KETOACID SUPPLEMENTATION PARTIALLY IMPROVES METABOLIC PARAMETERS IN PATIENTS ON PERITONEAL DIALYSIS

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Background: A low protein diet supplemented with ketoacids has been shown to improve the metabolic profile, including insulin resistance, in patients with chronic kidney disease (CKD), but whether ketoacids alone exert similar effects is unknown. In this prospective randomized controlled trial, we aimed to evaluate the effects of ketoacid supplementation on insulin resistance, systemic inflammation, oxidative stress and endothelial dysfunction among 100 CKD patients undergoing peritoneal dialysis (PD).

Methods: Patients from one Chinese PD center were randomly assigned to take ketoacids (12 tablets per day) (n = 50) versus a control group (n = 50) for 6 months in an open-label parallel-arm design. Daily protein intake of 0.8 - 1.2 g/kg/d and daily energy intake of 25 - 35 kcal/kg/d was prescribed to both groups. Insulin resistance was evaluated using homeostatic model assessment (HOMA-IR) index as the primary outcome. We assessed systemic inflammation using high-sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6), oxidative stress using plasma oxidized low density lipoprotein (oxLDL), adipokines using leptin and adiponectin and endothelial dysfunction using serum soluble intercellular adhesion molecule-1 (sICAM) and soluble vascular adhesion molecule-1 (sVCAM) as secondary outcomes.

Results: There were no significant differences in baseline characteristics between the 2 groups except a slightly higher age in patients assigned to the intervention. A total of 89% of participants completed the 6-month intervention. There was no significant difference in the change of HOMA-IR values from baseline between groups after adjusting for baseline age, gender, body mass index and HOMA-IR. For secondary outcomes, hs-CRP varied significantly between groups (p = 0.02), increasing over time for the control group while remaining stable for the ketoacid group. Similarly, the leptin/adiponectin ratio (LAR) differed between groups (p < 0.001), remaining stable in the ketoacid group but increasing in the control group.

Conclusion: Ketoacid therapy administered for 6 months had no effect on HOMA-IR but resulted in improvements in hs-CRP and LAR, suggesting metabolic benefit. Future studies are needed to confirm these results and any potential benefit in vascular health of PD patients.

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Received 29 May 2014; accepted 12 December 2014.

KEY WORDS: Ketoacids; insulin resistance; metabolic; peritoneal dialysis; PD.

Cardiovascular disease is highly prevalent in chronic kidney disease (CKD) patients, including those on maintenance dialysis. Certain metabolic abnormalities seen in CKD such as insulin resistance are shown to be independent predictors of cardiovascular mortality in non-diabetic maintenance dialysis patients (1,2). Peritoneal dialysis (PD) patients are considered to be at increased risk for insulin resistance (3), presumably due to the extra glucose load from the dialysate required for ultrafiltration (4,5) although data are scarce. Limited data indicate that the prevalence of insulin resistance combined with dyslipidemia and weight gain is increased in PD patients as components of metabolic syndrome (6,7). Peritoneal dialysis patients also suffer from other metabolic abnormalities, including but not limited to increased systemic inflammation, increased oxidative stress burden and endothelial dysfunction, which collectively predispose these patients to an exaggerated cardiovascular disease risk (8). Interventions targeted for improving one or more of these derangements could potentially ameliorate the cardiovascular disease risk and mortality in PD patients.

Several small-scale studies exploring the effects of low-protein diets supplemented with ketoacids on glucose metabolism have indicated that this intervention could improve liver and peripheral tissue insulin sensitivity in non-dialyzed CKD patients (9,10). One potential explanation is the reduction of circulating uremic toxins due to the reduced protein intake (11). In addition, the keto-analogs of essential amino acids could also have direct effects on insulin sensitivity (12–14). Further, components of ketoacid supplementation could improve other co-existing metabolic abnormalities such as inflammation and oxidative stress (15–17) and could indirectly prevent worsening of insulin resistance. There are currently no studies examining beneficial metabolic effects of ketoacid supplementation with a regular protein diet in PD patients.

