Application of Branched-Chain Amino Acids in Human Pathological States: Renal Failure

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ABSTRACT During renal failure, abnormalities of BCAA and branched-chain keto acid (BCKA) metabolism are due to both the lack of renal contribution to amino acid metabolism and the impact of renal failure and acidosis on whole-body nitrogen metabolism. Abnormal BCAA and BCKA metabolism result in BCAA depletion as reflected by low plasma BCAAs and cellular valine. BCAA metabolic disturbances can alter tissue activities, particularly brain function, and nutritional status. In dialysis patients, BCAA oral supplementation can induce an improvement of appetite and nutritional status. During chronic renal failure, the aims of nutritional interventions are to minimize uremic toxicity, avoid malnutrition and delay progression of kidney disease. BCAA and BCKA supplements have been proposed to decrease further protein intake while maintaining satisfactory nutritional status. In this setting, BCAAs or BCKAs have not been administrated solely but in association with other essential AA or keto analogs. Therefore, the proper effects of BCAs and/or BCKAs have not been studied separately. Protein restriction together with keto acids and/or essential AAs has been reported to improve insulin sensitivity and hyperparathyroidism and to be compatible with a preservation of nutritional status. Nonetheless, a careful monitoring of protein-calorie intake and nutritional status is needed. A recent meta-analysis concluded that reducing protein intake in patients with chronic renal failure reduces the occurrence of renal death by ~40% as compared with larger or unrestricted protein intake. The additional effect of essential amino acids and keto acids on retardation of progression of renal failure has not been demonstrated. J. Nutr. 136: 299S–307S, 2006.

KEY WORDS: branched-chain amino acids • valine, leucine • renal failure • protein metabolism • low-protein diets • nutrition

Patients with chronic renal failure (CRF) or end-stage renal failure treated by dialysis are characterized by multiple disturbances of amino acid (AA) metabolism, which particularly involve BCAAs. In renal failure patients, abnormal BCAA metabolism is a consequence of: 1) the disappearance of the normal role of kidneys in AA metabolism; 2) the impact of renal failure on both peripheral and hepatosplanchnic nitrogen metabolism; and 3) the possible effects of underlying renal disease on protein and AA metabolism. The abnormalities of BCAA and branched-chain keto acid (BCKA) metabolism result in BCAA depletion, as reflected by the decrease in the concentrations of plasma BCAAs and cellular valine. Abnormal plasma BCAA and BCKA may be responsible for disturbances in organ amino acid exchanges and subsequent organ dysfunction. Therefore, BCAA supplements were proposed in CRF and dialysis patients to improve plasma AA and nutritional status. Moreover, as protein restriction was reported to slow the progression of renal failure, essential AA and KA supplements, including BCAA and BCKA, were proposed to decrease protein intake as much as possible while maintaining protein status. This article refers to recent reviews on BCAA metabolism and therapeutic use during renal failure (1,2).

Branched-chain amino metabolism during renal failure

Role of the kidney in branched-chain amino-acid metabolism. Kidneys are involved in many aspects of protein

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4 Abbreviations used: AA, amino acid; BCKA, branched-chain keto acid; CRF, chronic renal failure; EAA, essential amino acid; GFR, glomerular filtration rate; KIC, ketoisocaproate; KIV, ketoisovalerate; KMV, ketomethylvalerate; LPD, low-protein diet; MDRD, modification of diet in renal disease; VLPD, very low-protein diet.
metabolism, including low-molecular weight protein degradation (3) and AA synthesis (4,5). Moreover, renal AA metabolism plays a key role in acid-base balance regulation via glutamine hydrolysis and ammonia excretion (6–8). Consequently, renal failure can be responsible for altered BCAA production and for overall alterations of BCAA metabolism due to metabolic acidosis.

To our knowledge, no human data are available concerning kidney AA exchanges during the absorptive phase. In dogs, measurements of arterio-venous AA exchange showed that the kidney significantly takes up valine, leucine, and isoleucine after an AA meal (8). Because of the high BCAA-transf erase and low BCKA-dehydrogenase activities in the renal parenchyma, it was proposed that BC AAs are mainly involved in transamination processes and/or ammoniogenesis. During the postabsorptive phase, renal AA exchanges were studied in normal humans: whole-blood renal AA exchanges are characterized by a release of leucine that accounts for one-third of whole-body leucine production, whereas no net renal exchange of valine or isoleucine was noted (9). From these data we can deduce that BCAA metabolism in kidneys is characterized by an uptake of BC AAs in the absorptive phase and by a substantial release of leucine during the postabsorptive phase.

