Peritoneal Dialysis with Solutions Containing Amino Acids Plus Glucose Promotes Protein Synthesis during Oral Feeding

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Inadequate food intake plays an important role in the development of malnutrition. Recently, an increased rate of protein anabolism was shown in fasting state in patients who were on automated peritoneal dialysis with combined amino acids (AA) and glucose (G) dialysate serving as a source of both proteins and calories. This study investigated the effects of such a dialysis procedure in the daytime in the fed state in patients who were on continuous ambulatory peritoneal dialysis (CAPD). A crossover study was performed in 12 CAPD patients to compare, at 7-d intervals, a mixture of AA (Nutrineal 1.1%) plus G (Physioneal 1.36 to 3.86%) versus G only as control dialysate. Whole-body protein turnover was studied by primed constant intravenous infusion of $^13$C-leucine during the 9-h dialysis. For meeting steady-state conditions during whole-body protein turnover, frequent exchanges with a mixture of AA plus G were done using an automated cycler. Fed-state conditions were created by identical liquid hourly meals. Using AA plus G dialysate, as compared with the control, rates of protein synthesis increased significantly ($2.02 \pm 0.08$ versus $1.94 \pm 0.07 \, \mu$mol leucine/kg per min [mean ± SEM]; $P = 0.039$). Rates of protein breakdown and net protein balance did not differ significantly between AA plus G and G. In conclusion, dialysate that contains AA plus G also improves protein synthesis in fed CAPD patients. The use of such a mixture may contribute to long-term improvement of the nutritional status in malnourished CAPD patients with deficient food intake.


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were collected before starting the oral feeding at 8:20 a.m. The dialysis one for continuous infusion of the tracer solution, the other for repeated a.m., two catheters were inserted into superficial veins on both arms, dialysis period between 3:30 p.m. and 6:30 p.m. At approximately 8:20

\[\text{Figure 1. Schematic diagram of the study-day protocol. } \text{△, portions of the liquid food, the first two portions given half-hourly and thereafter hourly; } \text{▲, time points of blood sampling; } \text{△ time points of breath sampling.}\]

Figure 1. Schematic diagram of the study-day protocol. △, portions of the liquid food, the first two portions given half-hourly and thereafter hourly; ▲, time points of blood sampling; △ time points of breath sampling.

exchanges of G-based dialysis fluid (Physioneal 1.36 to 3.86%) in the daytime and a nighttime dwell of Physioneal 1.36 to 3.86% or Extraneal (Baxter BV). The night before the study days, all patients underwent dialysis with Extraneal. Patients were randomly assigned by drawing one of 12 sealed envelopes to determine whether patients started with either AAG or G on the first study day. Six patients each were allocated to start with AAG dialysis and G dialysis. On the 2 study days, the patients stayed at the Department of Nephrology of the Erasmus MC. They came at 8:00 a.m. and left at the end of the study after inflow of their usual nightly dialysate. At the end of each study day, they continued their usual dialysis scheme. During the 2 study days, the patients consumed a liquid complete diet that was comparable in nitrogen and energy content to their habitual diet. In each patient, dietary counseling had been performed at least once per 6 mo as a standard practice in our department.

Subjective Global Assessment

Subjective global assessment (SGA) as described by Detsky et al. (19) is based on clinical parameters. Patients are classified according to their nutritional status into three groups: A, good nutritional status; B, moderate malnutrition; or C, severe malnutrition.

Dialysis Procedures

Six daytime exchanges were performed automatically using a cycler (HomeChoice; Baxter BV). The AAG dialysate was obtained by mixing one bag of 2.5 L of Nutrineal 1.1% (containing 27.5 g of AA), and four bags of 2.5 L of Physioneal 1.36 to 3.86% G. For G dialysis, five bags of 2.5 L of Physioneal 1.36 to 3.86% were infused. G concentrations were individualized depending on ultrafiltration targets. The composition of the AA 1.1% dialysis solution and the precise mixing procedures that were required to obtain metabolic steady-state conditions for WBPT studies were performed as described previously (18).