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In this study, we examined this issue through a randomized controlled trial involving the administration of ketoacids as part of a regular protein diet in prevalent PD patients over a period of 6 months. Since insulin resistance is intricately involved in other metabolic abnormalities such as systemic inflammation, oxidative stress and endothelial dysfunction (8,18,19), we also examined these factors as secondary outcomes to explore the potential additional benefits of ketoacids.

**METHODS**

**STUDY PARTICIPANTS**

Participants were recruited from the Renal Division, Peking University First Hospital. Inclusion criteria included medically stable non-diabetic patients 18 – 80 years old, who had a body mass index greater than 18.5, had been on PD for more than 3 months, and were delivered an adequate dose of dialysis (Kt/V ≥ 1.7 or Tccr ≥ 50 L/week/1.73 m²) using glucose lactate-buffered PD solutions. Patients with severe and unstable inflammation disease (active systemic infection, active connective tissue disorder, active cancer, human immunodeficiency virus (HIV), liver disease), overt protein-energy wasting, those who were pregnant, took anti-inflammatory medication chronically or had severe hematologic disease (active  systemic  infection, active connective tissue disorder, active cancer, human immunodeficiency virus (HIV), liver disease), overt protein-energy wasting, those who were pregnant, took anti-inflammatory medication chronically or had severe hematologic disease (active systemic infection, active connective tissue disorder, active cancer, human immunodeficiency virus (HIV), liver disease), overt protein-energy wasting, those who were pregnant, took anti-inflammatory medication chronically. Each participant was trained on dietary intake and 3-day dietary diary by a skilled dietitian at the start of the study. All subjects tried to maintain a diet of no more than 2.3 g/kg/d, 0.8–1.2 g/kg/d of daily protein intake (DPI) and 25–35 kcal/kg/d of daily energy intake (DEI), based on our previous data (20). During the follow-up, all patients completed 3-day dietary records before the visit each month. The dietitian checked the diary using food models and re-trained patients on how to keep the regular protein diet regime needed. The total daily sodium intake was calculated using a computer software program (PD information Management System, Peritoneal Dialysis Center, Peking University, Beijing, China). The total caloric intake includes intakes from dietary and dialysate sources. Both DPI and DEI were normalized for standard body weight (nDPI and nDEI).

**INTERVENTIONS**

**Regular Protein Diet (Control Group)**

Each participant was trained on dietary intake and 3-day dietary diary by a skilled dietitian at the start of the study. All subjects tried to maintain an intake of no more than 2.3 g/kg/d, 0.8–1.2 g/kg/d of daily protein intake (DPI) and 25–35 kcal/kg/d of daily energy intake (DEI), based on our previous data (20). During the follow-up, all patients completed 3-day dietary records before the visit each month. The dietitian checked the diary using food models and re-trained patients on how to keep the regular protein diet regime if needed. The actual daily nutrient intake was calculated using a computer software program (PD information Management System, Peritoneal Dialysis Center, Peking University, Beijing, China). The total caloric intake includes intakes from dietary and dialysate sources. Both DPI and DEI were normalized for standard body weight (nDPI and nDEI).

**Usual Protein Diet Supplemented with Ketoacids (Ketoacid Group)**

Patients assigned to the ketoacid group were prescribed the same dietary regimen as those in the control group. The ketoacids (Ketosterils, Fresenius Kabi, Ltd, Bad Homburg, Germany) consisting of 12 tablets were divided into 3 doses and were taken during meals. We elected to give a standard dose rather than a weight-based dose to improve compliance. Based on the patients’ weight at enrollment, 12 tablets a day corresponded to a dose range of 88–195 mg/kg.

**MEASUREMENTS**

Demographic data, biochemistry, nutrition status, and dialysis adequacy were collected at baseline. Demographic data included age, gender, body mass index, and comorbidity evaluated by the Charlson index as previously described. Biochemical indices, including hemoglobin, serum albumin, prealbumin, blood urea nitrogen, serum creatinine, calcium,
phosphate, potassium, and serum lipids, were examined using an automatic Hitachi chemistry analyzer. The dialysis prescription was recorded 1 day before clinic visit. Also, the 24-hour urine and dialysate sample was collected. The urea, creatinine and glucose levels in 24-hour urine, 24-hour dialysate and serum were simultaneously examined by using the automatic Hitachi chemistry analyzer. Weekly total, peritoneal and renal Kt/V urea, weekly total peritoneal and renal creatinine clearance (Ccr), and residual renal function were calculated using standard methods. Residual renal function was estimated using the average renal clearance of urea and creatinine.