Metabolic acidosis is a common feature during CRF. In such a situation, one priority of protein and AA metabolism is to increase bicarbonate via renal ammonia production and urinary excretion (10,11). Glutamine metabolism alone does not account for whole renal ammonium production. Ammoniagenesis from other AAs, which represents 20% of ammonia production in normal condition, is increased during acidosis (10,12). It is likely that BCAAs are involved in ammoniagenesis during metabolic acidosis. As a matter of fact, it was shown that acidosis stimulates BCAA oxidation in renal tubule cells by increasing both the amount and activation state of branched-chain α-keto acid dehydrogenase through a reduction of branched-chain α-keto acid dehydrogenase kinase (13).

Circulating and cellular branched-chain amino acids. Plasma concentrations of essential AAs (EAAs), except for methionine, are often decreased during untreated CRF as well as during dialysis. Changes in plasma and muscle BCAA observed in CRF and dialysis patients is shown in Table 1. Circulating valine concentrations are decreased in CRF as well as in hemodialysis and peritoneal dialysis patients. The decrease in plasma valine is associated with a decrease in muscle concentrations of valine. It should be noted that valine depletion is consistently reported during renal failure, even in nonmalnourished patients with moderate CRF (9,15). Plasma leucine and isoleucine are inconsistently altered depending on the stage of renal failure. Contrary to valine, muscle concentrations of leucine and isoleucine remain normal during uremia. Low intracellular and extra-cellular valine, frequently together with depleted leucine and isoleucine extra-cellular pools, have been described as a typical BCAA pattern for chronic uremia (15). A preferential catabolism of valine has been proposed to explain the depletion of valine pools during CRF (14,15).

An improvement of plasma and intracellular BC AAs has been reported after BCAA- and particularly valine-enriched supplementation, during hemodialysis (15,16,21), peritoneal dialysis (19), and after the correction of acidosis (22,23). Renal transplantation can achieve a normalization of BCAA status (24,25). Low plasma ketoisocaprate (KIC), ketoisovalerate (KIV) and ketomethylvalerate (KMV), the respective keto analogs of leucine, valine and isoleucine, have been consistently reported during CRF and hemodialysis (18,26–31). Plasma KIC and KMV are correlated with protein intake, glomerular filtration rate and plasma bicarbonate (30,31).

The postabsorptive plasma AA pool can be considered the result of AA release from muscle and kidney, and of AA uptake in the hepatosplanchnic area, the brain and kidney (32,33). In addition to the suppression of renal participation in leucine production, several factors can affect BCAA metabolism during renal failure. Catabolic factors such as acidosis and inflammation are responsible for an increase in muscle breakdown and BCAA degradation. During the postprandial phase, profound abnormalities of hepatosplanchnic AA release also contribute to abnormal plasma AA composition.

Metabolism of branched-chain amino acids in the hepatosplanchnic area. In postabsorptive healthy subjects, hepatosplanchnic AA exchanges are characterized by a large uptake of alanine and glutamine, representing >50% of the total AA uptake (34,35). During CRF, remarkable changes include the decrease in glutamine net uptake and the suppression of serine, valine, and citrulline exchanges (36). In normal conditions, a protein meal is followed by a shift from hepatosplanchnic AA uptake to its release. The AAs released are predominately BCAAs and proline, but also arginine, lysine, threonine, tyrosine, and phenylalanine. As a consequence, the protein meal is followed by an enrichment of arterial blood in EAAs and particularly in BC AAs (34,35,37,38). In CRF patients given a protein meal, the hepatosplanchnic AA exchanges are characterized by an increase of the total AAs released, particularly nonessential AAs (35). Such disturbances in hepatic AA exchanges were shown to induce a 2-fold increase in arterial nonessential AAs without a significant change in arterial BC AAs (38).

Thus, hepatosplanchnic AA exchanges are impaired during CRF, from both quantitative and qualitative points of view. The decrease in hepatosplanchnic utilization of AAs can be responsible of abnormal hepatic protein synthesis and ureagenesis (1). It also participates in the abnormalities of arterial AAs, as shown by the aggravation of these abnormalities after feeding (38,39). Acidosis is implicated in the abnormalities of AA metabolism during the absorptive phase: in rats, acidosis actually induces plasma AA changes similar to those of CRF (40); in CRF patients, variations in arterial concentrations and muscle uptake of BC AAs were reported to be inversely correlated with arterial bicarbonate concentration (39).

