Applied nutritional investigation

Effects of ketoanalogues on skeletal muscle mass in patients with advanced chronic kidney disease: real-world evidence

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\section*{A B S T R A C T}

Objective: Ketoanologue (KA) supplementation in patients with chronic kidney disease (CKD) on a restricted protein diet has been shown to maintain their nutritional status in clinical trials. However, a gap existed between the findings of the clinical trials and the real-world practice. The aim of this prospective observational study was to evaluate the KA effect on skeletal muscle mass in patients with stage 4–5 CKD. 

Methods: Among 170 patients with CKD screened, 148 were recruited. Patients were defined as KA or non-KA users. During a 12-mo follow-up, skeletal muscle and body fat mass were measured via bioelectrical impedance analysis at baseline, 6 mo (n = 108), and 12 mo (n = 85).

Results: Among the patients (mean age, 66.5 ± 12.9 y), KA users tended to maintain skeletal muscle and body fat mass, whereas non-KA users had a significantly reduced muscle mass (P = 0.011) and body fat gain (P = 0.004). Stratified by median age, in patients >68 y of age, non-KA users yielded the most significant muscle mass reduction and fat mass gain, whereas KA users revealed no changes in skeletal muscle and fat mass.

Conclusion: In real-world practice, we concluded that KA supplementation favorably prevents skeletal muscle mass loss and fat mass gain in elderly patients with stage 4–5 CKD.

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\section*{Introduction}

Protein-energy wasting (PEW), characterized by decreased body protein mass and energy reserves commonly observed in patients with chronic kidney disease (CKD), remains a major concern \cite{1}. It has been reported in a meta-analysis that \textless 54\% of patients with stage 3–5 CKD have PEW \cite{2}, which could be attributed to poor intake, uremic toxins, metabolic acidosis, increased oxidative stress, chronic inflammation, volume overload, and comorbid conditions \cite{3}. As CKD progresses, the risk for developing PEW is markedly increased, leading to grave outcomes. Therefore, manipulation of PEW while slowing down CKD progression is a challenge in clinical practice.

Ketoanalogues (KAs), a mixture of nitrogen-free ketoacid or hydroxy acid analogs of five essential amino acids in addition to four additional essential amino acids and one so-called “conditional” amino acid (tyrosine), have been prescribed as a supplement to low-protein diets (LPDs) or very low-protein diet (VLPDs) in patients who have had CKD for more than 4 decades \cite{4}. Through transammination in patients on a restricted protein diet, this KA can be resynthesized as a new essential amino acid and has been reported to maintain neutral nitrogen balance and improve skeletal muscle protein turnover rate \cite{5–7}. Moreover, several clinical trials and meta-analyses revealed that KA supplementation in patients with CKD who are on protein restriction not only maintained nutritional status but also preserved renal function \cite{8–15}.

Nevertheless, a gap usually exists between observations from clinical trials and real-world practice. Most clinical trials have focused on patients with CKD who were younger, had fewer comorbidities, were more motivated, and had better adherence to protein restriction. Conversely, patients who were older, had more...
comorbidities, and had poor adherence to LPDs are commonly found in clinical practice. In this setting, whether KA supplementation improves nutritional status and preserves skeletal muscle mass is rarely observed. Furthermore, most previous clinical trials assessed conventional nutritional markers only, and no direct measurement of skeletal muscle and body fat mass were included.

Thus, we conducted a 1-y prospective cohort study in patients with stage 4–5 CKD to compare skeletal muscle mass changes between KA and non-KA users in real-world practice.

Materials and methods

Study design and participants

This was a prospective observational study conducted in CKD outpatient clinics at a medical center in Hualien, with a total follow-up duration of 12 mo. Patients were recruited between April and December 2018. Non-dialysis patients with CKD who were ≥20 y of age and had an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m² were recruited using the Modification of Diet in Renal Disease (MDRD) study equation:[16]

\[
eGFR = 186 \times \left(\text{creatinine mmol/L}^{-1.154} \times \text{age years}^{-0.203}\right) 
\times (0.742 \text{ if female}).
\]

Patients who had malignancy, acute infection, stroke, apparent uremic symptoms or signs, serum albumin <3 g/dL, body mass index (BMI) <18 kg/m², were wheelchair-bound or bedridden were excluded.

