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PERSPECTIVES IN RENAL MEDICINE

Protein metabolism in patients with chronic renal failure: Role of uremia and dialysis

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Protein metabolism in patients with chronic renal failure: Role of uremia and dialysis. Individuals with chronic renal failure (CRF) have a high prevalence of protein-energy malnutrition. There are many causes for this condition, chief among which is probably reduced nutrient intake from anorexia. In nondialyzed patients with CRF, energy intake is often below the recommended amounts; in maintenance dialysis patients, both dietary protein and energy intake are often below their needs. Although a number of studies indicate that rats with CRF have increased protein catabolism in comparison to control animals, more recent evidence suggests that increased catabolism in CRF rats is largely if not entirely due to acidemia, particularly if these animals are compared to pair-fed control rats. Studies in humans with advanced CRF also indicate that acidemia can cause protein catabolism. Indeed, nitrogen balance studies and amino acid uptake and release and isotopic kinetic studies indicate that in nondialyzed individuals with CRF, who are not acidemic, both their ability to conserve body protein when they ingest low protein diets and their dietary protein requirements appear to be normal. For patients undergoing maintenance hemodialysis or chronic peritoneal dialysis, dietary protein requirements appear to be increased. The increased need for protein is due, in part, to the losses into dialysate of such biologically valuable nitrogenous compounds as amino acids, peptides, and proteins. However, the sum of the dietary protein needs for CRF patients (of about 0.60 g/kg/day) and the dialysis losses of amino acids, peptides and proteins do not equal the apparent dietary protein requirements for most maintenance dialysis patients. This discrepancy may be due to a chronic state of catabolism in the clinically stable maintenance dialysis patient that is not present in the clinically stable nondialyzed individual who has advanced CRF. Possible causes for such a low grade catabolic state include resistance to anabolic hormones (for example, insulin, IGF-1) and a chronic inflammatory state associated with increased levels of pro-inflammatory cytokines.

For at least three decades, virtually every review on nutrition in advanced chronic renal failure (CRF) underscores two important issues: (*1*) CRF engenders protein-energy malnutrition [1–3] and (*2*) dialysis aggravates protein catabolism [4–6]. Many investigators also suggested that uremia is a catabolic state [7, 8]. Because malnutrition is very prevalent in renal failure patients, there is a tendency to attribute, in part, the malnutrition to this presumed hypercatabolism.

The impetus to write this editorial stems from our perception that (*1*) there are few data to support the view that uremia is inherently catabolic, and (*2*) other than protein and amino acid losses, evidence suggests that additional net protein catabolism related to dialysis is not marked. If there is hypercatabolism associated with dialysis, it is not of a dramatic degree.

In this review, we first summarize data on protein metabolism in CRF rat models. These models have generated substantial literature documenting both increased protein breakdown and decreased protein synthesis, and have contributed much to our present concepts of uremia-associated catabolism. We present data concerning protein metabolism in pre–end-stage renal disease (ESRD) patients and in maintenance hemodialysis and chronic peritoneal dialysis populations. The presentation is organized according to the techniques used, including nitrogen balance, amino acid release across an extremity, and whole-body protein turnover kinetics. The potential roles of dialysis (of both an individual dialysis session as well as maintenance dialysis treatment), metabolic acidosis, insulin and insulin-like growth factor-1 (IGF-1) resistance, and inflammatory cytokines are addressed. The protein and energy requirements are also discussed.

Catabolism, according to Webster's dictionary, is destructive metabolism, that is, in living organisms the breaking down of more complex substances into simpler ones, with the release of energy. In this article, we use the term net catabolism to indicate negative balance. In situations in which degradation, oxidation, synthesis, and protein loss are individually measured, net catabolism or net protein breakdown is the condition in which the

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sum of protein degradation and protein loss exceeds protein synthesis.

PROTEIN METABOLISM IN THE UREMIC RAT MODEL

In citing literature from the rat model, we have included only those articles using the chronic uremic model of 5/6 nephrectomy or unilateral ligation of renal arteries with contralateral nephrectomy. Li and Wassner found that 3-methylhistidine (^{T}N-methylhistidine) release, an index of myofibrillar protein degradation, is elevated to a greater degree in CRF rats as compared with sham-operated controls following a 24-hour fast [9]. During in vivo infusion of ^{14}C leucine, Holliday et al found that following fasting, protein synthesis decreased in both control and CRF rats, but the decrement was greater in CRF rats [10]. Similarly, the same group of investigators found that during an anabolic state, that is, administration of a nutritionally adequate diet following a period of stress, including surgery and a tryptophan-deficient diet, body weight rose briskly in both the sham-operated controls and the partially nephrectomized rats, but muscle protein synthesis, measured by phenylalanine incorporation, was lower in the latter group [11].