Muscle metabolism of branched-chain amino acids. Muscle AA concentrations result from permanent exchanges characterized by an AA uptake during the absorptive phase and an AA release during the postabsorptive phase (32,41). In normal subjects given a protein meal, valine, leucine, and isoleucine account for >50% of muscle AA uptake (34). After the ingestion of an AA mixture simulating an animal

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>CRF</th>
<th>Hemodialysis</th>
<th>Peritoneal dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma valine</strong></td>
<td>↓ (14, 15)</td>
<td>↓ (15–16)</td>
<td>↓ (19)</td>
</tr>
<tr>
<td><strong>Muscle valine</strong></td>
<td>↓ (15)</td>
<td>↓ (15–17)</td>
<td>N (19)</td>
</tr>
<tr>
<td><strong>Plasma leucine</strong></td>
<td>↓ (15)</td>
<td>↓ (15–18)</td>
<td>N (19)</td>
</tr>
<tr>
<td><strong>Muscle leucine</strong></td>
<td>N (15)</td>
<td>N (15–17)</td>
<td>N (19)</td>
</tr>
<tr>
<td><strong>Plasma isoleucine</strong></td>
<td>↓ (15)</td>
<td>N (15–18)</td>
<td>N (19)</td>
</tr>
<tr>
<td><strong>Muscle isoleucine</strong></td>
<td>N (15)</td>
<td>N (15–17)</td>
<td>N (19)</td>
</tr>
</tbody>
</table>

↓ Decreased concentrations; N, concentrations similar to controls.
meal, the study of leg-muscle AA exchanges showed that total AA uptake was greater in CRF patients than in control subjects (+71%) because of an increase in the uptake of nonessential AAs (+156%) (39). BCAA uptake by the leg muscle was, in absolute values, similar to that of control subjects but represented only 30% of total AA extraction, compared with 46% in control subjects. Thus, muscle tissue faces the increased and unbalanced postprandial supply of AAs with an increased and unbalanced uptake (39).

During the postabsorptive phase, low muscle concentrations of valine, together with decreased release have been observed and shown to be responsible for low plasma valine (42,43). Moreover, an inverse correlation between intracellular valine and arterial bicarbonate was reported, showing the role of acidosis in the metabolism of this AA (16). The study of BCKA exchanges in muscle shows that during CRF, the release of KIC and KMV is reduced, whereas KIV is neither released nor taken up by the forearm (31).

In stable CRF patients, the study of forearm protein metabolism following arterial infusion of 3H-phenylalanine shows an increase in both protein synthesis and degradation without change in net proteolysis (43). Interestingly, proteolysis is inversely correlated with arterial bicarbonate concentrations, showing the potential catabolic effect of acidosis. It was shown that when acidosis was corrected by hemodialysis, protein degradation decreased and made it possible to adapt to low-protein intakes (44). Data on isolated perfused rat muscle demonstrates that acidosis induces an irreversible degradation of muscle BCAAs by stimulating BCKA dehydrogenase (45). In acidic rats, it has been shown that muscle BCKA dehydrogenase E1α and BCKA dehydrogenase E2, but not liver BCKA dehydrogenase activities, were stimulated (46). Cortisol, the secretion of which is stimulated by acidosis (47,48), was demonstrated to be necessary for metabolic acidosis to induce both BCAA oxidation (49,50) and ATP-ubiquitin–dependent proteolysis (51). During experimental acidosis, proteolysis and BCAA breakdown are associated with an increase in muscle glutamine synthesis and release (52,53).

Thus, metabolic acidosis both increases protein catabolism, BCAA breakdown, and glutamine release in the muscle and stimulates AA and glutamine metabolism toward ammonium excretion and bicarbonate generation in the kidney (7). Hence, muscle BCAA breakdown appears as an element of an integrated regulatory mechanism for the fight against acidosis (50,53). During chronic acidosis due to CRF such an adaptive mechanism becomes deleterious by inducing a progressive depletion of muscle mass (50).

Hemodialysis itself can interfere with both muscle protein and BCAA metabolism. During a primed-constant infusion of L-[1-13C]leucine, it was demonstrated that hemodialysis resulted in a net catabolic event because protein synthesis was reduced and amino acids were lost into the dialysate (54). Moreover, dialysis sessions are associated with an increase in BCAA catabolism. In particular, hemodialysis is shown to induce an increase in the mRNA levels of glutamine synthase and BCKA dehydrogenase E2 in the muscle (55). Intracellular concentrations of alanine and glutamine were maintained during hemodialysis by augmented release of the amino acids from muscle protein catabolism. In these experiments, although muscle protein breakdown increased intradialysis, the whole-body protein catabolism decreased, suggesting central utilization of amino acids released from skeletal muscle (55).

In uremic patients investigated before and after the initiation of hemodialysis, the study of whole-body leucine fluxes during insulin alone and insulin with amino acid infusion showed that CRF and hemodialysis patients were as sensitive as normal subjects to the protein anabolic actions of insulin. Insulin alone reduced proteolysis and leucine oxidation, and insulin given with amino acids increased net protein synthesis (56).

Abnormal branched-chain amino acid metabolism: clinical implications. During renal failure BCAA metabolic abnormalities can alter tissue activities, particularly brain function, and nutritional status (33,57–59). Changes in plasma BCAA concentrations can impair both blood–brain barrier AA exchanges and neurotransmitter synthesis (41,60). In healthy postabsorptive subjects, glutamine accounts for 25% of brain AA uptake, valine for 19%, leucine together with isoleucine for 16% (61,62). During CRF, no significant brain uptake of valine, isoleucine, and glutamine was found (61,62). The impairments of AA exchanges across the blood–brain barrier are responsible for abnormal cerebrospinal fluid composition including a decrease in leucine, valine, and tyrosine concentrations (63,64).