**PRIMARY AND SECONDARY OUTCOMES**

The primary outcome was insulin resistance measured at basal states using homeostatic model assessment (HOMA-IR) index in all subjects. The estimate of insulin resistance by HOMA-IR score was calculated with the formula: fasting serum insulin (μU/mL)**fasting plasma glucose (mmol/L)/22.5, as described by Matthews and colleagues (21). In PD patients, published data indicate a range of 2~8 with a standard deviation (SD) of 2.5 or so for HOMA-IR (22–24). Assuming a true difference between the intervention and control means to be 1.5, we need to study 45 intervention subjects and 45 control subjects to be able to reject the null hypothesis that this response difference is 0 with probability (power) 0.8. We recruited 100 subjects due to a 10–15% potential drop-out rate. The Type I error probability associated with this test of this null hypothesis was 0.05. As an alternative measure of insulin resistance more applicable to PD patients (18), we measured the leptin/adiponectin ratio (LAR).

Secondary outcomes were systemic inflammation, oxidative stress and endothelial dysfunction. We assessed systemic inflammation using high sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6). Oxidative stress was assessed using plasma oxidized low density lipoprotein (oxLDL). Endothelial dysfunction was evaluated using serum soluble intercellular adhesion molecule-1 (sICAM) and soluble vascular adhesion molecule-1 (sVCAM). The hs-CRP was measured by immune rate nephelometric analysis. Serum IL-6, leptin, adiponectin, sICAM and sVCAM were measured using the ELISA method (eBioscience, CA, USA). The plasma oxLDL was assayed using ELISA methods (Rapidbio, CA, USA). Blood samples were only collected for all above measurements if acute comorbidities were absent during 2 weeks.

The occurrence of PD-associated peritonitis and hospitalization was recorded for all subjects during the study period.

**STATISTICAL ANALYSIS**

Data are presented as proportions for categorical variables and mean ± SD for continuous variables. Patients’ 1-time data, including demographic data, biochemical, nutrition parameters, and markers of insulin sensitivity, inflammation, endothelial dysfunction, and oxidative stress, were compared using the chi-square test for categorical variables, and the Mann-Whitney U test for continuous variables. Changes over time were also compared between groups using a mixed-model analysis of variance, with bootstrap covariance accounting for correlation among repeated measures within a patient. The baseline value of the outcome variables was adjusted as a model covariate. Sensitivity analysis was performed with adjustment of patients’ age, gender, and body mass index in the model. In addition, changes in outcome variables over time were also assessed adjusting for treatment effect. All analyses were performed with SPSS software package (version 13.0, SPSS, Chicago, IL, USA) and a 2-sided significance level of at least 0.05 was required to reject the null hypothesis.

**RESULTS**

**SUBJECT ENROLLMENT AND FOLLOW-UP**

Out of 193 PD patients screened, 120 patients met the inclusion criterion and 100 patients were randomized in the study. Eight-nine patients completed the 6-month study; 42 in the ketoacids group and 47 in the control group (Figure 1). The reasons for 11 withdrawals were unwillingness to continue (3), gastrointestinal symptoms due to the ketoacids (3), death (1) and transfer to hemodialysis (4).

**BASELINE CHARACTERISTICS AND CLINICAL VARIABLES**

Baseline characteristics of the randomized subjects are shown in Table 1. In general, the study cohort had a preponderance of female subjects (59%) with a mean age of 53.8 ± 14.1 years and a Charlson index of 3 (2–4). The mean body mass index (23.3 ± 3.1 kg/m²) was consistent with the general PD population in China. The dialysis duration was 24 (7–47.8) months. Mean hemoglobin, serum albumin, total Kt/V and Ccr were indicative of a relatively well preserved nutritional status and adequate dialysis. The patients in the control group were slightly younger than those in the ketoacids group (p = 0.004). There were no statistically significant differences in study groups at baseline, month 3, or month 6 in other biochemical variables.