In vitro muscle incubation has been a popular research tool and was instrumental in generating substantial literature on muscle protein metabolism. Garber reported increased alanine and glutamine release from muscles of CRF rats, suggesting increased protein degradation [12]. Simultaneously, ^{3}H-leucine incorporation, reflecting protein synthesis, was reduced. He found no evidence of insulin resistance since the addition of insulin to the media corrected both abnormalities [12]. Instead, he proposed that excessive parathyroid hormone (PTH) may be the cause of the exaggerated protein wasting, because incubation of normal skeletal muscle with PTH led to increased protein degradation and reduced protein synthesis [13]. In a series of experiments, Harter et al demonstrated increased tyrosine and phenylalanine release from muscle of CRF rats as compared with controls; the difference was most marked when the rats were fed a 10% casein protein diet [14]. When the casein protein was increased to 20 or 40% of the diet, amino acid release was minimally changed in the controls, but it was markedly reduced in the partially nephrectomized rats, suggesting that a higher protein intake could down-modulate net protein breakdown in CRF. Additionally, they also noted that insulin effectively suppresses protein degradation in the CRF rat muscle. In other experiments, they found that the addition of $25(OH)D_3$, but not $1,25(OH)_2D_3$, reduced protein breakdown in the CRF rat muscle [15]; also, exercise training blunted protein degradation but did not enhance protein synthesis [16].

May, Kelly, and Mitch have contributed enormously to our understanding of the effects of metabolic acidemia on muscle protein metabolism. In perfused hindquarters, May, Kelly, and Mitch found an increase in net protein degradation and a reduction in the insulin-stimulated rise in protein synthesis in CRF rats; bicarbonate treatment reduced protein degradation, but had no effect on protein synthesis [17]. In incubated muscle, Hara et al found that branched-chain amino acid (BCAA) decarboxylation was increased, and its incorporation into protein was reduced in CRF rats as compared with the controls. Sodium bicarbonate supplements suppressed BCAA decarboxylation and, to a lesser extent, also enhanced protein synthesis [18]. Identical metabolic abnormalities were demonstrated in NH_4Cl-induced metabolic acidosis [19]. Recently, Bailey et al showed that the acidemia of CRF activated muscle proteolysis in the rats by stimulating the ATP-dependent ubiquitin-proteosome pathway. This activation was characterized by an increase in the mRNA for ubiquitin and two proteosome subunits as a result of an up-regulation of gene transcription [20]; glucocorticoids were essential for the activation of the ubiquitin-proteosome pathway [21].

PROTEIN METABOLISM IN HUMANS WITH CHRONIC RENAL FAILURE

Do humans with CRF have increased net protein catabolism as do the CRF rats? Data suggest that CRF, even when advanced, does not in itself engender net protein breakdown. During injury or sepsis, classic causes of a hypercatabolic state, energy expenditure is usually high, urea production is augmented, nitrogen balance is negative, and solid tissue loss is accelerated. Patients with acute renal failure also are often highly catabolic; increments of serum urea nitrogen of 20 to 50 mg/dL or more each day, and net protein losses up to 30 to 120 g/day or greater are not uncommonly observed. By contrast, exaggerated ureagenesis is not observed in clinically stable CRF patients.

Nitrogen balance studies

Nitrogen balance is conceptually simple and is measured by the difference between total nitrogen intake and output, adjusting for changes in body urea nitrogen and unmeasured nitrogen losses. However, it is very laborious and time consuming.