Brain lipid and protein synthesis, which are dependent on BCAA availability (65–69), as well as neurotransmitter synthesis from glutamine and tyrosine (70), can be compromised. Hence, abnormal brain BCAA metabolism may participate in uremic encephalopathy (57). Conversely, BCAA supplementation may improve brain functions. As a matter of fact, in hemodialysis patients, BCAA infusion has been associated with a return to normal of rapid eye movement sleep, and a significant decrease in end-tidal CO2 during both rapid eye movement and nonrapid eye movement sleep (71). Similarly, BCAA supplements have been reported to stimulate appetite in depleted hemodialysis patients (72).

The abnormal composition of arterial AAs influences organ AA uptake and compromises peripheral tissue replenishment, particularly during the absorptive phase (39). In CRF patients, nutritional indices such as body-mass index, muscle-mass indicators, and plasma transthyretin are correlated with plasma leucine, isoleucine, and particularly valine (73,74). Conversely, nutritional supplementation by intradialytic parenteral nutrition is reported to induce an improvement of nutritional status together with an increase in plasma leucine (75).

Increased protein turnover, unbalanced hepatoplasmonic AA release during the absorptive phase and subsequent abnormal BCAA metabolism result in a decrease in the efficacy of protein intake. Depending on the severity of renal failure, 2 regimens are currently used in clinical practice to counteract these abnormalities of AA and protein metabolism (76–80): 1) in nondialyzed CRF patients, correction of the abnormal plasma AA profile by the administration of EAAs or keto acids has been proposed to improve protein status while limiting nitrogen load; and 2) in dialysis patients, a protein supply of 1.2–1.4 g · kg BW−1 · d−1 has been recommended and BCAA and/or BCKA supplements have been used in some studies.

**Branch-chain amino and keto acid supply during chronic renal failure**

During CRF, the aim of nutritional interventions can be summarized as follows (76): 1) minimize uremic toxicity and avoid malnutrition; and 2) delay progression of kidney disease. The recommendations of the National Kidney Foundation (79) and of the European Society of Parenteral and Enteral Nutrition (76) concerning protein supply during CRF are summarized in Table 2. The use of BCAA and BCKA supplements cannot be studied separately from low-protein diets (LPDs): these compounds are usually given to patients with severe CRF to decrease further protein intake while maintaining satisfactory nutritional status. Moreover, in most animal and human studies, BCAAs and/or BCKAs were not...
given solely but in association with other essential AAs (EAs) and/or their keto analogs (15). Therefore, the effects of BCAA and/or BCKA supplementation cannot be studied separately.

**Rationale for the use of BCKAs.** The therapeutic use of BCKA is based on several rationales (81): 1) due to their ability to fix amine groups and to regenerate BCAAs, BCKAs behave as amino-free substitutes for BCAAs (26,82,83); 2) BCKAs, ketoleucine in particular, have been shown to reduce muscle protein degradation (81,84); and 3) BCKAs may favor a slower progression of renal insufficiency by reducing the severity of secondary hyperparathyroidism (27). The intestinal absorption of BCKA treatment is shown to be unaffected by chronic renal failure (CRF) (30). The effects of BCKA supplementation on liver protein metabolism has been poorly investigated. In a model of chronic protein malnutrition in rats, the addition of BCKAs to a low-protein diet (LPD) markedly improves liver microsomal proteins and glutathione, suggesting that BCKA may prevent the deterioration of the nutritional state of the liver in uremic patients (85).

EAA supplements in CRF patients usually include valine, leucine, isoleucine, phenylalanine, threonine, tryptophan, lysine, methionine, and histidine. Tyrosine, considered an EAA during CRF, was added to some preparations (15). Ketoacid mixtures contain BCKA as well as phenylalanine keto analog, methionine hydroxy analog, and other AAs considered essential for CRF patients.

**Metabolic adaptation to protein restriction: effect of essential amino and keto acids.** Nitrogen balance and kinetics of infused L-[15N,1-13C]leucine were measured during fasting and feeding in 6 adult CRF patients and 4 controls given 0.6 or 1.0 g protein · kg\(^{-1} \cdot \text{d}^{-1}\) diets (86). In both groups, LPD similarly reduced feeding-stimulated oxidation of leucine and protein degradation. Nitrogen balance and protein balance changes were not different (86). A similar adaptation of liver protein metabolism was reported: following a reduction in protein intake from 1.20 to 0.66 g · kg\(^{-1} \cdot \text{d}^{-1}\) for 1 mo, hepatic albumin synthesis decreased from 18.2 to 14.9 g · 1.73 m\(^2\)·\text{d}^{-1} and serum albumin rose from 28.8 to 30.6 g · L\(^{-1}\) (87).

