Adaptive Response to a Low-Protein Diet in Predialysis Chronic Renal Failure Patients

JACQUES BERNHARD,* BERNARD BEAUFRE,† MAURICE LAVILLE,* and DENIS FOUQUE*
*Department of Nephrology and Renal Nutrition, Hospital Edouard Herriot, Lyon, and †Laboratoire de Nutrition Humaine, Clermont-Ferrand, France.

Abstract. A randomized, controlled study of 12 patients with mild chronic renal failure was designed to assess the metabolic effects of a low-protein diet supplemented (n = 6) or not (n = 6) with ketoanalogs of amino acids. The protein intake was prescribed so that both groups were isonitrogenous. The dietary survey each month included a 3-d food record and a 24-h urine collection for urea measurement. After a 4- to 6-wk equilibrium period (standard occidental diet, 1.11 g of protein and 32 kcal/kg per d), patients reduced their protein intake to reach 0.71 g of protein/kg per d during the third month. Energy intake was kept constant (31 kcal/kg per d) during the 3-mo period. Compliance to the diet was achieved after 2 mo of training. Leucine turnover measurement was performed before and at the end of the 3-mo low-protein period. There was no clinical change, whereas total body flux decreased by 8% (P < 0.05) and leucine oxidation by 18% (P < 0.05). No difference could be attributed to the ketoanalogs themselves. Thus, under sufficient energy intake, a low-protein diet is nutritionally and metabolically safe during chronic renal failure. The nitrogen-sparing effect of a low-protein diet is still present during mild chronic renal insufficiency.

Many studies have addressed the safety of a moderate restriction in protein intake on the nutritional status during chronic renal failure (CRF). Whereas it is well established that in healthy individuals, low-protein diets result in a reduction of whole-body protein turnover and amino acid oxidation (1,2), there have been some discrepancies about this adaptive response in CRF (3). In addition, the metabolic effects of the ketoanalogs of amino acids have been evaluated only in CRF patients during more restricted protein diets (4,5). To clarify these adaptations during a short period, we designed a randomized, controlled study and administered a moderately low-protein diet supplemented or not with ketoanalogs of amino acids during 3 mo in 12 patients who presented with mild CRF.

Materials and Methods

Patients

Twelve patients with CRF (10 men and 2 women, aged 44.3 ± 4.6 [SEM] yr) were studied before and 3 mo after a reduction in their protein intake (Table 1). None of these patients was known to have any malignant or inflammatory illness. Three mo before inclusion, serum creatinine was measured to ensure that renal failure was not progressive (difference between serum creatinine at inclusion being <50 μmol/L). Patients did not experience any catabolic event or treatment during this study. All patients received a conservative treatment including calcium carbonate, vitamin-D supplement, sodium bicarbonate, and antihypertensive medication if needed. None received erythropoietin or vaccination against hepatitis B virus. No vascular shunt procedure was realized during the study.

Dietary Assessment

Patients were selected from our regular dietary program, which has been run in our unit since 1974. A trained dietitian conducted two interviews with each patient before inclusion. Patients were interviewed at the early diagnosis of renal failure and before any former diet. They were asked not to modify their diet and were selected if their dietary protein intake was between 1 and 1.5 g/kg per d and their energy intake was >30 kcal/kg per d. Estimation of the baseline diet was performed with a 3-d dietary record and a 24-h urea collection. Patients who were willing to lose weight or who had insulin or noninsulin diabetes mellitus or progressive renal failure were not included. After 4 to 6 wk of their usual diet, the patients were admitted to the metabolic ward for 4 d for the baseline study. Patients were then randomized to receive a low-protein diet (0.6 g of protein/kg per d with at least half of the protein being of high biologic value), with or without ketoanalogs of amino acids. Energy intake was kept constant (31 kcal/kg per d) during the 3-mo period. The dietary survey each month included a 3-d food record and a 24-h urine collection for urea measurement.