Many nitrogen balance studies have demonstrated that patients with advanced CRF who are not undergoing chronic dialysis are able to maintain neutral or positive nitrogen balance with low protein intakes. In several reports, a number of investigators showed that nitrogen balance in such patients was usually negative when protein intake was 20 g/day and became positive with 40 g/day or about 0.55 to 0.60 g/kg/day of protein intake [22–26]. Maroni, Steinman, and Mitch measured nitro-

gen balance in 19 predialysis patients whose creatinine clearances ranged from 3 to 15 mL/min while they were ingesting unrestricted and restricted protein diets; the former ranged from 40 to 90 g protein/day and the latter from 20 to 25 g/day. Nitrogen balance was not different (0.54 and 0.25 g/day, respectively) with the two diets [27]. However, adjusting for unmeasured nitrogen losses of about 0.5 g/day from respiration, sweat, skin exfoliation, nail and hair growth, blood drawing, and other quantitatively less important losses, a measured positive nitrogen balance of about 0.5 g/day is necessary for the balance to be actually neutral. Thus, nitrogen balance was probably slightly negative with the 20 to 25 g/day protein diet.

Kopple and Swendseid [24, 25] and Bergström, Fürst, and Norée [28] further observed that patients with advanced CRF (for example, GFR less than 10 to 15 mL/min) not receiving chronic dialysis therapy also maintained a neutral or positive nitrogen balance with low-nitrogen diets providing 20 g protein/day supplemented with the nine essential amino acids, or a diet providing virtually no protein but containing either 0.55 to 0.60 g/kg/day of a mixture of essential and nonessential amino acids, or about 20 g/day of the nine essential amino acids. Mitch, Abras, and Walser reported neutral or positive nitrogen balance in patients with advanced CRF who were fed diets providing about 22 g protein/day supplemented with a mixture of amino acids and the keto-analogs of essential amino acids [29]. The ability to conserve protein and amino acids may increase dramatically in clinically stable individuals with protein-energy malnutrition, and it is possible that the successful adaptation of CRF patients to these low-protein diets might be due to pre-existing malnutrition. However, although some CRF patients in the foregoing studies may have been malnourished, it is unlikely that substantial malnutrition was present in most of these patients. More important, long-term diet studies designed to examine the effect of low-protein diets on the progression of renal insufficiency have generally showed little or no adverse effects on nutritional status [30–32].

In an earlier study of three patients undergoing hemodialysis, Kopple et al showed that with twice weekly dialysis using the Kiil dialyzer, a diet that provided 0.75 g protein/kg/day for 22 to 31 days appeared to maintain neutral nitrogen balance, whereas a diet providing 1.25 g protein/kg/day for the same duration resulted in positive nitrogen balance [33]. Both diets contained 88% high biological value proteins. In a short-term, seven-day nitrogen balance study of five maintenance hemodialysis patients, Borah et al found that a diet providing 0.5 g protein/kg/day induced a negative nitrogen balance, whereas a 1.4 g protein/kg/day diet promoted a positive protein balance [34]. Slomowitz et al reported that six maintenance hemodialysis patients fed a diet providing 1.13 g protein/kg/day and 37 kCal/kg/day for 21 days each sustained a mean nitrogen balance of 0.57 ± 0.42 g/day [35]. Adjusting for estimated unmeasured nitrogen losses of about 0.5 g/day, the average nitrogen balance in these six patients would be neutral on this diet; however, only four of the six patients were in neutral or positive balance, whereas nitrogen balance was negative in the other two patients. On the other hand, Lim et al reported that seven clinically stable maintenance hemodialysis patients had positive nitrogen balance, not adjusted for unmeasured losses, of 0.58 g/day when they ingested a protein intake of 0.87 g/kg/day for seven days [36]. It should be mentioned that in the investigations of Kopple, Borah, and Slomowitz, study diets were prescribed with no relationship to their usual intake, whereas in Lim et al's study, the patients were given protein and energy intake similar to their customary intake before the study.

Blumenkrantz et al studied nitrogen balance in eight male continuous ambulatory peritoneal dialysis (CAPD) patients who were fed an average of 0.98 g protein/kg/day or 1.44 g protein/kg/day for an average of 18 ± 1.4 (SEM) and 23 ± 2.0 days, respectively [37]. The two diets contained a large proportion of high biological value protein. Nitrogen balance was neutral or positive when the dietary protein intake was approximately 1.1 g/kg/day or greater. Giordano et al reported that a diet providing 1.2 g protein/kg/day maintained neutral or positive balance in seven of eight CAPD patients who were studied for 14 days [38]. In 12 CAPD patients studied with protein intakes ranging from 0.76 to 2.09 g/kg/day, for only about seven days each, Bergström et al found that in most patients, including some individuals with protein intake of less than 1.0 g/kg/day, nitrogen balance was positive [39]. However, after an adjustment for unmeasured nitrogen losses, some patients were in negative protein balance. The magnitude of positive balance was more striking during the early months of dialysis.