Metabolic effects of LPD, with or without supplemented EAA keto analogs, were assessed in a randomized controlled study of 12 patients with mild CRF. In both groups, protein intake was isonitrogenous. After a 4–6-wk equilibrium period, protein intake was decreased to 0.71 g · kg\(^{-1} \cdot \text{d}^{-1}\) while energy intake was kept at 31 kcal · kg\(^{-1} \cdot \text{d}^{-1}\). After a 3-mo LPD, patients' body weights, serum albumin, or insulin growth factor-1 (IGF-1) were unchanged from that during the equilibrium period. Total-body L-C-leucine flux decreased by 8% and leucine oxidation by 18%. There was no significant difference between keto-analog–supplemented and unsupplemented groups (88).

In stable patients, very-low–protein diets (VLPDs) can reduce further AA oxidation. In a crossover study conducted in 6 CRF patients, a 0.35 g protein · kg\(^{-1} \cdot \text{d}^{-1}\) diet, supplemented with either keto acid or EAAs for 25 d, was able to maintain neutral nitrogen balance and body composition (89). These diets were associated with very low oxidation rates of leucine in ketoanalog- and EAA-supplemented patients (89). During a 16-mo follow-up of these patients, the fasting leucine oxidation rate remained at the low level of 10.0 ± 2.2 μmol · kg\(^{-1} \cdot \text{d}^{-1}\) (90).

In another study, EAA and keto acids were successfully used together with VLPDs to reduce proteinuria (2). A 6-mo follow-up of 15 patients with advanced renal failure and severe albuminuria, receiving a very-low–protein (0.3 g · kg\(^{-1} \cdot \text{d}^{-1}\)) diet with low-phosphorus (5–7 mg · kg\(^{-1} \cdot \text{d}^{-1}\)) diet supplemented with EAA and keto analogs, indicated that urinary albumin excretion and fractional renal albumin clearance were reduced significantly while serum albumin concentration increased (91). Similar data have been obtained in other studies (87,92,93).

**Nutritional effects of low–protein diets, essential amino and keto acids.** Insulin resistance can be improved by protein restriction. In 8 patients with advanced CRF, a VLPD supplemented by keto analogs of EAA for 3 mo induced a decrease in fasting serum glucose from 5.0 ± 0.1 to 4.7 ± 0.1 mmol/L and plasma insulin from 82.4 ± 20.7 to 48.8 ± 8.0 pmol/L. Endogenous glucose production was reduced by 66% for comparable plasma insulin levels. These data indicate an improved sensitivity to insulin (94).

Malnutrition in patients entering dialysis is a key determinant of mortality during the subsequent mo (95–97). Consequently, a critical point concerning LPDs and VLPDs given in association with keto acids or EAA supplements is to evaluate their long-term effect on nutritional status (98). Two prospective randomized studies, concluded that after a mean follow-up of ~18 mo, LPD and VLPD, in association with EAA and keto acids, made it possible to maintain arm-muscle circumference, triceps skin fold, and serum albumin (99,100). The modification of diet in renal disease (MDRD) study addressed, in a larger series, the safety of protein and phosphorus restriction. Patients were studied separately depending on their glomerular filtration rate (GFR). In study A, 585 patients with a GFR of 25–55 mL · min\(^{-1} \cdot \text{d}^{-1}\) were randomly assigned to a usual-protein diet (1.3 g · kg\(^{-1} \cdot \text{d}^{-1}\)) or a LPD (0.58 g · kg\(^{-1} \cdot \text{d}^{-1}\)). In study B, 255 patients with a GFR of 13–24 mL · min\(^{-1} \cdot \text{d}^{-1}\) were assigned to the LPD or a VLPD (0.28 g · kg\(^{-1} \cdot \text{d}^{-1}\)) supplemented with a keto acid–EAA mixture (0.28 g · kg\(^{-1} \cdot \text{d}^{-1}\)). Mean duration of follow-up was 2.2 y in both studies. Protein and energy intakes were lower in the LPD and VLPD groups than in the usual-protein group. An examination of patients in both diet groups in each study revealed that a lower achieved protein intake was not correlated with a higher rate of death, hospitalization, or stop points, or with a progressive decline in any of the indices of nutritional status. These analyses suggest