Basic characteristics, comorbid diseases, physical activity, and medications prescribed, such as ß-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), statins, dipeptidyl peptidase-4 (DDP4) inhibitors, and insulin were collected at baseline. Physical activity was assessed through interviews. The type, frequency, and duration of activity were recorded. Regular exercise was defined as moderate-intensity activity ≥150 min/wk or vigorous-intensity activity ≥75 min/wk [17]. Diabetes mellitus was defined according to history or antidiabetic drug use, hypertension according to history or with antihypertensive treatment, and hyperlipidemia according to history or currently receiving lipid-lowering medication. Cardiovascular disease (CVD) was defined as coronary artery disease, myocardial infarction, left ventricular hypertrophy, arrhythmias, or congestive heart failure. All participants signed an informed consent approved by the Institutional Review Board of Tzu Chi Hospital, and all methods were performed in accordance with relevant guidelines and regulations.

KA supplementation and adherence

All patients consumed six tablets of KA per day (Ketosteril, Fresenius Kabi, Bad Homburg, Germany), which is the maximal dose allowed by The Taiwan National Health Insurance. The composition of Ketosteril is listed in Supplementary Table 1. The adherence of KA was assessed at the end of the study, using the eight-item Morisky Medication Adherence Scale (MMAS-8) [18]. The total score ranged from 0 to 8 with a score <6 indicating low adherence; 6 to 7, moderate adherence; and 8, high adherence.

Anthropometry, skeletal muscle mass, handgrip strength, and gait speed measurement

Body weight was measured with light clothing and body height with bare feet. Body mass index (BMI) was calculated as body weight (kg) divided by height square (m²). Anthropometric data included midarm circumference (MAC) and triceps skinfold thickness (TSF), and midarm muscular circumference (MAMC) was calculated as

\[
\text{MAMC} = \text{MAC} \times \pi - \text{TSF}. 
\]

Waist circumference was measured at the midpoint between the lower margin of the last rib and the top of the iliac crest. With the patient in a supine position, a tetrastop bioelectrical impedance device (Biodynamics BIA 450 Bioimpedance Analyzer, Seattle, WA, USA), delivering an electric current of 800 μA at 50 kHz, was used to measure skeletal muscle mass (kg) and body fat mass (kg) [19]. Bilateral handgrip strength (HGS) was assessed using a hand-held dynamometer (Jamar Plus Digital Hand Dynamometer, SI Instruments Pty Ltd., Hilton, Australia). During the measurement, patients were instructed to hold the dynamometer as hard as possible in the standing position, with the arm at right angles and elbow at the side of the body. Three measurements were repeated, and each one had a 1-min rest; the average value was adopted for analysis. Patients were instructed to walk with their usual speed for 6 m on a flat and straight path, and through which the gait speed was calculated accordingly.

Biochemical investigations

Fasting blood and urine samples were obtained. After centrifugation, serum samples were collected for serum blood urea nitrogen (BUN), creatinine, albumin (bromocresol green method), total cholesterol, glucose, total calcium, and phosphorus measurement, by using an autoanalyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany). Urine protein/creatinine ratio (UPCR) was also measured. A blood gas analyzer (Cobas b221, Roche Diagnostics International AG, Rotkreuz, Switzerland) was used to determine venous blood bicarbonate levels.

Patient follow-up and dietary assessments

All patients visited our clinics every 1 to 3 mo to receive multidisciplinary renal care, which integrates nephrologists, nurses, and dietitians [20]. At baseline, daily protein intake (DPI) was calculated based on 24-h urinary urea nitrogen excretion amounts using the Maroni formula [21]. Daily energy intake (DEI) was assessed by a well-trained dietitian based on 24-h dietary recall. Dietary counseling was provided to achieve KD diet requirements that included low DPI of 0.6 to 0.8 g ideal body weight (IBW; with ≥50% were high biological value) and DEI of 20 to 25 kcal kg IBW.