Ketoanalogs of Amino Acids

After random allocation, six patients were asked to take a supplement of ketoacids (Cetolog; Clintec Corp., Veldizy, France), 1 tablet/5 kg body wt per d. Compliance was assessed by pill count; the overall dose per patient was 0.167 ± 0.007 tablets/kg body wt per d for the 3-mo period, i.e., 84% of prescribed dose. Each 900-mg tablet contained 76 mg of ketoisoleucine, 97 mg of ketoleucine, 68 mg of ketovaline, 26 mg of hydroxymethionine, 118 mg of L-ornithine, 129 mg of L-lysine, 26 mg of L-histidine, 75 mg of L-threonine, 152 mg of L-tyrosine, and 3.4 mg of calcium. The daily dosage, i.e., 10 to 15
started. Blood and expired air samples were taken at
Finland). Calorimetry (Deltatrac MBM-100; Datex Instrumentation, Helsinki,
2
(KIC) and CO
2 . Two boluses of
1
3
C-sodium bicarbonate (5 mg) were followed by a constant intravenous
infusion of
1
3
C\] leucine (1 mg/kg) and
\] leucine infusion of 0.08
m
mol/kg per min over the next
5 min
to determine the basal
13
C enrichment of plasma
KIC enrichment was determined by gas chromatography mass chromatography.
Pills, was divided into two to three doses and taken during meals. No
side effect from the ketoanalog supplement was reported.

Protocol Design

The leucine turnover procedure was carried out on the fourth day of the
metabolic assessment in the Center d’Explorations Métaboliques. Patients
fasted from 8:00 p.m. the day before the test until 12:00 a.m. the
following morning. At 8:00 a.m., a 3.5-h intravenous infusion of
\] leucine (Tracer Technologies, Inc., Woburn, MA) was
started. Blood and expired air samples were taken at −15 and −5 min
to determine the basal
13
C enrichment of plasma α-ketoisocaproate (KIC) and CO
2 . Two boluses of
\] leucine (1 mg/kg) and
\] sodium bicarbonate (5 mg) were followed by a constant intravenous
\] leucine infusion of 0.08 \( \mu \text{mol/kg per min over the next 3.5 h. }
Four times during the last hour of infusion, blood and gas were
collected and CO
2 production rate (VCO
2 ) was measured by indirect
calorimetry (Deltatrac MBM-100; Datex Instrumentation, Helsinki,
Finland).

Analytical Methods and Calculation of
Protein Turnover

\( ^{13}\text{CO}_2 \) was determined by isotope ratio mass spectrometry, and
plasma KIC enrichment was determined by gas chromatography mass
spectrometry (6). Leucine fluxes were calculated with the use of the
plasma KIC enrichment (7). Endogenous leucine rate of appearance,
an index of protein breakdown, is then equal to total leucine flux
minus the tracer infusion rate. Leucine oxidation was calculated from
the appearance of \( ^{13}\text{CO}_2 \) in the expired gas divided by the plasma \( ^{13}\text{C} \)
KIC times 0.90 to correct for retention of CO
2 in the bicarbonate pool.
Nonoxidative leucine disposal, an index of whole-body protein
synthesis, was calculated from the difference between the flux and
oxidation of leucine. In the fasting state, total leucine flux can be
assimilated to the leucine appearance from protein mobilization.

Amino Acid Determination

Plasma was drawn at 7:45 a.m. on the fourth day of the metabolic
study, after an overnight fast. Plasma amino acids were determined
with a Jeol automat (Jeol Corp., Tokyo, Japan) in the research laborato-
ry at Edouard Herriot Hospital, with the use of a standard liquid
chromatography.

Statistical Analyses

Values are reported as mean ± SD. Comparisons between baseline
and the follow-up admission were analyzed with the use of the paired
t test. Comparisons between subgroups at a given period were per-
formed with the Wilcoxon test on Statview statistical software (Aba-
cus Concept, Berkeley, CA). Differences were considered significant at
P < 0.05.

Results

As shown in Table 1, patients were not malnourished. The
degree of renal failure was mild, corresponding to a GFR of
approximately 30 ml/min per 1.73 m
2 . Renal failure was not
progressing rapidly, as evidenced by the fact that patients’
serum creatinine did not increase by more than 50
5
mol/L
within the last 3 mo. None of them experienced nephrotic
syndrome or massive proteinuria (Table 1). Patients did not
present metabolic acidosis or advanced renal osteodystrophy.