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**TABLE 2**

**Recommended protein intake in adults with chronic renal failure**

<table>
<thead>
<tr>
<th>GFR (mL · min(^{-1} \cdot \text{d}^{-1}))</th>
<th>Recommended protein intake (g · kg(^{-1} \cdot \text{d}^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR 25–70</td>
<td>0.55–0.60 (2/3 HBV)</td>
</tr>
<tr>
<td>GFR &lt;25 ml · min(^{-1})</td>
<td>0.55–0.60 (2/3 HBV) or 0.28 + EAA</td>
</tr>
</tbody>
</table>

| EAA | 0.60 or 0.75 (in case of intolerance or insufficient energy intake) |

ESPiN, European Society of Parenteral and Enteral Nutrition; NKF, National Kidney Foundation; GFR, glomerular filtration rate; HBV, high biological value.
that LPD and VLPD used in the MDRD study are safe for periods of 2–3 y. Nonetheless, because protein and energy intake declined during these studies, the authors stressed the need for carefully monitoring patients’ protein and energy intake and nutritional status (101). In a randomized study of 50 CRF patients, 25 patients receiving a VLPD (0.30 g · kg⁻¹ · d⁻¹) supplemented with a (0.17 g · kg⁻¹ · d⁻¹) preparation of keto analogs and hydroxy analogs of AAs (Ketosteril, Fresenius Kabi) were compared with 25 patients given a LPD (0.65 g · kg⁻¹ · d⁻¹). The follow-up varied from 3 to 40 mo. Body weight, serum transthyretin, and albumin were unaffected in the 2 groups. Plasma valine:glycine decreased in the severely protein-depleted patients and remained stable in the LPD group. The VLPD supplemented with keto analogs improved phosphate and calcium status (102). Chauveau et al. (103) assessed the nutritional status every mo for 1 y in 10 clinically stable patients with advanced CRF (mean GFR, 13.2 ± 4.8 mL·min⁻¹·1.73 m²). These patients received 0.3 g · kg⁻¹ · d⁻¹ of protein supplemented with EAA and keto analogs. Conventional nutritional markers remained unchanged after 1 y of the VLPD. During the same period, whole-body dual-energy x-ray absorptiometry showed a significant decrease in mean lean tissue from 46.2 to 45.0 kg; limb–trunk lean tissue ratio was reduced from 0.86 to 0.82, total-body fat increased from 20.0 to 21.4 kg, and the percentage of total-body fat increased from 29.2% to 31.7%. Of note, these different modifications occurred abruptly during the first 3 mo, then stabilized or slightly improved thereafter.

The impact of VLPD on survival after transplantation or initiation of dialysis has been addressed by several authors (103–107). Walser et al. (105,106) reported that protein restriction and close clinical monitoring before dialysis does not worsen and may substantially improve survival during the first 2 y on dialysis. Aparicio et al. (107) collected data from 239 consecutive patients with advanced CRF. Patients were given 0.3 g protein and 35 kcal · kg⁻¹ · d⁻¹ plus EAA and keto analogs, calcium carbonate, iron, and multivitamins. Protein intake decreased from 0.85 ± 0.23 to 0.43 ± 0.11 g · kg⁻¹ · d⁻¹ without change in body-mass index and serum albumin. Fourteen patients died during the follow-up, but deaths were unrelated to nutritional parameters. Hemodialysis was initiated in 165 patients at a mean GFR of 5.8 ± 1.5 ml·min⁻¹. During an average of 54 mo on hemodialysis, mortality was low (2.4% after 1 y) and correlated to age only, not to nutritional parameters observed at the end of the protein-restricted regimen. Similar results were obtained in 66 transplant patients. The authors concluded that VLPDs supplemented with EAs and keto analogs could be safely used in patients with CRF without adverse effects on the clinical and nutritional status of the patients (107). Although these data are encouraging, it should be stressed that no randomized study is available to assess the effects of long-term VLPDs on survival following dialysis or transplantation.

**Effects of low-protein diets on the progression of renal insufficiency.** A recent review addressed the influence of dietary protein intake on renal function (2). Elevated protein intake alters renal hemodynamics and impairs renal function in normal animals or during experimental renal insufficiency. High-protein intake increases glomerular filtration rate (GFR), provokes or increases proteinuria, and induces glomerulosclerosis and renal insufficiency. The effects of dietary protein on renal function involve multiple mediators such as hormones (glucagon, insulin, insulin-like growth factor-I, angiotensin II), cytokines, and kinins. Moreover, the AA load stimulates the proximal sodium/amino acid cotransporter, thus stimulating tubulo-glomerular feedback and increasing GFR. On the other hand, reduced protein intake lowers hyperfiltration, retards the onset of proteinuria and glomerular fibrosis, and increases survival during experimental uremia (2).

In CRF patients, the effect of BCAA and keto acid supplementation on renal-disease progression cannot be distinguished from protein restriction. Moreover, it is difficult to evaluate the effect of LPDs because numerous factors can modify the progression of nephropathy (76): hypertension, proteinuria, type of nephropathy, hyperlipoproteinemia, dietary phosphorus, type of protein intake (vegetable vs. animal proteins). Fouque et al. (108) reviewed >50 trials assessing the effects of protein restriction on the occurrence of renal death (defined as the need for starting dialysis, the death of a patient or kidney transplant during the trial). A total of 1494 patients were analyzed: 753 had received a reduced protein intake and 741 a higher protein intake. There were 242 renal deaths recorded, 101 in the low-protein diet group, and 141 in the higher-protein diet group, giving an odds ratio of 0.61 with a 95% confidence interval of 0.46 to 0.83 (P = 0.006). The authors concluded that reducing protein intake in patients with CRF reduces the occurrence of renal death by ~40% as compared with larger or unrestricted protein intake.