Amino acid release from the extremity

Measurement of net amino acid release across a body part is essentially an amino acid balance study for that body part, usually an arm or a leg. The net amino acid release is determined as the product of the blood flow across the body part and the difference between the venous and arterial blood amino acid concentrations. In the postabsorptive state, muscle releases amino acids, which help to maintain plasma amino acid levels and provide substrates for hepatic gluconeogenesis. The greater the degree of proteolysis, the larger will be the net release of amino acids, generally reflected by an increase in arteriovenous amino acid concentration difference, higher in the venous blood.

Deferrari et al and Alvestrand et al found that femoral arteriovenous amino acid differences in the postabsorp-

tive state were not higher in the predialysis patients as compared with normal subjects [40, 41]. If uremic patients were catabolic, one should observe greater arteriovenous amino acid differences. Garibotto et al using the combined techniques of arteriovenous amino acid difference with ^{3}H-phenylalanine kinetics further confirmed that total amino acid release from the forearm was similar in predialysis patients and normal controls [42]. Moreover, net phenylalanine balance across the forearm was not different between the two groups. Thus, there is no evidence of increased proteolysis from the muscles of the pre-ESRD patients.

Whole body amino acid turnover kinetics

Quantitation of whole-body protein turnover kinetics involves infusion of an isotopically labeled amino acid into the plasma amino acid pool. Measurements are then made of the magnitude of isotopic dilution, which under isotope and substrate steady-state conditions, is proportional to the appearance of the same nonlabeled amino acid into the same pool. The appearance of the nonlabeled amino acid is the sum of amino acid release from body proteolysis and protein ingestion. CO_2 production and expired gas isotopic activity (labeled CO_2) are also measured to determine the amount of irreversible oxidation of amino acid to form CO_2. Synthesis is then calculated from the difference between total flux and oxidation. Thus, this technique measures protein breakdown, protein synthesis, and amino acid oxidation. Intake is either zero during postabsorption or of a known quantity depending on the amount of amino acid given during the measurement. In comparing data from different study groups or different experimental protocols within the same groups, the most important information derived would be the net protein balance, that is, and the difference between synthesis and degradation. Net protein balance is normally negative during the postabsorption and is positive only in the fed state [43].

Using [^{15}N, 1-^{13}C] leucine as the tracer, Goodship et al compared protein flux in predialysis CRF patients and normal subjects fed low- and high-protein diets and during the fasted and fed states [44]. They did not find any differences in protein flux between the controls and the CRF patients. Reduced protein intake did not significantly alter any of the flux parameters. Feeding resulted in a marked reduction in protein degradation, an increase in amino acid oxidation, and little change in protein synthesis; these led to a net positive balance. Lim et al found that during a primed-constant infusion of [$^{2}H_3$] and [^{15}N] leucine, protein degradation was not increased, and net protein balance in the postabsorptive state was not more negative in the hemodialysis patients as compared with the controls [45]. In hemodialysis patients, Berkelhammer et al confirmed a lack of increased proteolysis, but they found that amino acid oxidation was higher. Hence, calculated protein synthesis was reduced, and net protein catabolism was greater [46]. It should be emphasized that these patients were acidotic with a mean plasma CO_2 of 18 mmol/L. Such acidosis may have increased the amino acid oxidation rate. Goodship et al measured whole-body protein flux in normal controls and ESRD patients before and after they commenced CAPD. They did not find any difference in the flux rates or net protein balance among the three-study groups [47]. Using [L-^{15}N] lysine as the tracer, Conley et al measured protein flux in CRF children before and after initiation of maintenance hemodialysis. They found that compared with normal children, protein flux was reduced in children who had CRF and children who were undergoing hemodialysis and that the flux rate was directly related to dietary protein intake [48]. None of these previously mentioned kinetic studies showed any increase in protein breakdown or a reduction in net protein balance in the predialysis patients. Furthermore, in the fed state, protein degradation was suppressed to a similar degree in both the control subjects and the CRF patients.

Effect of the dialysis procedure

The concept that dialysis augments protein catabolism is widely accepted in the nephrology community. Obligatory protein and amino acids losses occur during both hemodialysis and peritoneal dialysis. Furthermore, it has been contended that exposure to the hemodialysis membrane enhances protein breakdown. Bioincompatible cellulosic membranes activate complement and monocytes [49], whereas the high-flux biocompatible membranes may allow passage of endotoxin fragments into the blood [50]. Both processes might then cause a release of the inflammatory cytokines. It is possible that these changes might induce net protein catabolism, although this hypothesis has never directly been tested.

