AA from muscle and the decrease in intracellular free AA found in CRF (Alvestrand *et al.* 1983). However, the action of insulin on the transport of α-amino-isobutyrate, cycloleucine (Arnold & Holliday

(1979) and leucine (Garber, 1978) was inhibited in ARF and CRF rat muscle in vitro, whilst the effect on alanine was enhanced (Garber, 1978) and the inhibition of muscle tyrosine and phenylalanine release was normal (Harter *et al.* 1979). More recently, Alvestrand *et al.* (1988) found a normal inhibition of AA release from leg tissues and normal alanine uptake by splanchnic tissue in response to hyperinsulinaemia in uraemic patients. It appears, therefore, that the phenomenon of insulin resistance does not apply to AA transport in uraemia.

One of the problems of providing ARF patients with sufficient nutritional intake has been the necessity to infuse large volumes of fluid, with the likely complication of extracellular fluid overload. This has been alleviated over the last few years by the advent of CAVH (Kramer *et al.* 1982). This has allowed the removal of large volumes of fluid together with small-molecular-weight solutes and the simultaneous infusion of fluids containing drugs, nutrients and electrolyte replacement. As this is a continuous therapy, feeding would need to be continued whilst CAVH was in progress. This could potentially lead to high AA losses in the filtrate, whereas with intermittent HD feeding can be stopped during the therapy. However, Paganini *et al.* (1982) claimed that AA losses with 39 h of CAVH were low compared to 5 h of HD (Wolfson *et al.* 1982) whilst intravenous feeding was in progress. However, Talbot (unpublished results) found no difference in AA-N losses (mg N/kg per d), averaged over a minimum 3 d of observation, between CAVH and HD therapies, with continuous TPN infusions during both treatments.

One disadvantage of CAVH is the need to carefully monitor fluid replacement. This problem has been removed by the use of 'nutritional HD' (Feinstein, 1987). With this method nutrients are added to the dialysate and the dialysate flow rate is reduced to allow adequate diffusion of nutrients into the blood: 78 % of nutrients are absorbed by the blood.

In conclusion, it is clear that mortality rates remain at an unacceptably high level in ARF, although the use of early dialysis has had some impact on this. Also, some nutritional studies have had encouraging results on the effect of nutrition on both mortality and rate of recovery of renal function, but so far these have been inconclusive and contradictory.

As there is evidence that ARF patients can utilize up to 200 mg N/kg per d and that N requirements for treatment by intraperitoneal dialysis, CAVH or HD are in excess of this (Talbot, 1989*a*), we recommend that this intake be given to reduce muscle wasting, impaired immune competence, wound healing and morbidity.

As has been found in other groups of patients, it is likely that there is a limit to the N intake that will improve N balance. Consequently, therapies used to combat the effect of catabolism may well concentrate on pharmaceutical measures such as the use of indomethacin (Arisi *et al.* 1989), anti-glucocorticoids, (Schaefer *et al.* 1989) and the addition of glutamine peptides to TPN solutions (Furst *et al.* 1989).

CHRONIC RENAL FAILURE

A number of observations (Rosman, 1984; Maschio *et al.* 1982; Brenner *et al.* 1982) have shown that the introduction of low-protein diets for patients with CRF of various aetiologies can decelerate the rate of deterioration of renal function. Much of the work hitherto published has been uncontrolled, not comparing like with like, and the associated conditions, e.g. hyperuricaemia, hypertension, hyperphosphataemia, have been handled in different ways, therefore possibly masking the effects of low-protein diets or, indeed, leading to alternative interpretations. However, this seeming lack of knowledge about how low-protein diets work in such patients is not a reason for not seriously considering their use.

It is also well understood that a number of factors can interfere with the monitoring of

such patients, e.g. basically measuring serum creatinine. For example, a decreased meat intake will automatically bring about a reduction in serum creatinine and likewise an increased meat intake can lead to a transient rise. Diminution in muscle mass will also lead to a reduction in serum creatinine without implying any change in renal function. Other factors, too, can influence serum creatinine via renal function, e.g. control of hypertension, control of hyperphosphataemia, control of hyperuricaemia and even possibly control of serum lipid abnormalities.

