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Safety of Low-Protein Diets and Ketoanalogue Supplementation in CKD

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Dietary protein restriction, with or without supplementation of ketoanalogues of certain amino acids, have long been considered as an attractive intervention to slow progression of chronic kidney disease (CKD).[1] As suggested by several meta-analyses, this effect is real, albeit relatively small in the context of progressive kidney disease.[2] Several smaller studies indicate that the favorable effects of dietary protein restriction extend beyond slowing the progression. These include amelioration of metabolic acidosis and insulin resistance, antioxidant effects, and decreasing dietary phosphorus load. In addition to protein restriction alone, several studies also have examined the effects of keto or amino acid–supplemented low-protein diets or very low protein diets on certain metabolic and kidney outcome parameters. Data suggest that protein-restricted diets supplemented with keto/amino acids result in a significant decrease in urea production and a beneficial effect on insulin resistance and oxidative stress in humans. Given the limited options for slowing progression of kidney disease, especially in geographic regions where access to renal replacement therapy is limited due to logistical and financial reasons, this particular dietary intervention strategy has gained traction within the past decade.[2] Based on these considerations, a consensus statement provided recommendations for obtaining maximum benefit from keto/amino acid–supplemented protein-restricted diets (Table 1).[3]

There are still several aspects of these interventions that are not fully explored. The optimal range of dietary protein restriction with or without keto or amino acid supplementation to exert the most beneficial outcome is not established, and the applicability of dietary protein restriction is limited by compliance. Another important consideration regarding dietary protein restriction in progressive CKD is the potential to adversely affect the nutritional status of patients. These concerns have been mostly defied by several uncontrolled studies showing that well-designed diets, planned by skilled dietitians, and followed by motivated and compliant patients are effective and do not have harmful effects on the nutritional condition. Long-term follow-up of several relatively large uncontrolled cohorts of patients with CKD who received 0.47 g/kg per day of protein with the ketoacid supplementation showed no detrimental effect on the outcome of the patients after initiating any kind of renal replacement therapy. In this issue of *KI Reports*, Garibotto *et al.*[4] tackled another important question regarding the safety of these interventions; that is, whether low-protein diets, with or without ketoacid supplementation, would lead to undesirable consequences in skeletal muscle homeostasis.[4] Using well-established stable isotope methodology, they measured skeletal muscle protein turnover in 2 separate cohorts by using 2 protocols: (i) a randomized parallel group trial of usual (1.1 g protein/kg body weight) versus low-protein (0.55 g protein/kg body weight) diet for 12 weeks, and (ii) a crossover study of low-protein (0.55 g protein/kg body weight) diet versus very low protein diet supplemented by keto acid/amino acid (0.45 g protein/kg body weight plus 0.1 g/kg body weight keto acid/amino acid) over periods of 12 weeks each. Skeletal muscle protein balance was measured as the primary outcome at several time points for comparison between groups.

The compliance with the diets was excellent during the studies, and there were no notable changes in nutritional biomarkers, such as serum albumin, body mass index, or anthropometric measurements during either study. Protocol 1 included 11 subjects (6 in low-protein diet and 5 in usual protein diet). The results suggested that compared with usual diet, a gradual decrease of protein diet to 0.55 g/kg body weight per day led to a 17% decrease in muscle protein degradation at the end of the

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Table 1. Considerations for maximum efficacy and safety of administration of keto/amino acid–supplemented protein-restricted diets

- Patient selection: motivation and ability to follow a protein-restricted diet
- Gradual implementation of intervention (i.e., progressive 0.2-g/kg body weight/day decrements over 2–4 weeks)
- Support and educational tools along with regular dietary counseling (every 2–3 months initially)
- Involvement of a multidisciplinary team, including an experienced dietician
- Close clinical follow-up

study, while muscle protein synthesis was not affected substantially. These changes led to a marked and statistically significant improvement in net muscle protein balance. Protocol 2 included 6 subjects serving as their own controls in a crossover study design. After a run-in period of 6 weeks, dietary protein intake was gradually decreased to 0.55 g/kg body weight per day, where it was maintained for 6 weeks (baseline period). The diet was subsequently changed to 0.45 g protein/kg body weight plus 0.1 g/kg body weight keto acid/amino acid (treatment period) for 6 weeks followed by another 6 weeks of 0.55 g/kg body weight per day protein intake (washout period). The subjects underwent metabolic studies at the end of each period. In contrast to protocol 1, there were no statistically significant differences between time points for muscle protein degradation or protein synthesis. However, net protein balance at the end of the treatment period was statistically significantly less negative compared with baseline or washout periods, indicating a potential beneficial effect with ketoanalogue-supplemented very low protein diet.