![Flow chart of the study. KA, ketoanalogue.](Image)
The anthropometric data, skeletal muscle mass, HGS, and gait speed measurements were collected by a well-trained operator at baseline, 6 mo, and 12 mo. Major clinical outcomes, including entry to dialysis and death, were recorded during the study period.

Statistical analysis

Continuous variables were expressed either as mean ± SD or as median and interquartile range (IQR). The variables between KA and non-KA users were compared using either the Student’s independent t test or the Mann–Whitney U test, according to the data distribution from the Kolmogorov–Smirnov test. Categorical variables were expressed as absolute (n) and relative frequency (%) and analyzed using χ² test or Fisher’s exact test. To test the effect of KA supplementation, the generalized estimating equation (GEE) with first-order autoregressive covariance structure was applied. Baseline clinical variables with significant differences between KA and non-KA users were adopted as covariates in the GEE model. A significant group-by-time interaction suggested a significant effect of KA supplement. Paired t tests were also used to examine within-group changes between each study point. The mean changes of skeletal muscle mass and body fat mass (%) were determined by calculating the differences between baseline and the 1-y follow-up visit divided by baseline skeletal muscle mass and body fat mass. An analysis of covariance (ANCOVA) model was used to estimate the adjusted mean skeletal muscle mass changes over 12 mo between KA and non-KA users with adjustment for covariates including the baseline skeletal muscle mass, body fat mass, and clinical variables with significant differences between groups. Furthermore, a sensitivity analysis using multivariable logistic regression analysis was performed to determine the factors associated with 12-mo skeletal muscle loss.

To explore the potential effects of KA between young and old age groups, we further divided participants into two groups according to median age of the study population: <68 and ≥68 y of age. The adjusted mean differences between KA and non-KA users between the two age groups were compared with ANCOVA. Finally, the correlation of DPI with 1-y changes of skeletal muscle and body fat mass were evaluated using Spearman’s correlation. Statistical analysis was performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA). P < 0.05 was considered statistically significant.

Results

Among 170 CKD patients screened, 148 were recruited. Of these, 108 and 85 completed the assessments at 6 and 12 mo, respectively. The number of patients who were lost to follow-up and the occurrence of major clinical events, including entry to dialysis and death, are summarized in Figure 1. Regarding the adherence to KA, 48.1% were reported as high, 26.9% moderate, and 25% poor.

Table 1 shows the baseline clinical characteristics of the study participants. The mean age was 66.5 ± 12.9 y, and 56.8% were men. Among them, 58.8% had diabetes mellitus, 81.1% had hypertension, 60.8% had hyperlipidemia, and 66.9% had CVDs. Notably, 20.4% had chronic kidney disease (CKD) stage 3 or higher.