It is considered that low-protein diets have an effect by the so-called Brenner (Brenner et al. 1982) mechanism in patients whose kidneys are still vasoreactive to a protein challenge. Immediately the problem arises in trying to differentiate those patients who can respond to a protein challenge and those who can not. Whether this is best done by a protein-meal challenge or via an intravenous bolus of AA made comparable to an oral intake is the subject of current research. Furthermore, whether a single reading should be used or, say, two or three readings over a 3-month period is again a matter of debate. Some studies have suggested that patients with pyelonephritis respond best of all to low-protein diets, whereas other studies have suggested that patients with polycystic renal disease respond best and yet others that those with glomerulonephritis do so. In the final analysis there is no doubt that many patients in all subdivisions of renal disease can respond. Whether a low-protein diet should be given in isolation or always associated with a reduced phosphate intake is a matter of continuing debate (Maschio et al. 1982). There is still debate as to how long a low-protein diet may be given and still have beneficial effects; this partly reflects the relatively short period of time over which such diets have been studied.

There can be little doubt that low-protein diets (0·6 g protein/kg body-weight; high biological value protein) should be used early in the management of CRF when the clinician has observed a progressive rise in the serum creatinine over, say, a 3-month period (Walls, 1987; Lee, 1978). Since in some patients the disease process may fluctuate wildly, to institute a low-protein diet on the basis of one reading alone may be to condemn the patient to dietary restriction at a time when no benefits might accrue.

The introduction of low-protein diets must be made with the help of a qualified dietitian who can afford to spend some time with patients, who naturally have different likes and dislikes and different intellects, to ensure optimal results from dietary restriction. This is particularly so when often patients in the early stages of their CRF syndrome have little in the way of symptoms and, therefore, compliance might be difficult.

It is also important to make sure that other problems such as hypo- or hypercalcaemia, hyperphosphataemia, hyperuricaemia, hyperlipidaemia, (usually hypertriglyceridaemia), hypertension and any urinary tract infections are dealt with at the same time. For example, treating an occult urinary tract infection may considerably improve metabolic acidosis and thereby alter the renal excretion of creatinine.

It is important that patients are told how they might benefit by the introduction of a low-protein diet, not only in terms of diminished secondary side effects of their disease, e.g. less pruritis and nausea, but also by the possible considerable retardation of the time when they might anticipate dialysis treatment. Furthermore, if this approach could be extended, then a greater case for primary transplantation from a large cohort of CRF patients maintained on low-protein diets could become a reality. This might, in turn, reduce the overall need for dialysis facilities and would have considerable cost-effective implications.

When patients are first started on low-protein diets, they should be seen at regular intervals, say two monthly, to ensure (a) compliance, (b) an effect is obtained and (c) to ensure no complications with the diet itself. Once they seem to be stable, then such patients can be reviewed four- or six-monthly depending on progression of events. Also, it is important that these patients can have access at any time to expert dietetic advice. At

review, not only their physical status, but also their serum biochemistry, is reviewed and note made of their nutritional status in terms of serum albumin, simple anthropometric measurements, e.g. skinfold thickness, mid-arm muscle circumference, weight, serum calcium and phosphorus and serum uric acid. Blood pressure should be checked regularly.

It is also advisable that the clinician, even with the most compliant patient, should do random spot checks to ensure that dietary compliance is being maintained. This can be done either by requesting an occasional 24 h urine collection for the measurement of urinary urea or urinary sulphate excretion.