Compliance to the diet was obtained after training with our
specialized renal dietitian. Patients were asked not to reduce their
energy intake; this was accomplished by increasing slightly the
daily oil intake mainly in salad dressing. As shown in Table 2 and
based on dietary interviews, the energy intake of patients, al-
though not excessive, was kept within acceptable values, e.g.,
\( >30 \text{ kcal/kg per d. }
Protein intake was assessed by two different
methods. We determined protein nitrogen appearance (PNA)
from urinary urea output (Table 2), according to Maroni’s formula
(8). We also monitored protein intake from the 3-d home dietary
records obtained monthly (Table 2). The protein equivalent of the
nitrogen content in the ketoanalog was not included in the esti-
mated dietary protein intake (DPI) and averaged 0.08 ± 0.004 g

Table 1. Patient characteristics before and after a 3-mo low-protein diet

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control Period ( (N = 12) )</th>
<th>LPD ( (N = 6) )</th>
<th>LPD + Keto Acids ( (N = 6) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44.3 ± 4.6</td>
<td>39.0 ± 5.8</td>
<td>49.5 ± 7.0</td>
</tr>
<tr>
<td>ABW (kg)</td>
<td>68.5 ± 2.6</td>
<td>69.0 ± 3.6</td>
<td>68.9 ± 4.2</td>
</tr>
<tr>
<td>Gender ratio (M/F)</td>
<td>10/2</td>
<td>6/0</td>
<td>4/2</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>23.2 ± 2.7</td>
<td>23.6 ± 3.1</td>
<td>22.7 ± 2.0</td>
</tr>
<tr>
<td>Serum creatinine (( \mu \text{mol/L} ))</td>
<td>248.0 ± 97.0</td>
<td>262.0 ± 77.0</td>
<td>244.0 ± 155.0</td>
</tr>
<tr>
<td>Serum protein (g/L)</td>
<td>68.8 ± 4.1</td>
<td>71.0 ± 3.5</td>
<td>69.3 ± 2.4</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>42.0 ± 4.3</td>
<td>44.5 ± 4.5</td>
<td>40.3 ± 4.6</td>
</tr>
<tr>
<td>Serum bicarbonate (mmol/L)</td>
<td>22.3 ± 3.8</td>
<td>24.1 ± 3.89</td>
<td>23.3 ± 2.67</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>4.9 ± 0.7</td>
<td>5.0 ± 0.5</td>
<td>4.6 ± 0.2</td>
</tr>
<tr>
<td>Serum calcium (mmol/L)</td>
<td>2.2 ± 0.07</td>
<td>2.34 ± 0.2</td>
<td>2.27 ± 0.05</td>
</tr>
<tr>
<td>Serum phosphorus (mmol/L)</td>
<td>1.15 ± 0.2</td>
<td>1.31 ± 0.16</td>
<td>1.25 ± 0.27</td>
</tr>
<tr>
<td>Serum PTH (ng/L)</td>
<td>48.2 ± 30.5</td>
<td>30.2 ± 16.0</td>
<td>62.0 ± 42.0</td>
</tr>
<tr>
<td>Proteinuria (g/d)</td>
<td>0.62 ± 0.72</td>
<td>0.63 ± 0.39</td>
<td>0.62 ± 0.28</td>
</tr>
</tbody>
</table>

\(^a\) LPD, low-protein diet; BMI, body mass index; ABW, actual body weight; PTH, parathyroid hormone. Values are expressed as mean ± SD.
\(^b\) Values obtained before randomization; no significant difference between the two subgroups of patients during the control period.
of protein/kg per d, partly explaining a greater PNA than the DPI (Table 2). Overall, patients gradually reduced their daily protein intake by approximately 40% (diet records), 44% (24-h urinary urea), and 50% (Maroni’s estimation; Table 2). Patients did not present body weight or body mass index changes over 3 mo (Table 1).

Effect of Overall Reduction in Protein Intake on Leucine Turnover

Because there was no difference between the two groups, results are presented for all 12 patients (Table 3). The reduction in protein intake induced a decrease in leucine oxidation by approximately 18% (P < 0.05), associated with a parallel 8% reduction (P < 0.05) in leucine rate of appearance, an estimation of protein degradation. There was no change in the nonoxidative leucine disposal during the low-protein diet period (Table 3).

Effects of Ketoanalogs on Leucine Turnover

The effect of ketoanalogs on leucine turnover was estimated from the comparison of the variation in leucine kinetics from baseline (Table 3). Although there was a trend for a reduction for all measurements and these variations seemed to be more pronounced in the nonketoanalog group, no statistical difference could be observed between group that received a ketoanalog supplement and group that did not.