**METABOLIC PARAMETERS: INSULIN RESISTANCE, INFLAMMATION, OXIDATIVE STRESS AND ENDOTHELIAL DYSFUNCTION**

The primary outcome of the study was the change in HOMA-IR during the study period between the ketoacid and control groups. As depicted in Table 2, the change of HOMA-IR was not significant between groups (p = 0.90) or within groups (p = 0.13 in ketoacids group and 0.53 in control group). In terms of secondary outcomes, changes in serum adiponectin levels differed statistically significantly between groups (p = 0.01). Patients taking ketoacid tablets had a significant increase in serum adiponectin levels (p = 0.01) whereas those assigned to the control group had a decrease (p = 0.003) over 6 months. The changes of serum leptin levels did not differ between groups and within groups. The leptin/adiponectin ratio, which is
TABLE 1
Baseline Patient Characteristics (n=100)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=100)</th>
<th>Ketoacids (n=50)</th>
<th>Control (n=50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, %</td>
<td>41, 41%</td>
<td>23, 46%</td>
<td>18, 36%</td>
<td>0.31</td>
</tr>
<tr>
<td>Female, %</td>
<td>59, 59%</td>
<td>27, 54%</td>
<td>32, 64%</td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>53.8±14.1</td>
<td>57.7±12.2</td>
<td>49.8±14.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.3±3.1</td>
<td>23.3±2.8</td>
<td>23.3±3.5</td>
<td>0.98</td>
</tr>
<tr>
<td>Charlson index</td>
<td>3 (2–4)</td>
<td>3 (2–5)</td>
<td>2 (2–4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Dialysis duration, months</td>
<td>24 (7–48)</td>
<td>17 (6–47)</td>
<td>26 (9–61)</td>
<td>0.35</td>
</tr>
<tr>
<td>Primary disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN, %</td>
<td>16, 10%</td>
<td>10, 20%</td>
<td>6, 12%</td>
<td>0.13</td>
</tr>
<tr>
<td>CGN, %</td>
<td>45, 45%</td>
<td>19, 38%</td>
<td>26, 52%</td>
<td></td>
</tr>
<tr>
<td>CTIN, %</td>
<td>23, 24%</td>
<td>11, 22%</td>
<td>12, 24%</td>
<td></td>
</tr>
<tr>
<td>Other, %</td>
<td>16, 16%</td>
<td>10, 20%</td>
<td>6, 12%</td>
<td></td>
</tr>
<tr>
<td>Other variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>120±13</td>
<td>121.7±11.8</td>
<td>117.7±14.3</td>
<td>0.12</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>39±3</td>
<td>38.6±3.3</td>
<td>39.4±3.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Creatinine, umol/L</td>
<td>87±246</td>
<td>84±218</td>
<td>89±271</td>
<td>0.32</td>
</tr>
<tr>
<td>TKt/V</td>
<td>1.9 (1.7–2.2)</td>
<td>2.1 (1.8–2.3)</td>
<td>1.8 (1.7–2.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Tccr, L/w/1.73 m²</td>
<td>56.9 (49.2–70.8)</td>
<td>60.2 (53.0–71.3)</td>
<td>55.9 (47.9–68.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>RRF, mL/min</td>
<td>2.0 (0.5–4.2)</td>
<td>2.5 (0.9–4.4)</td>
<td>1.6 (0–3.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>2.0±1.2</td>
<td>1.8±0.9</td>
<td>2.2±1.4</td>
<td>0.97</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.9±0.9</td>
<td>4.9±1.2</td>
<td>4.9±0.8</td>
<td>0.61</td>
</tr>
</tbody>
</table>

HTN = hypertension; CGN = chronic glomerulonephritis; CTIN = chronic tubulointerstitial nephritis; TKt/V = total urea clearance; Tccr = total creatinine clearance; RRF = residual renal function.

Values are mean ± SE, median (25th – 75th percentile) or absolute numbers with percentages.

Ketoacids group: regular protein diet supplemented with keto acids; control: regular protein diet.

The change in hs-CRP levels was statistically significant between groups after adjusting for age, gender, body mass index and baseline levels of each metabolic parameter. The change in serumb IL-6 and oxLDL over time between groups (p = 0.22 and 0.29, respectively). Although the sICAM and sVCAM significantly decreased in the ketoacids group (p = 0.036 and 0.012, respectively) and did not change in the control group (p = 0.24 and 0.25, respectively), the comparisons in the change of these 2 variables over time were not significantly different between groups (p = 0.22 and 0.52, respectively) (Table 2).