Whether the supplementation, substitution or addition of EAA or keto-acid analogues have anything to offer over and above a strict low-protein diet remains to be seen (Lee & Jackson, 1981; Mitch et al. 1982; Mitch, 1988). It has been argued that by having available EAA supplements then the nature of the protein intake can be derestricted inasmuch as high and low biological value proteins can be eaten, thereby increasing dietary choice (Lee et al. 1980, 1987). Such an approach is probably more valuable in patients with advanced CRF (serum creatinine > 850 μmol/l) where symptomatic relief is sought more than any pretence at particular deceleration of renal function deterioration. Again, for some patients, particularly in the elderly age group, the modified protein intake with EAA supplementation may be the only form of treatment that can be offered because dialysis options are not available, based on medical criteria, not lack of facilities. A number of studies have clearly shown the value of EAA supplementation in advanced CRF and modern preparations of the AA supplements are quite palatable. At present the case for keto-acid analogues (Lee & Jackson, 1981; Mitch et al. 1982; Gretz et al. 1983) has not been proven and compliance with their intake can be problematic. Furthermore, when one considers that large numbers of CRF patients are being dealt with, then there is a certain attraction to keeping to simple low-protein diets alone rather than complicating the issue by either giving EAA supplements or by the addition of keto-acid analogues.

The emphasis of nutritional support in CRF has been based on the N content of modified protein intake (Mitch, 1988). Whether or not the nature of the energy intake has an important effect in certain types of patients remains to be determined. Certainly, in some animal experiments, it has been shown that carbohydrate (glucose) loading can adversely affect renal function. Thus, low-protein diets have a valuable role in the management of CRF patients, but those most likely to benefit have yet to be defined more precisely, and the optimal time of introduction for them is still under debate.

In diabetic nephropathy there is a growing school of thought that suggests that protein restriction should be introduced when the serum creatinine is still normal but the patient has been found to have microalbuminuria. Thus, whilst every effort must be made to control the hyperglycaemia, early introduction of low-protein diets in the diabetic may yield further benefit. Indeed, the literature allows the clinician to tell the diabetic patient that from the time they have proteinuria, then end-stage renal failure is only 3–5 years away. This is further complicated and accelerated if they have hypertension. Fortunately, with the advent of angiotensin-converting enzyme inhibitors, like Captopril and Enalapril, combined with a low-protein diet, the outlook for diabetic nephropathy may be considerably improved.

CHRONIC AMBULATORY PERITONEAL DIALYSIS

Most nephrologists would agree that if a CAPD patient receives 1·25 g protein/kg body-weight then their nutritional requirements will be met, assuming they are well and undergoing three or four 2-l bag exchanges daily (Diamond & Henrich, 1988). The problem arises, however, when patients have recurrent episodes of peritonitis when their dietary

Table 2. *The relationship of serum albumin to cadaveric renal transplantation (Tx) in a cohort of fifty-six patients*

Treatment and outcome	Serum albumin (g/l)
Deaths post nephrectomy*	< 20
CAPD patients	
Successful Tx	> 27†
Failed Tx	22·8‡
Deaths after Tx	< 16·2§
Haemodialysis patients	
Successful Tx	> 29·3†
Failed Tx	28‡
Deaths after Tx	< 24·8§

CAPD, chronic ambulatory peritoneal dialysis.
* Serum albumin concentration is given for six out of eight patients who died. † Lower limit, ‡ mean, § upper limit.

intake falls due to anorexia, when their peritoneal protein loss increases and the patients become generally depressed and apathetic, the 'burnt-out' phenomenon. This picture is compounded in the elderly CAPD patient who may live in social isolation, whose mental agility may have deteriorated and who may be edentulous. Furthermore, elderly patients tend to have predilection for soft carbohydrate foods which, in turn, are easier to prepare and not so expensive. Therefore, the elderly CAPD patient requires expert dietetic advice and support, and often this is sadly lacking.

Thus, the vicious cycle happens whereby a patient has CAPD peritonitis, is brought into hospital, feels anorexic, is given antibiotics, which may cause diarrhoea, they have increased peritoneal loss of protein, they may undergo peritoneal 'lavage' and the serum albumin rapidly drops. Then, because of pressure on beds, the patient is discharged prematurely from hospital back to pyscho-social isolation where there continues to be a diminished food intake, leaving the patient once again prone to infection, their mental and physical dexterity decreases and yet a further episode of peritonitis may occur.