WBPT Studies

Rates of WBPT were determined with a primed continuous intravenous infusion of [1-13C]-leucine, which was carried out at the end of the 9-h dialysis period between 3:30 p.m. and 6:30 p.m. At approximately 8:20 a.m., two catheters were inserted into superficial veins on both arms, one for continuous infusion of the tracer solution, the other for repeated blood sampling. Baseline blood samples and expiratory breath samples were collected before starting the oral feeding at 8:20 a.m. The dialysis started at 9:30 a.m. (T_0). At 3:30 p.m., priming doses of [1-13C]-leucine (3.8 μmol/kg) and of NaH13CO3 (1.7 μmol/kg) were given to label the leucine and CO2 pools, followed by a continuous infusion of [1-13C]-leucine (infusion rate 0.063 μmol/kg per min) and continued for 180 min until the end of the dialysis period at 6:30 p.m. (T_540). For measurement of plateau plasma keto-isocaproic acid (KIC) and CO2 [13C] enrichment, blood and expired air samples were collected simultaneously at T_480, T_510, T_525, and T_540 min (i.e., at 120, 150, 165, and 180 min) after priming and starting the tracer infusion. Indirect calorimetry (Deltatrac metabolic monitor; Datex, Helsinki, Finland) was performed to measure CO2 production. Patients were not allowed to eat except their liquid diet during the whole study day; however, noncaloric beverages were permitted.

Liquid Diet

A renal dietitian instructed the patients to keep a 4-d food diary. On the basis of these food records and a subsequent dietary interview, the appropriate calorie and protein content of the study diet was calculated. The prescribed study diet consisted of a combination of two commercially available complete liquid nutritional products (NutraCare, Fortimel; Nutricia, Zoetermeer, The Netherlands). The total food volume was divided into 11 equal portions. The first two meal portions were given at half-hourly intervals, and the remaining nine portions were given at hourly interval thereafter (Figure 1).

Analytical Determination

Leucine carbon flux was calculated from the [13C] enrichment of KIC as described previously (18,20). In brief, the [13C] enrichment was determined by gas chromatography–mass spectrometry by measurement of the fragments 259 and 260 of natural- and [13C]-KIC, respectively. Oxidation of [1-13C]leucine was determined by measurement of breath CO2 [13C] enrichment.

Blood Chemistries

Blood samples were taken before the first dialysate exchange (fasting state) and at the end of the study days. Insulin was measured by a chemiluminescent immunoassay (Immulite 2000 Insulin; DPC, Los Angeles, CA). The other determinations were performed by routine laboratory procedures.

Calculations of WBPT

Metabolic leucine carbon flux was calculated as described previously (21). On the basis of the one-pool model at equilibrium, leucine carbon flux (Q) is equal to the sum of endogenous leucine appearance from protein breakdown (B) plus exogenous leucine appearance through oral intake (I_o) and via dialysate (I_d). At metabolic equilibrium, Q is equal to the sum of leucine disappearance into body proteins (S) plus leucine oxidation (O). Thus, Q = S + O = B + I_d + I_o. Plasma KIC enrichment provides a better estimate of intracellular leucine enrichment than does plasma leucine enrichment because KIC is derived from intracellular leucine metabolism (20). Leucine flux in μmol/kg per hr is calculated as Q = Inf (E_i/Plasma KIC − 1), where Inf is the leucine infusion rate (μmol/kg per hr), E_i is the [13C] enrichment of the I-[1-13C]leucine infused, and E_plasma KIC is the [13C] enrichment of plasma KIC as measured at isotopic equilibrium. Isotopic steady state (plateau plasma [13C]KIC enrichment) was found between T_460 and T_540 max. Leucine oxidation (O, μmol/kg per hr) is calculated as O = F^13CO2 (1/E KIC – 1/E_i) × 100, where F^13CO2 (in μmol [13C]/kg per hr) is the rate at which [13C]CO2 is expired as calculated from CO2 [13C] enrichment in expired air and from CO2 production. Leucine absorption from dialysate (I_d) was calculated by subtracting the amount of leucine in spent dialysate from that in fresh dialysate. Loss of leucine (L_d) in G dialysate was included in the total rate of disappearance of leucine. Thus, during G dialysis, Q = B + I_d + L_d = S + O. A fraction of 0.25 of absorbed leucine was assumed for the retention in the splanchnicus bed (22). This correction factor was ap-
plied for leucine both from diet and dialysate. A fraction of 0.32 was assumed for the oxidation of leucine taken up by the splanchnic region (22). Therefore, leucine fluxes and rates of whole-body protein synthesis and breakdown corrected for splanchnic uptake were calculated as follows: \( Q_c = \text{measured flux} + (I_o + I_d) \times 0.25 \), where \( Q_c \) is the corrected flux. The corrected oxidation \( (O_c) \) was calculated as \( Q_c = \text{measured oxidation} + (I_o + I_d) \times 0.25 \times 0.32 \). The corrected protein synthesis \( = Q_c - O_c \). The corrected breakdown \( B_c = Q_c - (I_o + I_d) \).