Plasma Amino Acid Pattern

Plasma amino acids were obtained on the fourth day of the metabolic study, after an overnight fast. There were almost no change from baseline (Table 4), with the exception for arginine, which decreased in the nonsupplemented group from 177 ± 37 to 105 ± 33 μmol/L (P < 0.05). In the ketoanalog-supplemented group of patients, the only significant change was a 14% reduction in plasma tyrosine from baseline (P < 0.05; Table 4). When we compared the changes from baseline between groups to test the effects of ketoanalog supplement, there was no significant difference for any single amino acid, ratio, or total amino acids. Particularly, plasma branched-chain amino acids (leucine, isoleucine, and valine) did not change significantly between the start and the end of the study and between the two groups of patients.

Discussion

The present study shows that compliance with a low-protein diet can be obtained by intensive dietitian interviews and that a moderately low-protein diet can be prescribed safely with an adequate energy intake. In addition, we provide further data that show clearly an adequate metabolic response when patients with mild CRF consume a moderately low-protein diet for an extended period.

Compliance with any diet is the key to success. Renal diets often are complicated by superimposed diseases, chronic med-

Table 2. Monthly compliance with the low-protein diet

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>LPD</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 1</td>
<td>Month 2</td>
<td>Month 3</td>
<td></td>
</tr>
<tr>
<td>EI (kcal/kg per d)</td>
<td>31.7 ± 8.2</td>
<td>32.8 ± 7.1</td>
<td>32.2 ± 6.6</td>
<td>31.4 ± 5.6</td>
</tr>
<tr>
<td>PI (g/kg per d)</td>
<td>1.13 ± 0.32</td>
<td>0.69 ± 0.17</td>
<td>0.59 ± 0.16</td>
<td>0.56 ± 0.09</td>
</tr>
<tr>
<td>Urinary urea (mmol/d)</td>
<td>360 ± 128</td>
<td>266 ± 86</td>
<td>272 ± 101</td>
<td>201 ± 92</td>
</tr>
<tr>
<td>PNA (g/kg per d)</td>
<td>1.11 ± 0.33</td>
<td>0.88 ± 0.25</td>
<td>0.88 ± 0.23</td>
<td>0.71 ± 0.23</td>
</tr>
</tbody>
</table>

* EI, energy intake; PI, protein intake; PNA, protein nitrogen appearance. Estimation of EI and PI was performed through a 3-d dietary record.
* Protein equivalent content of the ketoanalog supplement (n = 6) was not included and averaged 0.08 g/kg per d.
* PNA was estimated by a 24-h urea collection using Maroni’s formula.
* P < 0.05 from baseline (ANOVA).

Table 3. Effects of reducing protein intake with or without KA supplementation on protein metabolism as assessed by whole-body leucine turnover

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3-Mo LPD Effect</th>
<th>% Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n = 12)</td>
<td>LPD (n = 12)</td>
</tr>
<tr>
<td>Ra</td>
<td>1.93 ± 0.24</td>
<td>1.78 ± 0.18</td>
</tr>
<tr>
<td>Ox</td>
<td>0.28 ± 0.07</td>
<td>0.23 ± 0.04</td>
</tr>
<tr>
<td>NOLD</td>
<td>1.71 ± 0.22</td>
<td>1.59 ± 0.18</td>
</tr>
</tbody>
</table>

* Values are expressed as μmol/kg per min (mean ± SD). KA, ketoanalogs; Ra, endogenous leucine flux; Ox, amino acid oxidation; NOLD, nonoxidative leucine disposal.
* P < 0.05 versus baseline (paired t test); no difference was observed between percentage change from baseline within subgroups that did or did not receive KA (Wilcoxon, P > 0.1).
Table 4. Absolute variation in fasting plasma amino acids before and after a 3-mo LPD supplemented with KA or not