Many CAPD patients will be on active transplant lists. It is important that these patients should go to operation in the best nutritional status.

In a review of a small cohort of patients in our Department (Table 2) it was found that those on CAPD going to operation with a low serum albumin did less well with respect to morbidity and mortality than those with a normal serum albumin. Furthermore, those being transplanted, with an ultra low serum albumin (less than 20 g/l), had a much higher mortality rate. Thus, the expectations of transplantation in a CAPD patient may be poor when they are nutritionally depleted and this may result from simple inanition post-transplantation, the use of catabolic drugs, such as steroids, multiple anaesthetic and surgical interventions, poor previous nutritional status, or pyrexial episodes which for each degree centigrade rise in temperature causes the basal metabolic rate to increase by 12%. Unless such nettles are grasped then considerable resources can be wasted in the unnatural haste to have a patient transplanted, believing that all their ills will come to an end when, in fact, a little more thought spared to getting them into optimal nutritional status before operation could be of benefit. Considerable research is currently underway to see whether the addition of AA to the peritoneal fluid could not only replace any of the N losses associated with CAPD but actually act as a substitution for a poor dietary protein intake. Such an approach has considerable merits provided the AA added to the CAPD fluid do

not prematurely cause, by biochemical reactions, a loss of peritoneal dialysance; that the patient can tolerate, e.g. pain-free, such solutions; and that such preparations remain cost effective.

The alternative approach at present is that any patient who is brought in with CAPD peritonitis and who is anorexic should be given enteral nutrition via a nasogastric tube. Fortunately, with CAPD peritonitis gut function usually remains satisfactory, and it is important to ensure that the patient actually receives their nutritional support via a nasogastric tube (this balanced against the discomfort of inserting a tube) rather than assuming they receive it (see comments on ARF, p. 4). Rarely, depending on the severity of the infection problems in the CAPD patient, is there a case for TPN. Although TPN is clearly costly, compared to time spent in hospital and the possible hazards of undernutrition associated with CAPD peritonitis, the cost and effort are worth the end result. Such an approach is even more important in the diabetic renal failure patient.

REGULAR HAEMODIALYSIS PATIENTS

With modern approaches and better dialysis machines and the use of bicarbonate dialysis malnutrition problems, as part and parcel of regular HD treatment, are far less frequent. Here, again, provided these patients receive 1–1·25 g protein/kg body-weight, then the chances of malnutrition are remote. The actual nutritional losses incurred in 12 h dialysis per week (irrespective of how the hours are divided up per session) are not significant. Although in the past studies have been made as to the effectiveness of giving (a) AA supplements intravenously or (b) adding AA to dialysis fluid, there is really little merit in this approach.

On the other hand, if a regular HD patient has an intercurrent illness, then the nutritional complications of that illness should be dealt with as in a non-renal compromised patient. Thus, if the patient is anorexic, there should be no hesitation to use enteral feeding via a fine-bore tube. Furthermore, every effort should be made to meet their increased nutritional requirements and, if necessary, increase the number of dialysis hours. It is a nonsense to try to reduce the protein intake in such patients in the hope that dialysis hours can be reduced when they are ill. Such an approach will only increase nutritionally related problems, not improve them.

As mentioned previously HD patients coming to operation who are in a poor nutritional status again fare less well than those who are nutritionally replete.

CONCLUSION

Thus, as the literature supports and experience dictates, in patients with ARF or CRF, nutritional support can have a profound impact on the outcome of definitive treatments such as HD, CAVH or cadaveric renal transplantation. It is interesting to note that nutritional support may be the difference between life and death in ARF or, in CRF, may lead to an increased use of the concept of primary transplantation or delay the inevitable onset of CRF and improve the success of cadaveric renal transplantation.

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