**Statistical Analyses**

Data were analyzed using the statistical program SPSS, version 11.0, for Windows (SPSS Inc., Chicago, IL). Data are expressed as mean ± SEM or indicated otherwise. The paired \( t \) test was used to compare differences between the two treatment regimens (AAG versus G dialysis). This comparison also was done in the subgroup of malnourished patients. The unpaired \( t \) test was used to compare differences regarding protein synthesis, protein breakdown, and net protein balance between the present fed state study and the previous published fasting state study. Differences were considered statistically significant when the two-sided \( P \) value was < 0.05. Power calculations, based on our previous study (18), had led to 12 patients for this crossover study.

**Results**

The baseline characteristics of the 12 patients are shown on Table 1. Three patients (1, 3, and 5) were anuric, whereas most of the other patients had a substantial residual renal function. According to the SGA classification in this study, four of the 12 patients were moderately malnourished. None of the patients used prednisone. The study protocol was well tolerated by all patients. No complaints of nausea or other adverse reactions were reported during the AAG dialysis. None of the patients dropped out of the study.

**WBPT**

Essential conditions for measuring WBPT were met as shown in Figures 2 and 3, showing that isotopic steady state in plasma \( ^{13}\text{C} \)-KIC and exhaled breath \( ^{13}\text{C} \)-CO\(_2\) was reached within the time frame of sampling (T\(_{480}\) to T\(_{540}\)). There was a slight increase in breath \( ^{13}\text{C} \)-CO\(_2\) enrichment on feeding with liquid food. However, a new steady state was reached before sampling for analytical purposes was started (Figure 3). In this study, we measured that net peritoneal absorption of leucine was 39.3 ± 7.1% of the supplied amount.

Protein turnover results in Table 2 show that the leucine flux with AAG mixture was increased compared with G dialysis (2.90 ± 0.13 versus 2.67 ± 0.11 \( \mu \)mol leucine/kg per min; mean difference 0.23 ± 0.05 \( \mu \)mol leucine/kg per min; \( P = 0.001 \)). Leucine oxidation increased significantly with AAG dialysate compared with G dialysate (0.88 ± 0.06 versus 0.74 ± 0.06 \( \mu \)mol leucine/kg per min; mean difference 0.14 ± 0.02 \( \mu \)mol leucine/kg per min; \( P = 0.001 \)). Protein synthesis increased significantly with the mixture (2.02 ± 0.08 versus 1.94 ± 0.07 \( \mu \)mol leucine/kg per min; mean difference 0.08 ± 0.04 \( \mu \)mol leucine/kg per min; \( P = 0.039 \)). Overall, net protein balance was not significantly increased using AAG dialysate compared with G dialysate (mean difference 0.03 ± 0.03 \( \mu \)mol leucine/kg per min; \( P = 0.347 \)). There also were no significant differences regarding protein breakdown (\( P = 0.346 \)).

Within the subgroup of malnourished patients (Table 1, SGA classification B, \( n = 4 \)), the net protein balance with AAG was significantly higher than with G dialysis (mean difference 0.13 ± 0.02 \( \mu \)mol leucine/kg per min; \( P = 0.0063 \)). This difference was significantly higher (unpaired \( t \) test \( P = 0.0058 \)) than the corresponding value in the group of eight well-nourished patients (difference −0.02 ± 0.03 \( \mu \)mol leucine/kg per min).

**Protein and Energy Intake**

Table 1 shows the average prestudy (i.e., habitual) dietary protein and calorie intake estimates based on a dietary interview and 4-d food records. The proportion of dietary energy and protein varied between 107 and 157 kcal/gN (mean 141 kcal/gN). The liquid food contained on average 0.96 ± 0.2 g protein/kg per d and 22 ± 5.0 kcal/kg per d, which was consumed completely and was well tolerated in all patients.

**Table 1. Baseline characteristics of the patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Primary Diagnosis of Renal Disease</th>
<th>Time on PD (mo)</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>BMI (wt/h(^2))</th>
<th>SGA</th>
<th>PET</th>
<th>Kt/V</th>
<th>nPNA (g/kg per d)</th>
<th>Protein (g/kg per d)</th>
<th>Energy (kcal/kg per d)</th>
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<td>M</td>
<td>69</td>
<td>32.8</td>
<td>B</td>
<td>H</td>
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<td>0.59</td>
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<td>43</td>
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<td>B</td>
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<td>H</td>
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<tr>
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<td>HA</td>
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<td>1.37</td>
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<td>0.40</td>
<td>0.24</td>
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</table>

* A, good nutritional status; B, moderate malnutrition; BMI, body mass index; H, high; HA, high average; LA, low average; nPNA, normalized protein equivalent of nitrogen appearance (PD Adequeat 2.0 software; Baxter); PET, peritoneal equilibrium test; SGA, subjective global assessment.
The proportion of dialysate energy and protein ranged from 124 to 243 kcal/gN (mean 161 kcal/g/N).