<table>
<thead>
<tr>
<th>Amino Acid Variation from Baseline (μmol/L)</th>
<th>LPD + KA</th>
<th>LPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histidine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−3.5 ± 12.5</td>
<td>1.5 ± 46.9</td>
</tr>
<tr>
<td>Isoleucine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−2.5 ± 16.3</td>
<td>−5.0 ± 20.2</td>
</tr>
<tr>
<td>Leucine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−18.2 ± 20.7</td>
<td>−12.2 ± 42.2</td>
</tr>
<tr>
<td>Lysine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−82.0 ± 100.5</td>
<td>−80.2 ± 113.7</td>
</tr>
<tr>
<td>Methionine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.5 ± 14.4</td>
<td>0.8 ± 10.9</td>
</tr>
<tr>
<td>Phenylalanine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−9.5 ± 22.1</td>
<td>−3.5 ± 26.7</td>
</tr>
<tr>
<td>Threonine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.2 ± 107.0</td>
<td>−8.8 ± 42.1</td>
</tr>
<tr>
<td>Valine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.8 ± 93.6</td>
<td>−23.2 ± 63.9</td>
</tr>
<tr>
<td>Alpha alanine</td>
<td>53.5 ± 108.7</td>
<td>136.8 ± 137.8</td>
</tr>
<tr>
<td>Arginine</td>
<td>−20.3 ± 59.9</td>
<td>−71.5 ± 52.8&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>0.7 ± 19.0</td>
<td>4.2 ± 10.3</td>
</tr>
<tr>
<td>Cysteine</td>
<td>−14.3 ± 37.8</td>
<td>13.3 ± 38.0</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>30.0 ± 168.9</td>
<td>25.3 ± 80.1</td>
</tr>
<tr>
<td>Glutamine</td>
<td>122.5 ± 123.2</td>
<td>125.8 ± 110.4</td>
</tr>
<tr>
<td>Glycine</td>
<td>−9.8 ± 94.9</td>
<td>30.8 ± 101.5</td>
</tr>
<tr>
<td>Ornithine</td>
<td>−25.5 ± 100.7</td>
<td>16.5 ± 65.2</td>
</tr>
<tr>
<td>Proline</td>
<td>−3.2 ± 47.1</td>
<td>40.6 ± 125.0</td>
</tr>
<tr>
<td>Serine</td>
<td>−16.2 ± 45.7</td>
<td>8.7 ± 40.4</td>
</tr>
<tr>
<td>Taurine</td>
<td>−15.5 ± 74.0</td>
<td>35.3 ± 57.0</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>−8.5 ± 7.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>−7.8 ± 13.2</td>
</tr>
<tr>
<td>Gly/Val</td>
<td>0.06 ± 0.71</td>
<td>0.05 ± 0.42</td>
</tr>
<tr>
<td>Phe/Tyr</td>
<td>0.06 ± 0.36</td>
<td>0.16 ± 0.16</td>
</tr>
<tr>
<td>EAA</td>
<td>−104.8 ± 260.0</td>
<td>−179.7 ± 345.3</td>
</tr>
<tr>
<td>NEAA</td>
<td>−80.8 ± 717.1</td>
<td>132.3 ± 855.3</td>
</tr>
<tr>
<td>TAA</td>
<td>−185.7 ± 828.7</td>
<td>−47.3 ± 1179.4</td>
</tr>
<tr>
<td>EAA/NEAA</td>
<td>−0.02 ± 0.13</td>
<td>−0.07 ± 0.04&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are expressed as mean ± SEM, n = 6. Blood was obtained for plasma amino acid measurements before breakfast, between 7:45 a.m. and 8:00 a.m., after an overnight fast. EAA, the sum of serum essential amino acids; NEAA, the sum of serum nonessential amino acids; TAA, the sum of EAA + NEAA. No significant change was observed between groups.

<sup>b</sup> Essential amino acid.

<sup>c</sup> A significant decrease from baseline (P < 0.05).

A diet record underestimated protein intake by 20 to 22 kcal/kg per d, are sometimes reported without concomitant severe malnutrition and/or impaired outcome (14). Another study comparing diet records and weighting food trays at the same time concluded that a diet record underestimated energy intake by <2% (15). In any event, the present energy intake of patients could be considered to be adequate, thus allowing a valid interpretation of the metabolic study (12).

Protein metabolism was assessed by the leucine turnover measurement. This technique has been used extensively in healthy humans. Adaptation to a reduction in protein intake is associated with a decrease in amino acid oxidation during fasting and postprandial states in healthy volunteers (16–19) and in patients with renal disease and/or renal failure (3–5, 20–22). Table 3 indicates the values obtained before and after 3 mo on a low-protein diet. The fasting leucine rate of appearance (Table 3) and fasting leucine oxidation (Table 3 and Figure 1) decreased by 8% and 18%, respectively (P < 0.05) after reducing protein intake. These facts indicate that a protein-sparing mechanism occurred in response to the reduction of
mostly during shorter studies. Goodship and sustained protein-sparing mechanism. (18%, Table 3 and Figure 1) is suggestive of an important oxidation decrease we observed after 3 mo of protein reduction patients with mild CRF, and the magnitude of the amino acid protein intake. The metabolic adaptation, hence, is present in patients with mild CRF, and the magnitude of the amino acid oxidation decrease we observed after 3 mo of protein reduction (−18%, Table 3 and Figure 1) is suggestive of an important and sustained protein-sparing mechanism.