The results of these studies have important clinical and research implications. First and foremost, these data provide further evidence that in clinically stable patients with CKD, low-protein diet and ketoanalogue-supplemented very low protein diet appear to be nutritionally safe in terms of skeletal muscle homeostasis, at least for a period of up to 12 weeks. This conclusion is supported by the fact that net skeletal muscle protein balance was either maintained or improved during both dietary interventions. Also, no significant changes were noted in any of the well-established nutrition markers in any of the study patients at the end of treatment periods. Nevertheless, an important caveat that one needs to keep in mind when assessing the safety of these interventions is that the subjects in these studies were well nourished and clinically very stable with minimal comorbidities. Practitioners need to exert appropriate clinical judgment in terms of dietary nutrient intake based on each individual's needs, especially during times of stress, such as acute illness or hospitalizations.

A unique aspect of the studies presented herein is the mechanism by which the skeletal muscle metabolism adapts to low-protein diets. The investigators astutely show that the primary adaptation to low-protein diet is a decrease in skeletal muscle degradation with a notable increase in efficiency in amino acid recycling. They estimate that low-protein diet and ketoanalogue-supplemented very low protein diet can increase protein efficiency up to 12% to 14%, respectively. Unfortunately, these data do not provide a clear explanation as to which signaling pathways at the cellular level are activated or suppressed in response to these diets. A notable observation when comparing the response to each intervention is that although a low-protein diet primarily suppresses protein degradation, a very low protein diet supplemented with keto acids seems to exert its beneficial effect mostly by improving protein synthesis. Because the latter intervention had only a small decrease in protein intake (i.e., 0.55 vs. 0.45 g/kg body weight per day), one can speculate that further metabolic benefit from this minor decrease in protein intake would not have a noticeable effect on protein degradation, as observed in this study. In most studies examining very low protein diets, the prescription is approximately 0.3 g/kg body weight per day, which could potentially amplify the beneficial effects on protein degradation. On the other hand, the numerical improvement in protein synthesis suggests that the keto acid supplementation *per se* might have activated anabolic signaling pathways. This is in line with studies examining leucine administration, a key component of the keto acid supplementation, in other patient populations and elderly individuals.

Although the studies by Garibotto *et al.*[4] provide very encouraging data in terms of the safety of a low-protein diet and ketoanalogue-supplemented very low protein diet, there are certain caveats that one should take into account when interpreting these results. In addition to the relatively small sample size and excellent clinical condition of the study patients, the results presented herein provide only a snapshot of their metabolic milieu. Whether these beneficial effects can be maintained over a longer period, especially if the patients undergo any unforeseen metabolically stressful events, needs to be carefully examined by additional studies. In that context, the excellent safety profile of a recently published long-term randomized clinical trial examining ketoanalogue-supplemented vegetarian very low protein diet in patients with CKD does indeed suggest that the observations in this particular study can be extrapolated to long-term effects.[5]

In summary, the results of these elegant studies by Garibotto *et al.*[4]

suggest that low-protein and ketoanalogue-supplemented very low protein diets improve amino acid utilization, resulting in appropriate metabolic adaptations in clinically stable patients with stage 4 CKD, provided there is adequate caloric intake and close medical supervision. These data provide further evidence that dietary interventions, such as administered in these studies, can be implemented for extending the time to initiation of renal replacement therapy in clinically suitable patients with advanced CKD without significant concern for development of protein energy wasting.

DISCLOSURE

TAI is a consultant for Fresenius-Kabi, Inc.

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