Biochemical Parameters

As shown in Table 3, serum bicarbonate, creatinine, urea, G, and insulin concentrations did not show a statistically significant difference between AAG and G dialysis. Insulin levels significantly increased during both AAG and G dialysis as compared with fasting baseline conditions. During dialysis, serum creatinine decreased. Mean plasma leucine concentrations were significantly increased with AAG compared with G dialysate (P = 0.003). The loss of leucine into dialysate during G dialysis was 0.65 ± 0.11 μmol/L. Protein loss and excretion of urea in dialysate did not differ with either type of dialysate.

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Discussion

Recently, we reported that intraperitoneal administration of calories combined with AA to fasting automated peritoneal dialysis patients as part of their regular nightly dialysis scheme improved protein anabolism (18). In this study, we investigated whether AAG dialysate could serve as a useful extra supply of nutrients to CAPD patients in a fed state, considering that many of these patients have deficient intake of protein and calories as a result of anorexia. WBPT studies were carried out in fed-state CAPD patients in the daytime using a primed constant infusion of a stable isotope. Instead of manual changes of dialysis fluids, AAG solutions frequently were exchanged using an automated cycler to achieve the steady-state conditions that were required for the WBPT studies.

Administration of AAG dialysate increased both leucine flux and leucine oxidation significantly compared with G dialysate. Although the amount of AA absorbed from the peritoneal cavity was small in comparison with dietary AA intake, there were significant metabolic effects. These metabolic responses are in line with other studies that reported that an increased protein supply stimulates both flux and oxidation. In contrast, in the fasting state (18), AAG dialysate did not stimulate oxidation, which agrees with studies that showed that low protein intake does not increase oxidation (23,24). Despite the increased oxidation, extra intraperitoneal AA stimulated protein synthesis significantly. Protein breakdown and net protein balance (i.e., synthesis minus breakdown) did not change significantly with AA dialysate.

Figure 2. Plateau 13C-ketoisocaproic acid (KIC) enrichment during whole-body protein turnover (WBPT) study. 13C-KIC values (mean ± SD) in 12 patients in moles percent excess (MPE). ▲, amino acids plus glucose (AAG) dialysis; △, glucose dialysis.

Figure 3. The course of the breath 13CO2 levels during consumption of the liquid meals and during the WBPT study with AAG dialysate. Values (mean ± SD) in 12 patients are expressed in Atom % 13CO2.
Retention of absorbed leucine in the splanchnic bed may have influenced the results of the net protein balance. Splanchnic extraction cannot be measured directly, and a reliable assessment is difficult. Retention of 10 to 32% of gut-absorbed dietary leucine has been reported (22,25–28). Little is known about splanchnic retention of peritoneally absorbed AA (15). We assumed a value of 25% for both orally and peritoneally absorbed AA (22). Assuming increasing values of splanchnic retention brings about that the effects of protein intake shift from inhibition of protein breakdown to stimulation of protein synthesis.

The peritoneal absorption of leucine, calculated as the difference between the amounts in fresh and spent dialysate, ranged from 29 to 51% with a dwell time of approximately 1 h. These values are similar to those reported elsewhere (15,17). In the standard CAPD procedure with a dwell time of 4 to 6 h, AA absorption is considerably higher (15,29,30). Plasma leucine levels increased significantly with the AA dialysis fluid.

Table 2. Whole-body protein turnovera

<table>
<thead>
<tr>
<th>Patient</th>
<th>Fluxb</th>
<th>Oxidationc</th>
<th>Intake</th>
<th>Synthesisd</th>
<th>Breakdowne</th>
<th>Net Protein Balancef</th>
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<td>0.28</td>
<td>0.21</td>
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</table>

aIndividualized data are expressed in /mol leucine/kg per min. AAG, combined amino acids plus glucose dialysis; G, glucose dialysis.
bP = 0.001 for flux on AAG versus G dialysis.
cP < 0.001 for oxidation on AAG versus G dialysis.
dP = 0.039 for synthesis on AAG versus G dialysis.
eP = 0.346 for breakdown on AAG versus G dialysis.
fP = 0.347 for net protein balance (is synthesis minus breakdown) on AAG versus G dialysis.