Three randomized trials addressed the ability of VLPD associated with keto acid–EAA mixtures to slow the decline in renal function. Junger et al. (109) studied 19 patients randomly assigned to receive either 0.6 g protein · kg⁻¹ · d⁻¹ or 0.4 g protein · kg⁻¹ · d⁻¹ in association with a 0.10 g · kg⁻¹ · d⁻¹ mixture of BCKA, ketophenylalanine, hydroxymethionine, L-lysine, L-threonine, L-tryptophane, L-histidine, and L-tyrosine (Ketosteril, Fresenius Kabi). Mean duration of treatment was 11.8 mo in the keto analog group and 7.1 mo in the low-protein diet group. As far as it could be deduced from such a small number of patients, this study suggested that VLPD supplemented with keto acids and EAs was more effective than LPD in terms of a decrease in blood and urinary urea, a decrease of 1/creatinine slope and lengthened time interval until the start of dialysis. In a prospective randomized study of 50 patients by Malvy et al. (102), a VLPD (0.30 g · kg⁻¹ · d⁻¹) supplemented with the same preparation of (0.17 g · kg⁻¹ · d⁻¹) keto, hydroxy, and amino acids (Ketosteril, Fresenius Kabi), was compared with a LPD (0.65 g · kg⁻¹ · d⁻¹). No statistically significant differences were found between the 2 dietary regimens for renal survival. Uremia decreased significantly in the keto acid group and increased in patients in the LPD. At the end of the study, the keto acid group showed higher calcemia and lower phosphoremia, alkaline phosphatase, and parathormone plasma levels when compared with patients on the LPD. Thus, keto acid and the EAA-enriched VLPD did not limit GFR decrease but improved phosphocalcic plasma parameters (102). In the MDRD study B, 255 patients with GFR of 13 to 24 ml·min⁻¹·1.73 m² were randomly assigned to the LPD (0.58 g · kg⁻¹ · d⁻¹) or a VLPD (0.28 g · kg⁻¹ · d⁻¹) with a keto-EAA supplement. An 18–45-mo follow-up was performed, evaluations of the patients each mo. The VLPD group had a marginally slower decline in the GFR than did the LPD group (P = 0.07). The authors concluded that there was no delay in the time to the occurrence of end-stage renal disease or death (110). Since then, numerous secondary analyses of the MDRD study have been undertaken to clarify the effect of protein restriction on the rate of decline in GFR and the onset of end-stage renal disease (2,111). When actual protein intake was considered independently of the group to which patients were assigned, a strong relation was found between the magnitude of protein intake and the GFR slope (P = 0.011) or renal death (P = 0.001) (111). No additional effect of keto-analog supplements...
on retardation of progression of renal failure was found using these new analyses.

Branched-chain amino and keto acid supply in dialysis patients

In malnourished hemodialysis patients, EAA and/or keto acid supplementation, including BCAAs and their keto analogs, was used for 30 y. Besides malnutrition itself, the rationale for the use of these supplements was the decrease in plasma EAs. Findings on the effect of EAs, and more specifically, BCAAs, in the promotion of protein synthesis launched new arguments for their use in renal failure patients. As a matter of fact, EAA appeared to be able to activate the eukaryotic initiation factor 2B, which begins protein synthesis by permitting the fixation of the tRNA bringing the first methionine link on the 40S ribosomal subunit (112). Similarly to insulin, BCAAs influence protein synthesis by activating the serine/threonine kinase mammalian target of rapamycin (mTOR), which then stimulates downstream targets such as eukaryotic initiation factor 4E (113,114). Short-term administering of leucine stimulates protein synthesis by enhancing mRNA translation through an increase in both the number of polysomes and the rate of formation of 40S initiation complex (115). Furthermore, it was recently shown that the long-term supplementation with leucine and non-leucine in rats results in stimulation of postprandial protein synthesis in adipose tissue, muscle, and liver, independent from changes in the mTOR-signaling pathway and from adaptation of the first steps of leucine metabolism (mitochondrial branched-chain AA transaminase, branched-chain AA dehydrogenase, and branched-chain AA dehydrogenase kinase) (114).