COMPLIANCE TO DIETARY PRESCRIPTION AND KETOACIDS USAGE

All the subjects in the ketoacids and control groups completed 3-day dietary records and were evaluated with nutrient intake by a skillful dietitian. The mean nDPI and nDEI values at baseline, month 3, and month 6 were in accordance with the prescribed ranges (DPI: 0.93 ± 0.22, 0.93 ± 0.22, and 0.94 ± 0.18 g/kg/d for the ketoacids group, and 0.91 ± 0.18, 0.85 ± 0.18, and 0.84 ± 0.22 g/kg/d for the control group; DEI: 29.2 ± 6.1, 30.7 ± 6.1, 30.7 ± 6.1 kcal/kg/d for the ketoacids group, and 28.9 ± 5.2, 29.1 ± 5.2, and 29.5 ± 7.6 kcal/kg/d for the control group). The change of DPI but not DEI during the study period was significantly different between groups. The DPI was stable in the ketoacid group but gradually decreased in the control group after adjustment for the baseline value (p = 0.009). There was no difference in the change of serum albumin between groups (data not shown). In terms of the compliance to ketoacids, all subjects took 12 tablets of ketoacids per day as prescribed except for 3 cases that dropped out due to drug-associated gastrointestinal symptoms.

PD-ASSOCIATED PERITONITIS AND HOSPITALIZATION

During the study period, there were 3 episodes of peritonitis in the ketoacid group and 2 episodes of peritonitis in the control group. There were 3 (2 for peritonitis and 1 for tumor) and 2 (1 for peritonitis and 1 for severe volume overload) hospitalizations in the ketoacids and control groups, respectively.
TABLE 2
Markers for Insulin Resistance, Inflammation, Oxidative Stress and Endothelial Dysfunction at the Follow-Up Time Points During the Study Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 month (n=50)</th>
<th>3 month (n=45)</th>
<th>6 month (n=42)</th>
<th>p</th>
<th>0 month (n=50)</th>
<th>3 month (n=49)</th>
<th>6 month (n=47)</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-IR</td>
<td>3.1 (1.9–5.9)</td>
<td>4.9 (2.7–8.7)</td>
<td>5.1 (3.0–7.7)</td>
<td>0.13</td>
<td>4.3 (1.6–10.3)</td>
<td>4.9 (2.3–12.3)</td>
<td>5.3 (2.7–10.9)</td>
<td>0.53</td>
<td>0.90</td>
</tr>
<tr>
<td>Hs-CRP, mg/L</td>
<td>1.9 (0.9–5.4)</td>
<td>2.2 (0.9–5.3)</td>
<td>1.5 (0.4–5.5)</td>
<td>0.98</td>
<td>2.0 (0.8–5.6)</td>
<td>2.6 (1.1–5.7)</td>
<td>3.9 (1.3–10.9)</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>7.3 (5.3–9.8)</td>
<td>6.6 (5.3–10.3)</td>
<td>5.9 (4.6–10.7)</td>
<td>0.72</td>
<td>7.7 (4.5–12.7)</td>
<td>7.3 (4.9–13.1)</td>
<td>5.8 (4.0–9.0)</td>
<td>0.73</td>
<td>0.23</td>
</tr>
<tr>
<td>sICAM, ng/mL</td>
<td>450±178</td>
<td>416.2±171.8</td>
<td>346.9±171.9</td>
<td>0.036</td>
<td>446.7±157.4</td>
<td>491.9±231.0</td>
<td>421.7±239.7</td>
<td>0.24</td>
<td>0.22</td>
</tr>
<tr>
<td>sVCAM, ng/mL</td>
<td>1,330.6±509.7</td>
<td>1,390.2±620.2</td>
<td>1,018.8±538.8</td>
<td>0.012</td>
<td>1,217.8±501.8</td>
<td>1,417.4±625.9</td>
<td>1,376.5±675.8</td>
<td>0.25</td>
<td>0.52</td>
</tr>
<tr>
<td>OxLDL, ug/dL</td>
<td>27.3 (16.0–51.7)</td>
<td>23.7 (16.3–35.2)</td>
<td>22.1 (11.6–33.4)</td>
<td>0.17</td>
<td>27.5 (12.8–52.8)</td>
<td>28 (14.8–59.9)</td>
<td>24.1 (9.8–35.6)</td>
<td>0.33</td>
<td>0.29</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>21.9 (16.8–31.1)</td>
<td>23.7 (15.8–33.0)</td>
<td>24.6 (15.9–36.2)</td>
<td>0.24</td>
<td>23.6 (14.9–31.5)</td>
<td>23.6 (18.8–32.7)</td>
<td>23.0 (16.7–31.4)</td>
<td>0.63</td>
<td>0.53</td>
</tr>
<tr>
<td>Adiponectin, ug/mL</td>
<td>15.6 (7.7–22.4)</td>
<td>15.2 (7.3–26.1)</td>
<td>18.3 (7.4–31.3)</td>
<td>0.01</td>
<td>16.8 (11.0–29.8)</td>
<td>15.0 (10.5–27.2)</td>
<td>12.6 (8.0–25.0)</td>
<td>0.003</td>
<td>0.01</td>
</tr>
<tr>
<td>Leptin adiponectin ratio</td>
<td>1.5 (0.7–3.1)</td>
<td>1.5 (0.7–3.6)</td>
<td>1.3 (0.6–4.0)</td>
<td>0.75</td>
<td>1.2 (0.8–2.0)</td>
<td>1.4 (0.9–2.5)</td>
<td>1.7 (0.8–2.9)</td>
<td>0.008</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HOMA-IR = homeostatic model assessment; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; sICAM = soluble intercellular adhesion molecule-1; sVCAM = soluble vascular adhesion molecule-1; OxLDL = oxidized low density lipoprotein.
Values are mean ± SE or median (25th–75th percentile).
Ketoacid group: regular protein diet supplemented with ketoacids; control: regular protein diet.