In earlier years, Farrell and Hone and Ward et al reported increased urea generation postdialysis and suggested that the hemodialysis procedure accelerated protein degradation [51, 52]. In Borah et al's study, nitrogen balance was always less, either more negative or less positive depending on the protein intake, on dialysis days [34]. Lim et al noted that dialysate nitrogen removal, expressed as g/day, was higher during a two-day interdialytic interval as compared with a three-day interdialytic interval [53]. All of these data were originally considered to be consistent with dialysis-induced proteolysis. While facts remain, interpretation varies. Viewed with today's knowledge, the increased urea generation observed post-hemodialysis is now believed to be due to urea rebound. This phenomenon, which is due to the relatively slow rate of urea equilibration between body compartments, may cause errors in the mathematical calculations of urea kinetics if they were based on a single pool model. Calculation of nitrogen balance from urea kinetics could

be deceiving, and failure to take into consideration the urea rebound tends to overestimate the urea nitrogen appearance. The findings of Borah et al are consistent with obligatory nonurea nitrogen losses into the dialysate. When dialysis parameters were relatively fixed, as in Lim's study, nitrogen loss, measured as g/dialysis, was also relatively constant. Dividing this constant by a factor of two versus three made a significant difference. On the other hand, these results do not absolutely exclude the possibility that there was some increase in net protein and amino acid catabolism during the hemodialysis procedure.

The most convincing evidence that suggests increased protein breakdown induced by hemodialysis was provided by Gutierrez et al [54]. These investigators showed increased amino acid release from the leg during sham hemodialysis in normal subjects using a bioincompatible dialyzer, but not with biocompatible membranes. To further pursue the issue of dialysis-related proteolysis, Lim et al measured whole-body leucine flux continuously before, during, and after completion of hemodialysis in patients using a bioincompatible cuprophane dialyzer. Compared with baseline data obtained before hemodialysis, protein degradation remained constant during and for four hours after hemodialysis. Amino acid oxidation and protein synthesis, on the other hand, were both reduced during dialysis. Conventionally, the mass balance equation dictates that when flux is stable and amino acid oxidation is reduced, synthesis rate is increased ($Q = B + I = C + S$, where Q is total flux, B and I represent breakdown and intake, and C and S, oxidation and synthesis, respectively). During dialysis, the equation, however, needs to be modified as follows: $Q = B + I = C + D + S$, where D is dialysate loss. Because of this D, both synthesis and net balance were reduced. The hemodialysis procedure, therefore, is not catabolic, but rather, anti-anabolic in the sense that protein synthesis was reduced [55].

It has been stated that a biocompatible membrane is less protein catabolic than a bioincompatible membrane. Lindsay and Spanner concluded from their study that hemodialysis with a biocompatible membrane resulted in greater protein anabolism, that is, higher protein intake. At every level of Kt/V, the protein equivalent of total nitrogen appearance (PNA), also called protein catabolic rate (PCR), which in steady-state conditions is assumed to reflect the dietary protein intake, was higher in patients dialyzed with a biocompatible membrane as compared with those dialyzed with the bioincompatible membrane [56]. Since dietary intake was not directly determined, the data could also be interpreted as indicating a greater protein and amino acid loss into the dialysate with the use of a biocompatible dialyzer. In fact, amino acid and protein losses have been documented to be higher with a high flux biocompatible dialyzer [57], and bleach sterilization of the dialyzer may further augment amino acid and albumin losses [58].

Effect of maintenance dialysis treatment

Notwithstanding the evidence from nitrogen balance studies suggesting that the dietary protein requirement is higher in patients undergoing hemodialysis and that dialysis treatment may promote protein catabolism, patients undergoing maintenance hemodialysis can be anabolic and gain solid tissue mass. Lim et al measured whole-body leucine flux longitudinally in the same CRF patients before and after they commenced maintenance hemodialysis treatment, and found that measured dietary intake was constant and identical during the two periods. The results were compared with data obtained from normal control subjects. Prior to maintenance dialysis (after correction of acidemia), these patients had adapted to a lower protein diet with a lower rate of protein degradation and amino acid oxidation, and they maintained protein synthesis at a normal level. Approximately 10 weeks following initiation of maintenance hemodialysis, both protein flux and amino acid oxidation increased, but the magnitude of the increment in amino acid oxidation was less than that of the total protein flux. By mass balance calculations, protein synthesis was increased to a greater degree than the increase in protein degradation, and, hence, net protein balance was improved [59]. Conley et al reported that in children with ESRD who were ingesting different protein diets, at every level of protein intake, protein flux was higher following initiation of maintenance hemodialysis [48]. Thus, as an aggregate, patients undergoing maintenance hemodialysis can have net protein anabolism, especially during the early period following initiation of treatment.