Other studies have reported similar findings in CRF patients who were undergoing different types of diet intervention but mostly during shorter studies. Goodship et al. (3) studied six patients with moderate CRF during a short-term (1 wk) regular (1 g of protein/kg per d) or reduced protein intake (0.6 g of protein/kg per d) and energy intakes of 32.5 kcal/kg per d. Fasting leucine oxidation did not change significantly during the lower protein intake, whereas postprandial leucine oxidation decreased by approximately 25% (P < 0.05). Extending a comparable diet up to 3 mo in the present study induced a significant and sustained reduction in fasting leucine oxidation (Table 3). Altogether, these data show that patients with moderate CRF can adapt their protein metabolism during acute and chronic protein intake reductions by reducing amino acid oxidation during both postprandial and fasting states.

More profound protein restrictions reduce amino acid oxidation to a greater magnitude. Masud et al. (5) showed in six predialysis patients that a diet that provided 0.35 g of protein/kg per d supplemented with either ketoacids or essential amino acids for 25 d allowed for maintaining neutral nitrogen balances and body composition. These diets were associated with very low leucine oxidation values, which were not different whether patients were supplemented with ketoanalogs or essential amino acids (5). In a long-term follow-up of these patients (16 mo), the fasting leucine oxidation remained at a low level of 10.0 ± 2.2 μmol/kg per h (4). As compared with the present study (baseline, 16.8 ± 4.2; low-protein diet, 13.8 ± 2.4 μmol/kg per h; Table 3), these amino acid oxidation values seem to be even lower in response to a lower protein intake, thus suggesting a potential “functional reserve” for protein sparing in CRF patients.

The addition of ketoacid supplements to the low-protein diet did not modify the protein metabolism as assessed by leucine turnover measurement (Table 3). Although there was a trend to a greater decrease in turnover values in the nonsupplemented group, none of these changes was significant. It could be argued that the protein restriction that we studied here was not restricted enough to observe the nitrogen-sparing effect of ketoacid administration. Indeed, in other diet intervention studies in uremia, the protein intake was reduced to a greater extent and generally averaged 0.3 to 0.5 g of protein/kg per d (4,5,23).

Amino acids were measured before and after the protein intake reduction (Table 4). Overall, there was almost no change in plasma essential, nonessential, and total amino acids. Branched chain amino acids did not vary between periods and within groups, whether patients received ketoacids or not, as reported by Masud et al. (5). In the ketoanalog-supplemented group, plasma tyrosine decreased by 15% (P < 0.05; Table 4), although tyrosine was included in the ketoanalog supplement (153 mg/pill, corresponding to an intake of 1.2 to 2 g/d). In the low-protein group that was not supplemented with ketoanalogs, arginine decreased by 34% (P < 0.05). More important, the essential/nonessential amino acid ratio (EAA/NEAA) decreased by 23% from 0.47 ± 0.07 to 0.36 ± 0.04 (P < 0.05) as a result of an increase in nonessential amino acids. These values are in agreement with those published by Kopple et al. (11,14). The absence of a comparable decrease of EAA/NEAA in the ketoanalog-supplemented group may be compatible with a better nutritional response. However, the absence of significant essential amino acid decrease in both groups during the study also is an important fact to consider (Table 4).

Finally, another indirect index for an adequate protein metabolism response is that serum insulin-like growth factor-1, a sensitive marker of body protein status (24,25), did not decrease during the 3-mo diet in each group (all patients: baseline, 278 ± 20 μg/L; end, 257 ± 20 μg/L) (26), thus indicating a well-preserved body protein compartment.

In summary, this is the first report of a 3-mo moderate reduction in protein intake in mild CRF patients that shows an adequate metabolic and body composition response. This suggests that under an energy intake >31 kcal/kg per d, a protein intake of 0.7 g/kg per d is metabolically and nutritionally safe. According to the current evidence for prescribing a low-protein diet to patients with mild CRF (27–29), this study confirms that such a diet therapy is worth being proposed to patients. Whether patients eventually will accept it certainly may rely more on physicians’ beliefs and enthusiasm.

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