**DISCUSSION**

In this study, we examined the effects of ketoacid supplementation on several metabolic abnormalities that are commonly observed in PD patients and are closely associated with cardiovascular risk. Our results showed that there was no statistically significant effect of ketoacids on insulin resistance as assessed by HOMA-IR index while LAR was significantly better in the ketoacid-supplemented group. We also showed that the ketoacid group maintained a lower inflammatory status as measured by hs-CRP values, but not by IL-6 measurements. There were no differences in biomarkers of oxidative stress and endothelial dysfunction in patients randomized to either group. Overall, these data indicate that ketoacid supplementation over 6 months improves the metabolic profile in our prevalent PD patients to some extent.

The primary outcome of interest in our study was insulin resistance. In contrast to studies showing that a low-protein diet supplemented with ketoacids improves insulin sensitivity in non-dialyzed CKD patients, we were not able to replicate these results in our PD patients, when insulin resistance is assessed by HOMA-IR. On the other hand, we were able to show a significant difference between groups in LAR in favor of ketoacid supplementation. There are several potential explanations for these conflicting results regarding measures of insulin resistance. First, the HOMA-IR index might not be the most sensitive marker to determine insulin resistance status in PD patients. We cannot determine whether the gold standard method to measure insulin resistance, the hyper-insulinemic euglycemic clamp technique, would have yielded different results. This technique was not included in the study due to its complexity. On the other hand, LAR has been recently suggested as a better marker of insulin resistance based on the biological properties of serum adiponectin and its effects on glucose homeostasis (18). Adiponectin has insulin-sensitizing effects that are mediated through the activation of AMP-activated protein kinase, which increases fatty acid oxidation and activates the peroxisome proliferator-activated receptor α (25). The role of leptin in insulin resistance is complex due to its combined insulin-sensitizing and insulin-resistance properties (26). Accordingly, LAR has been shown to have a better correlation with clamp technique than HOMA-IR in HD patients (27). Studies in both PD and HD patients have further indicated that LAR is a novel marker for atherosclerosis in...
KETOACIDS IMPROVE METABOLIC PARAMETERS