Role of metabolic acidosis

Much evidence indicates that in humans, as well as animals, metabolic acidemia, a common complication of CRF, promotes protein catabolism. This has been observed in both predialysis and dialysis patients. Papadoyannakis, Stefanidis, and McGeown found that correction of acidemia with sodium bicarbonate improved nitrogen and potassium balance [60]. Williams et al changed the diet of predialysis patients from 1.2 g protein/kg/day to an isocaloric but lower protein (0.6 g/kg/day) intake. Two weeks later, while the urea nitrogen appearance declined, skeletal muscle protein degradation, as reflected by the urinary 3-methylhistidine:creatinine ratio, increased. This ratio declined to normal with the bicarbonate supplement [61]. Using the amino acid turnover kinetic technique, Reaich et al found that in pre-ESRD patients, the presence of metabolic acidemia increased both protein degradation and amino acid oxidation [62]. Lim et al found increased amino acid oxidation in the presence of acidemia [59]. In maintenance

hemodialysis patients, Graham et al found increased protein degradation as determined by leucine flux in the presence of acidemia [63]. In this particular study, the increase in protein degradation during acidemia was accompanied by a proportional rise in protein synthesis. As a result, net protein balance was not different in the presence or absence of acidemia.

Insulin and insulin-like growth factor-1 resistance

Insulin and insulin-like growth factor-1 (IGF-1) are potent anabolic hormones; these hormones inhibit protein degradation and stimulate protein synthesis. Resistance to both insulin and IGF-1 has been observed in a number of experiments in the CRF rat model [64, 65]. Thus far, data from human studies indicate that the expected insulin-induced reduction in protein degradation is intact [66, 67]. The insulin-induced increase in protein synthesis was reported to be impaired by Castellino et al [67]. Our preliminary experiment found that during combined insulin and amino acid infusion, protein synthesis in ESRD patients was stimulated to a similar degree as in normal subjects (abstract; Lim et al, *J Am Soc Nephrol* 9:615A, 1998); however, this observation needs further confirmation. In patients undergoing maintenance hemodialysis or CAPD, there is clear evidence for resistance to IGF-1 [68]. However, large doses of recombinant human IGF-1 strongly enhance protein balance in CAPD patients [69].

Cytokines, uremia, and dialysis

The "interleukin hypothesis" states that hemodialysis with a bioincompatible membrane leads to activation of complement and monocytes. This activation releases proinflammatory cytokines that, in turn, induce a constellation of dialysis-related symptoms, including hypotension, leg cramps, nausea, malaise, and headaches [49, 70]. Subsequent measurements confirmed increased plasma levels of several proinflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and IL-6 and IL-8. The increase in circulating cytokines, however, is not confined to patients dialyzed with bioincompatible membranes. Increased plasma cytokines are also found in patients treated with the high-flux biocompatible dialyzers, in peritoneal dialysis patients, and even in patients with CRF not yet in need of dialysis [50, 71–75].

Recently, serum concentrations of acute phase reactant proteins, such as C-reactive protein and α-amyloid protein, have been shown to be elevated in some ESRD patients and to correlate inversely with measures of nutritional status and particularly with serum albumin [76, 77].

In the presence of an inflammatory state, synthesis of albumin is reduced, while that of the acute phase reactant proteins is increased. The elegant work of Kaysen and associates showing that in ESRD patients, reduced hepatic albumin synthesis is a primary cause of hypoalbuminemia, suggests that low serum albumin in CRF patients may be related to an inflammatory state [78]. The foregoing findings have been interpreted by some investigators as further confirmation of the existence of a protein hypercatabolic state engineering protein-energy malnutrition in ESRD patients.