Table 3. Serum biochemistry at baseline and at the end of dialysisa

<table>
<thead>
<tr>
<th></th>
<th>Baseline AAG Dialysis</th>
<th>End AAG Dialysis</th>
<th>Baseline G Dialysis</th>
<th>End G Dialysis</th>
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</thead>
<tbody>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>23.7 ± 3.3</td>
<td>25.6 ± 3.3b</td>
<td>24.1 ± 3.6</td>
<td>25.8 ± 2.8c</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>22.0 ± 7.6</td>
<td>21.8 ± 6.5</td>
<td>20.5 ± 7.6</td>
<td>20.0 ± 6.9</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>841 ± 225</td>
<td>762 ± 213b</td>
<td>835 ± 240</td>
<td>773 ± 208b</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.8 ± 1.0</td>
<td>6.2 ± 2.6c</td>
<td>4.2 ± 1.1</td>
<td>5.7 ± 2.1c</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>134 ± 76</td>
<td>495 ± 339b</td>
<td>133 ± 86</td>
<td>458 ± 243b</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>12.2 ± 6.9</td>
<td>12.2 ± 7.8</td>
<td>9.1 ± 10.6</td>
<td>10.8 ± 13.3</td>
</tr>
<tr>
<td>Plasma leucine (μmol/L)</td>
<td>108 ± 17.4</td>
<td>198 ± 40.8b</td>
<td>102 ± 10.3</td>
<td>172 ± 37b,d</td>
</tr>
<tr>
<td>Dialysate leucine (μmol/L)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0.65 ± 0.11</td>
</tr>
<tr>
<td>Dialysate urea (mmol/9 h)</td>
<td>ND</td>
<td>174 ± 59.1</td>
<td>ND</td>
<td>163 ± 61.1</td>
</tr>
<tr>
<td>Dialysate protein (g/9 h)</td>
<td>ND</td>
<td>3.9 ± 2.9</td>
<td>ND</td>
<td>4.0 ± 2.8</td>
</tr>
</tbody>
</table>

aData are mean ± SD. CRP, C-reactive protein; ND, not determined.
bP < 0.01 and cP < 0.05 versus baseline.
dP < 0.01 versus end AAG dialysis.
higher plasma leucine levels as a result of feeding may have caused a slightly lower absorption rate of intraperitoneal AA as a result of a decreased gradient compared with the fasting state.

Calories have an inhibitory effect on protein breakdown via stimulation of insulin secretion, whereas AA may exert a separate and additive effect (31,32). In this study, the intake of calories was virtually the same during AAG and G dialysis. Intraperitoneal AA did not lead uniformly to lower protein degradation; neither was it associated with a different insulin response.

Comparing the results of this and our previous published studies (18) in similar patients, we found that protein synthesis rates were significantly higher in the fed state as compared with the fasting state with both AAG and G dialysis. The synthesis rates (mean values in µmol leucine/kg per min) using AAG dialysate were 2.02 (fed state; n = 12) as compared with 1.20 (fasting state; n = 12) versus 1.10 (fasting state; n = 8; P < 0.001) and using G only dialysate were 1.94 (fed state; n = 12) versus 1.10 (fasting state; n = 8; P < 0.001). Protein breakdown did not significantly differ in response to feeding between the two studies with both AAG and G dialysis. This suggests that ingested protein was used mainly for stimulation of protein synthesis. That G-containing dialysate has been found to inhibit protein breakdown in fasting patients during moderate hyperinsulinaemia may explain why feeding did not inhibit proteolysis further (16). Net protein balance was negative during fasting but became positive in all patients who were taking oral food, as also has been demonstrated in healthy people and hemodialysis patients (23,33).

Giving dialysis fluid that contains a mixture of AA and G guarantees simultaneous supply of both protein and calories when oral intake of proteins and calories is deficient in anorectic CAPD patients. In this study, most patients were not malnourished according to the SGA classification.

In a subgroup analysis, we compared the results of WBPT in the four malnourished patients (SGA-B) with the eight well-nourished ones (SGA-A). In malnourished patients, the AAG dialysate showed a statistically significant increase in net protein balance compared with the G dialysate. This suggests that the nutritional state may play a role in the metabolic effects of AAG dialysis.

This study is the first to examine the metabolic effects of AA absorbed from AAG-containing dialysate on WBPT in fed CAPD patients. The results represent acute effects that were obtained in a relatively well-nourished and stable CAPD population. Further work is needed to evaluate the metabolic effects of AAG dialysate in the presence of inflammation or in malnourished patients.

Conclusion

Even in a fed state, dialysis solutions that contain AAG improve protein synthesis in CAPD patients. These solutions could function as a nutritional supplement and may help to improve the nutritional state in CAPD patients with deficient intake of both proteins and calories. For assessment of the long-term effects on nutritional status, morbidity, and mortality in different subgroups, studies in a large number of patients are needed.

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Disclosures

None.

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