In addition, the administration of branched amino acids has been reported to decrease serum tumor necrosis factor-alpha (TNF-α) and increase serum adiponectin levels in animal models (15). Similarly, in overweight or obese subjects, leucine and pyridoxine combination administered for 4 weeks improved insulin resistance, accompanied by reduced inflammatory markers (TNF-α and CRP) and increased adiponectin levels (16). In addition, the administration of branched amino acid granules improved microinflammation and the metabolism of iron in hepatitis C Virus (HCV)-positive patients with liver cirrhosis and subsequently seemed to reduce the production of oxidative stress (17). While we observed significant benefits of ketoacids on systemic inflammation, these data should be interpreted with caution since the study was not primarily designed to assess that effect and we did not observe a significant effect on IL-6 levels.

In addition, it was noted that sICAM and sVCAM levels significantly decreased in the ketoacid group although no differences in those parameters between groups were observed. This data provided a novel clue for improving the endothelial dysfunction except for aerobic exercise and weight loss (29) in obese women, or low-carbohydrate/low-fat diets in diabetes (30). Overall, combined with the significant improvement observed in serum CRP and adiponectin levels, these results are encouraging and suggest a possible beneficial metabolic effect of ketoacid supplementation to some extent in PD patients.

This study has several strengths. This is one of the first randomized controlled trials to examine the effects of ketoacids on surrogate markers of cardiovascular disease in maintenance dialysis patients. The 6-month observation period with low dropout rate and good compliance to dietary and medication prescription is also a strength. The consistency within several outcomes indicates a biologically plausible beneficial metabolic effect.

There are also several limitations. The design did not include a placebo and the subjects were not blinded. We elected to use a standard dose while several studies suggest a weight-based regimen. This was primarily done to help with logistical aspects and ease of administration. The study was powered based on published data in a PD study (22–24) whereas we observed a higher than expected SD for HOMA-IR (2,24). Accordingly, we might have had a Type II error when assessing our primary outcome. The slight age difference at baseline could have also influenced our results but notably towards the null given the

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**Figure 2** — The trend of hs-CRP over 6 months between the ketoacid and control groups represented as a box and whisker plot showing a statistically significant difference between groups for changes from baseline to 6 months (box represents the interquartile range, whiskers extend to the most extreme data point which is no more than 1.5 times the interquartile range from the box, and circles beyond the whiskers are extreme values; the line within the box represents the median). P value comparing the 2 treatments over time was obtained from the general linear model with bootstrap covariance accounting for correlated measures within a subject. hs-CRP = high-sensitive C-reactive protein.

**Figure 3** — The trend of serum leptin adiponectin ratio (LAR) between the ketoacid and control groups represented as a box and whisker plot showing a statistically significant difference between groups for changes from baseline to 6 months (box represents the interquartile range, whiskers extend to the most extreme data point which is no more than 1.5 times the interquartile range from the box, and circles and squares beyond the whiskers are extreme values; the line within the box represents the median). P value comparing the 2 treatments over time was obtained from the general linear model with bootstrap covariance accounting for correlated measures within a subject.
younger age of the control group. Finally, we are not able to clarify the mechanisms of the beneficial effects of ketoacids on hs-CRP and LAR. Neither did we determine which component of ketoacid tablets, branched, non-branched amino acids, or keto analogues play the major role on these results.

In conclusion, 6 months of ketoacid supplementation improved LAR but not HOMA-IR in prevalent PD patients. The improvement in LAR was driven by a notable beneficial effect in serum adiponectin levels. We further showed that ketoacid supplementation prevented worsening of inflammatory status reflected by serum hs-CRP levels. While these results are encouraging for some metabolic benefits of ketoacid supplementation in PD patients, these data should be considered as preliminary and additional studies with a larger sample size and longer period of observation should be performed to confirm these findings. Whether these potential beneficial effects could be translated into improvements in overall cardiovascular disease risk profile in PD patients should be examined in more comprehensive studies.

DISCLOSURES
This study is in part supported by Ketosteril Research Award, Fresenius Kabi Deutschland GmbH, Germany. New Century Excellent Talents from Education Department, China, K24 DK062849 from the National Institute of Diabetes and Digestive and Kidney Diseases, and Clinical Translational Science Award 1UL1RR024975 from the National Center for Research Resources. The sponsors had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have no financial conflicts of interest to declare.

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