Table 1. Baseline demographic and clinical characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (N = 148)</th>
<th>KA users (n = 91)</th>
<th>Non-KA users (n = 57)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>66.5 ± 12.9</td>
<td>66.6 ± 12.7</td>
<td>66.5 ± 13.4</td>
<td>0.960</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>84 (56.8)</td>
<td>49 (53.8)</td>
<td>35 (61.4)</td>
<td>0.366</td>
</tr>
<tr>
<td><strong>CKD stage, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>61 (41.2)</td>
<td>28 (30.8)</td>
<td>33 (57.9)</td>
<td>0.001*</td>
</tr>
<tr>
<td>5</td>
<td>87 (58.8)</td>
<td>63 (69.2)</td>
<td>24 (42.1)</td>
<td></td>
</tr>
<tr>
<td><strong>eGFR (mL/m/1.73 m²)</strong></td>
<td>13.7 [10.5–18.8]</td>
<td>12.8 [10–16.3]</td>
<td>16.2 [11.2–22.1]</td>
<td>0.003*</td>
</tr>
<tr>
<td><strong>Comorbid diseases, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic mellitus</td>
<td>87 (58.8)</td>
<td>54 (59.3)</td>
<td>33 (57.9)</td>
<td>0.862</td>
</tr>
<tr>
<td>Hypertension</td>
<td>120 (81.1)</td>
<td>72 (79.1)</td>
<td>48 (84.2)</td>
<td>0.442</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>90 (60.8)</td>
<td>57 (62.6)</td>
<td>33 (57.9)</td>
<td>0.565</td>
</tr>
<tr>
<td>CVD</td>
<td>99 (66.9)</td>
<td>62 (68.1)</td>
<td>37 (64.9)</td>
<td>0.685</td>
</tr>
<tr>
<td><strong>Body composition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67 ± 14.2</td>
<td>67.2 ± 13.9</td>
<td>66.6 ± 14.8</td>
<td>0.798</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 4.5</td>
<td>26.1 ± 4.5</td>
<td>26 ± 4.7</td>
<td>0.962</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>91.7 ± 11.6</td>
<td>91.8 ± 11.6</td>
<td>91.8 ± 11.8</td>
<td>0.994</td>
</tr>
<tr>
<td><strong>Estimated DEI (kcal kg d⁻¹)</strong></td>
<td>29.3 ± 3.6</td>
<td>29.4 ± 3.5</td>
<td>29.1 ± 3.7</td>
<td>0.722</td>
</tr>
<tr>
<td><strong>Protein intake</strong></td>
<td>0.92 ± 0.29</td>
<td>0.91 ± 0.29</td>
<td>0.91 ± 0.28</td>
<td>0.626</td>
</tr>
<tr>
<td><strong>Low DPI, n (%)</strong></td>
<td>44 (34.9)</td>
<td>29 (37.7)</td>
<td>15 (30.6)</td>
<td>0.418</td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
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</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10.2 ± 1.7</td>
<td>10.1 ± 1.4</td>
<td>10.3 ± 2.0</td>
<td>0.353</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>20.4 ± 3.9</td>
<td>20.4 ± 4</td>
<td>20.4 ± 3.7</td>
<td>0.974</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.1 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>4 ± 0.4</td>
<td>0.681</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>153 [131–179]</td>
<td>153 [134–181]</td>
<td>150 [129–177]</td>
<td>0.780</td>
</tr>
<tr>
<td>UPCK (g/g)</td>
<td>1.5 [0.6–3.6]</td>
<td>1.8 [0.8–3.8]</td>
<td>1.2 [0.4–3.2]</td>
<td>0.197</td>
</tr>
<tr>
<td>&lt;1, n (%)</td>
<td>58 (39.2)</td>
<td>31 (34.1)</td>
<td>27 (47.4)</td>
<td>0.245</td>
</tr>
<tr>
<td>1–2, n (%)</td>
<td>30 (20.3)</td>
<td>21 (23.1)</td>
<td>9 (15.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;2, n (%)</td>
<td>60 (40.5)</td>
<td>39 (42.9)</td>
<td>21 (36.8)</td>
<td></td>
</tr>
<tr>
<td>Mediations, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>59 (39.9)</td>
<td>37 (40.7)</td>
<td>22 (38.6)</td>
<td>0.803</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>64 (43.2)</td>
<td>43 (47.3)</td>
<td>21 (36.8)</td>
<td>0.213</td>
</tr>
<tr>
<td>CCB</td>
<td>88 (59.5)</td>
<td>55 (60.4)</td>
<td>33 (57.9)</td>
<td>0.759</td>
</tr>
<tr>
<td>Statin</td>
<td>63 (42.6)</td>
<td>41 (45.1)</td>
<td>22 (38.6)</td>
<td>0.439</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>19 (12.8)</td>
<td>9 (9.2)</td>
<td>10 (17.5)</td>
<td>0.176</td>
</tr>
<tr>
<td>Insulin</td>
<td>36 (24.3)</td>
<td>24 (26.4)</td>
<td>12 (21.1)</td>
<td>0.463</td>
</tr>
<tr>
<td><strong>Clinical outcomes, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>37 (25)</td>
<td>24 (26.4)</td>
<td>13 (22.8)</td>
<td>0.626</td>
</tr>
<tr>
<td>Death</td>
<td>9 (6.1)</td>
<td>5 (5.5)</td>
<td>4 (7)</td>
<td>0.706</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; DEI, daily energy intake; DPI, daily protein intake; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; KA, ketoanalogue; UPCK, urine protein to creatinine ratio

*P < 0.05 considered statistically significant.