The fact that proinflammatory cytokines cause anorexia, tissue breakdown, and wasting has led the nephrology community to consider them as candidate molecules that participate in a chronic inflammatory process and are an important cause of protein wasting in the ESRD population [79]. Although the issue is not settled, we do not think that these or other proinflammatory cytokines cause a marked increase in the net protein catabolism of stable CRF patients or are the sole cause of protein-energy malnutrition in these individuals for the following reasons: (*1*) The cytokines are equally elevated in predialysis patients, and these individuals have no evidence of net protein hypercatabolism [71, 74, 75]. (*2*) The elevated proinflammatory cytokines are accompanied by elevations of cytokine antagonists, including IL-1β antogonist and the two TNF-α–soluble receptors [71–73]. These antagonists may neutralize the effects of the proinflammatory cytokines. In fact, recombinant soluble TNF-α receptors are now being used to treat a variety of autoimmune/inflammatory diseases [80]. (*3*) The magnitude of increase in both the cytokines and their antagonists is directly proportional to the decline in renal function, suggesting that decreased renal clearances may play a role in the pathogenesis of their increment [71]. (*4*) The correlation between acute-phase reactants and nutritional parameters, such as serum albumin, is of a low order; *r* values between serum albumin and C-reactive protein range from 0.2 to 0.5 [76, 78]. (*5*) In most maintenance hemodialysis patients, the positive acute-phase reactants are not elevated. (*6*) A longitudinal study in maintenance hemodialysis patients showed wide fluctuations in serum C-reactive protein levels even when there were no changes in the dialysis protocol or other treatment procedures (abstract; Kaysen et al, *J Am Soc Nephrol* 9:254A, 1998). These findings may indicate that currently available markers of inflammation are not very precise or sensitive. However, these findings are also consistent with the thesis that inflammation in many ESRD patients is transient and not a persistently serious problem [7]. There are no interventional studies that have tested whether chronic inflammation does increase net protein catabolism and promote protein wasting.

It should be emphasized that theoretically cytokines might contribute to protein-energy malnutrition in CRF and maintenance dialysis patients by causing anorexia. Such an effect would not, in itself, engender hypercatabolism.

Protein and energy requirements

The Food and Nutrition Board of the National Academy of Sciences considered the quantity of dietary high biological value protein necessary to attain neutral nitrogen balance in most healthy adults to be 0.60 g/kg/day [81]. The fact that individuals normally ingest proteins of widely variable biological value and because people commonly incur mild intercurrent illnesses or stresses, the daily dietary protein allowance was raised by about 25% to 0.80 g/kg/day of mixed quality protein [81].

As indicated previously in this article, the ability of patients with advanced CRF not undergoing dialysis to maintain nitrogen balance with low-protein diets appears to be as effective as in normal adults. The magnitude of the reduction in urine urea nitrogen, total nitrogen, or the urea nitrogen appearance with dietary protein restriction in stable CRF patients is similar to that of normal adults [22–28]. Thus, a protein intake of about 0.60 g/kg/day, composed largely of high biological value protein, is generally considered to be adequate for nondialyzed CRF patients. One should emphasize that this amount is only to maintain nitrogen balance and does not include a wide safety margin for individual variability or possibly for a diet composed primarily of low biological value protein.

During hemodialysis, amino acid losses average about 6 to 12 g per treatment depending on whether high-flux dialyzers are employed and whether the patient is fasting or postprandial [82]. With peritoneal dialysis, protein losses range from about 8 to 12 g/day and amino acid losses range from about 3 g/day [83]. Bound amino acid or peptide losses are less well studied and are reported to be about 2 to 3 g with a low-flux dialyzer [84]. To our knowledge, there are no studies of peptide losses during peritoneal dialysis. It is unclear as to how much of the peptides lost into dialysate are metabolic waste and how much of these peptides are biologically valuable.

Assuming maximal losses, in a 70 kg patient, the calculated additional protein needs for hemodialysis patients would be about 0.06 g/kg/day (9 g of amino acids per session, 27 g/week, 3.8 g/day or 0.06 g/kg/day) and about 0.2 g/kg/day for peritoneal dialysis patients (15 g of protein and amino acids per day or 0.2 g/kg/day). If these amounts of protein and amino acid losses are added to the basic protein requirement of about 0.60 g/kg/day established for the predialysis patients, a protein intake of 0.66 and 0.80 g/kg/day should theoretically be sufficient to maintain nitrogen balance in maintenance hemodialysis and chronic peritoneal dialysis patients, respectively. However, according to the nitrogen balance data discussed earlier in this article, the quantity of protein needed to maintain nitrogen balance is greater. A conservative estimate of dietary protein needs would be 0.9 to 1.0 g/kg/day for chronic hemodialysis and peritoneal dialysis patients. However, a more generous protein intake is usually recommended.