In elderly patients, EAs were recently shown to be more effective in promoting protein synthesis than a mixture of essential and nonessential AAs (116). In hemodialysis patients, 6 controlled studies of EAA and/or keto acid supplementation were conducted from 1977 to 2001. Two studies were performed in nonmalnourished patients given keto-EAA mixtures and, as expected, did not show any benefit (117,118). The 4 other studies administered EAA mixtures, 6.6 to 15.7 g · d⁻¹, in depleted patients and achieved an improvement of nutritional parameters (Table 3). Hiroshige et al. (72) specifically studied BCAA supplementation. Twenty-eight anorectic patients with low plasma albumin concentration (<3.5 g · dl⁻¹) were included. In a crossover trial, patients were followed during 1 y and received, in random order during 6-mo periods, oral BCAA supplementation (12 g · d⁻¹) or a placebo. In patients receiving first the BCAA treatment, oral protein and caloric intakes improved within 1 mo, along with improvement in plasma BCAA levels. After 6 mo of BCAA supplementation, anthropometric indices showed a statistically significant increase and mean plasma albumin concentration increased from 3.31 g · dl⁻¹ to 3.93 g · dl⁻¹. After exchanging BCAA for a placebo, spontaneous oral food intake decreased, but the beneficial nutritional status persisted for the next 6 mo. In the 14 patients initially treated with a placebo, no significant changes in nutritional parameters were observed during the first 6 mo. However, positive results were obtained by BCAA supplementation during the subsequent 6 mo, and mean plasma albumin concentration increased from 3.27 g · dl⁻¹ to 3.81 g · dl⁻¹. The authors concluded that normalization of low plasma levels of BCAA by oral supplementation can reduce anorexia and significantly improve overall nutritional status in elderly malnourished hemodialysis patients. However, because this study did not include a third group of patients given isonitrogenous protein supplementation, the proper role of BCAA in improving appetite could not be established.

Conclusions

During renal failure, BCAA status is characterized by low plasma and cellular valine together with low plasma leucine and isoleucine, and most often decreased plasma BCKAs. These abnormalities of circulating and cellular BCAAs are secondary to abnormal muscle and hepatosplanchnic AA metabolism. In muscle, metabolic acidosis induces protein breakdown via an activation of both cytosolic ATP-ubiquitin–dependent proteolytic pathway and BCKA dehydrogenase, responsible for an irreversible BCAA breakdown. The decrease in hepatosplanchnic retention of nonessential AAs contributes to the abnormalities of arterial AAs associated with renal insufficiency. Abnormal BCAA metabolism can alter both tissue activities, particularly brain function, and nutritional status. In dialysis patients, it has been reported that the normalization of plasma BCAAs by BCAA oral supplementation was associated with an improvement of appetite and nutritional status. During CRF, the correction of the plasma AA profile through the administering of EAs or keto acids, has been proposed to improve protein status, avoid uremic toxicity, and delay the progression of renal disease. BCAA and BCKA supplements are integrated in a therapeutic strategy that includes protein restriction and supplementation with EAs. Consequently, the specific effect of either BCKA or BCKA cannot be evaluated. Based on nutritional status, the data from the literature suggest that LPD and VLPD, given in association with keto acid or keto-EAA mixtures, are well tolerated. Nonetheless, the need to carefully monitor patients’ protein and energy intake and nutritional status has been stressed by several authors. A recent meta-analysis concluded that reducing protein intake in

### Table 3

Controlled studies of essential (EAA) and keto acid (KA) supplementation in malnourished dialysis patients

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study design, Patients</th>
<th>EAA and/or KA supply</th>
<th>Length d</th>
<th>Changes in nutritional parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>(119)</td>
<td>Double blind, crossover study, n = 13</td>
<td>EAA 15.7 g · d⁻¹</td>
<td>90</td>
<td>Increase in predialysis urea and plasma C₃ complement fraction</td>
</tr>
<tr>
<td>(120)</td>
<td>Double blind randomized study treated, n = 7 controls, n = 8</td>
<td>EEA + histidine 6.6 g · d⁻¹</td>
<td>105</td>
<td>Increased serum albumin and transferrin, improved bone density.</td>
</tr>
<tr>
<td>(121)</td>
<td>Double blind randomized study treated, n = 23 controls, n = 24</td>
<td>EAA + histidine + tyrosine 10.8 g · d⁻¹</td>
<td>90</td>
<td>Increased serum albumin and muscle strength</td>
</tr>
<tr>
<td>(72)</td>
<td>Double blind, crossover study, n = 14</td>
<td>BCAA, 12 g · d⁻¹</td>
<td>180</td>
<td>Improved appetite and plasma AA, increase in serum albumin</td>
</tr>
</tbody>
</table>
patients with CRF reduces the occurrence of renal death by 
~40%, compared with higher or unrestricted protein intake (108). The optimal level of protein intake cannot be confirmed from these studies. The additional effect of keto-EAAs supplements on retarding the progression of renal failure has not been demonstrated. VLPD together with EAAs or keto-EAA mixtures have been shown to improve insulin sensitivity and hyperparathyroidism and to reduce proteinuria.

LITERATURE CITED