*24-h urine samples were available for estimation of daily protein intake in 126 participants.
only 34.9% had low-protein intake. Comparing with KA and non-KA users, the former had significantly lower eGFR (P = 0.003) and a higher proportion of patients with CKD stage 5 (P = 0.001) at baseline, 6, and 12 mo of follow-up (Supplementary Table 2). Otherwise, the groups were comparable in age, sex, comorbid diseases, physical activity, body composition, DPI, DEI, laboratory data, and medications prescribed. Clinical outcomes, including entry to dialysis and death, were also similar between groups.

Table 2 shows BMI, anthropometric data, skeletal muscle mass, HGS, and gait speed changes between KA and non-KA users. No significant changes in BMI, MAMC, HGS, and gait speed were found between groups. In contrast to KA users, non-KA users significantly lost skeletal muscle mass (P = 0.011) and gained body fat (P = 0.004), especially at 12 mo of follow-up. As shown in Table 3, no changes in laboratory data between KA and non-KA users were observed. The decline of eGFR was observed in both KA and non-KA users, without significant between-group difference (P = 0.827).

The adjusted mean changes of skeletal muscle and body fat mass in KA and non-KA users at 12 mo are depicted in Figure 2. Compared with non-KA users, only KA users could maintain their skeletal mass (1.1 versus −4.9%, P = 0.031). Additionally, the KA group tended to have less gain in body fat mass (7.1 versus 29.0%, P = 0.179). A sensitivity analysis using multivariable logistic regression analysis to determine the factors associated with 12-mo skeletal muscle loss showed that KA use was independently associated with preserved skeletal muscle mass (Supplementary Table 3).

Stratified by two age groups, patients ≥68 y of age without KA supplementation yielded a 9.3% skeletal muscle mass loss and 34.3% body fat gain within 12 mo after adjustment, whereas those aged <68 y with KA supplementation revealed no skeletal muscle and body fat mass changes. However, no significant changes in skeletal muscle and body fat mass between groups were observed in patients <68 y of age (Figure 3).
The correlation of DPI with 1-y changes in skeletal muscle and body fat mass are shown in Figure 4. A weak positive correlation between DPI and skeletal muscle mass change was observed (r = 0.229; P = 0.045).

Discussion

In the study cohort of patients with advanced CKD, characterized by overt proteinuria and high prevalence of comorbidities, including diabetes mellitus, hypertension, and CVD, KA supplementation was found to protect against skeletal muscle loss and body fat accumulation during a 1-y follow-up. Stratified by median age, patients ≥68 y of age without KA supplementation yielded the most significant skeletal muscle loss and body fat gain; in contrast, KA supplementation appeared to mitigate the deleterious muscle wasting and fat accumulation.

Effects of protein restriction with KA supplements on skeletal muscle homeostasis were examined in several previous experimental and clinical studies. In animal studies, KA supplementation protected against skeletal muscle atrophy, by downregulating ubiquitin-proteasome systems and reducing oxidative damage and mitochondrial dysfunction [22,23]. Garibotto et al. further demonstrated that, in patients with CKD, shifting from the usual protein diet (1.1 g/kg) to a LPD (0.55 g/kg) decreased muscle protein degradation by 17% to 40%; whereas adding KA further improved muscle protein turnover [5]. After a 2- to 3-year follow-up in the MDRD study, the implication of either LPD (0.58 g/kg) or VLPD (0.28 g/kg) supplemented with KA was regarded as safe in maintaining nutritional status [24]. In an 18-mo randomized control trial comparing KA-supplemented very low-protein vegetarian diet (0.3 g/kg) with a LPD (0.6 g/kg), the KA-supplemented VLPD group exhibited slower renal deterioration without compromising the nutritional status [8]. In line with previous studies, our study observed that KA supplements had beneficial effects against skeletal muscle mass loss and body fat accumulation in advanced CKD.