A sufficient energy intake is equally important. The recommended daily energy allowance for normal men and women who are 25 to 50 years of age and who are performing light to moderate physical activity is 37 and 36 kcal/kg/day, respectively. For individuals 51 years and older who are performing light to moderate physical activity, the recommended dietary energy allowance is 30 kcal/kg/day [81]. In most studies, estimates of energy needs for maintenance dialysis patients are similar. Lim et al found that resting VO_2 was not different between 14 hemodialysis patients and 8 normal controls [85]. Kopple et al reported that resting energy consumption did not differ between predialysis patients, maintenance hemodialysis patients, and normal controls [35]. Olevitch et al found no increase in energy expenditure during hemodialysis treatment [86]. Ikizler et al, however, reported that ESRD patients have a somewhat higher energy consumption [87]. Virtually all dietary surveys in the ESRD population showed that energy intake is low, ranging from 23 to 29 kcal/kg/day [88]. A sufficient energy intake will reduce the quantity of daily dietary protein necessary to maintain protein balance. An adequate energy intake is protein sparing in the sense that less protein will be degraded by oxidation. Furthermore, a higher carbohydrate intake will increase the secretion of insulin, which is a potent anabolic agent. The National Kidney Foundation Nutrition DOQI Clinical Practice Guidelines on Nutrition in CRF recommend 35 kcal/kg/day for maintenance hemodialysis and peritoneal dialysis patients who are under 60 years of age and 30 to 35 kCal/kg/day for patients who are 60 years or older [89].

SUMMARY AND CONCLUSIONS

In summary, available data indicate that uremia, per se, does not stimulate net protein catabolism. In predialysis patients fed low-protein diets, the ability to conserve protein is well maintained if metabolic acidemia is not present, and there is no concomitant illness. Protein turnover kinetics suggest that the mechanisms of protein conservation include down-regulation of protein degradation and amino acid oxidation and maintenance of protein synthesis at near normal levels. Dialysis promotes protein wasting at least partly because of obligatory protein and amino acid losses into the dialysate. These protein and amino acid losses are approximately 0.06 g/kg/day for three times weekly hemodialysis and 0.2 g/kg/day for peritoneal dialysis and are easily replaced with modest increases in dietary protein intake.

However, two sets of nitrogen balance studies show that hemodialysis patients have greater protein requirements than can be accounted for by these obligatory amino acid and protein losses. Two sets of studies in

CAPD patients show similar results. Whether this unexplained increase in dietary requirement is due to enhanced net protein catabolism engendered by the dialysis procedure is unsettled. One study showed increased amino acid release across the lower extremity during sham hemodialysis with bioincompatible membrane [54].

Chronic inflammation and enhanced levels of cytokines may contribute to this increase in protein requirements. Such inflammation and catabolic cytokines may be induced by the dialysis membrane, the dialysate itself, contamination of peritoneal dialysis with plasticizers, chemical or immunologic reaction to the vascular access or peritoneal catheter, altered bacterial flora in the intestinal tract, or chronic subclinical infection. The increase in net protein catabolism appears to be of a mild magnitude. It should be emphasized that most of the kinetic studies of protein turnover do not show increased net protein catabolism in either maintenance hemodialysis or chronic peritoneal dialysis patients.

It is possible that the apparent discrepancy between nitrogen balance studies, which indicate an increase in protein requirements in maintenance dialysis patients and studies of isotopic amino acid kinetics and amino acid uptake and release across the limbs, which indicate no increase in net protein catabolism, can be explained as follows: There is an alteration in the protein catabolic and/or synthetic state of the maintenance hemodialysis patients that does not actually increase net protein degradation when the patients ingest a diet providing about 1.2 to 1.3 g protein/kg/day. However, this altered state prevents these individuals from adapting normally to lower protein diets, so that a rather modest reduction in protein intake (for example, to 0.80 to 1.0 g protein kg/day) is associated in many patients with a failure to adapt adequately. Hence, nitrogen losses exceed nitrogen intake on these lower protein diets and the patients enter a state of negative nitrogen balance.

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