The effects on skeletal muscle and body fat changes with diet manipulation in elderly patients with CKD, who are vulnerable to develop PEW but seldom recruited in previous clinical trials, should be studied. Although a wide-range criterion for age was adopted in our recruitment, the mean age of 148 participants was 66.5 y. This age distribution in our patients with CKD is compatible with that in CKD populations worldwide [25,26]. Regarding the growing prevalence of aging patients with CKD, it is crucial to prevent the development of PEW in this susceptible group [27–30]. In the present cohort, patients ≥68 y of age without KA supplementation were found to yield skeletal muscle loss and body fat gain after a 1-y follow-up, whereas KA supplementation appeared to mitigate the deleterious muscle wasting and fat accumulation. This finding implicated that the beneficial effect of KA supplementation appears to be more prominent in elderly patients.

Several studies in CKD patients reported poor adherence to protein restriction. For example, in the MDRD study, adherences to LPD were only 35% and 46% in study part A and B, respectively [31]. Cianciaruso et al. reported that, among 392 participants with stage 4–5 CKD, the compliances to LPD (0.8 g kg⁻¹ d⁻¹) and VLPD...
(0.55 g kg\(^{-1}\)) were 53% and 27%, respectively [32]. However, in real-world practice, this adherence is expected to be even lower. In our study cohort, only 34.9% were adherent to LPD (an estimated DPI of <0.8 g kg\(^{-1}\)) even under multidisciplinary renal care.

Although most of the clinical trials illustrated the safety of dietary protein restriction, we observed a modest trend of skeletal muscle mass reduction in patients with lower DPI. These discrepancies could be explained by the following reasons. First, these clinical trials recruited patients who were younger, had fewer comorbidities, and had stronger motivation to comply with protein-restricted diets; whereas our participants were older and had a higher prevalence of diabetes mellitus, hypertension, hyperlipidemia, and CVDs. Second, among our participants with low-protein intake, differentiating between those with good compliance to dietary protein restrictions and those with spontaneous protein intake reduction due to suppressed appetite is difficult, which has different clinical relevance. Third, the average energy intake in our participants was below the recommended range and it is crucial to exacerbate muscle wasting, especially in older patients [33,34].

Notably, most of the previous trials only assessed traditional nutritional markers such as BMI, MAMC, and serum albumin levels, but did not measure skeletal muscle mass and body fat mass directly. We observed a significant loss of skeletal muscle mass accompanied by body fat gain in our non-KA group, independent of BMI, MAMC, and serum albumin levels. Our findings supported that applying body composition measurement directly can be more precise than using the traditional anthropometric and laboratory markers to detect muscle wasting in advanced CKD [34].

The present study can help to fill the gap between clinical trials and real-world practice. However, our results should be interpreted in consideration of several limitations. First, due to the observational nature of this study, selection bias and unmeasured confounding factors, such as inflammatory status and oxidative stress between KA and non-KA groups may interfere with our results. Second, because most of our patients were elderly, with high prevalence of comorbidities and overt proteinuria, <31.1% of them either required dialysis or deceased during study period, which precluded our complete assessment of skeletal muscle mass and body fat mass. However, the numbers of patients who enter to dialysis or death were comparable between KA and non-KA users. Furthermore, similar results were obtained when we adopted both ANCOVA and GEE models. Third, the cumulative dose of KA was not recorded, and a dose–response analysis couldn’t be performed. Fourth, given the limited sample size, the interaction between KA use and DPI could not be assessed. Fifth, hydration status in advanced CKD may interfere the measurement of skeletal muscle mass. Finally, the proportion of high biological value protein was not assessed.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2021.111384.

References


