Low-protein diets and keto-analogues in CKD: A medical and health perspective

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The conundrum of dietary protein intake in CKD

Nutritional therapy has been the cornerstone of chronic kidney disease (CKD) management since the early days of nephrology. Historically, protein restriction has been one of the earliest and most controversial interventions in managing CKD. The rationale behind this approach was that it might reduce the accumulation of potentially toxic metabolic products derived from protein and amino-acid degradation, maintain a healthier balance of body water, electrolytes and minerals, mitigate metabolic acidosis, alleviate proteinuria and interstitial fibrosis, and ultimately delay CKD progression and the need for dialysis. Nevertheless, earlier findings from studies on dietary protein restrictions have been inconsistent. The Modification of Diet in Renal Disease (MDRD) study argued that the progression of kidney disease is only minimally abated by low protein intake. Also, in contemporary clinical practice, there are multiple interventions, supported by robust evidence, that retard the progression of CKD, such as blood pressure control, RAAS inhibitors, SGLT2 inhibitors, and novel aldosterone receptor antagonists. Finally, rehabilitation with quality dialysis or kidney transplantation is now widely available for patients with advanced kidney failure.

On the other hand, over the last two decades, a substantial number of well-designed studies comprehensively analysed the effectiveness of protein restriction, with or without supplementation with keto-acid analogues. Most of them consistently observed better blood pressure control, reduction in proteinuria, and improvement of insulin resistance with a low-protein diet (LPD), all of which contribute to the abatement of kidney function decline. Therefore, the latest National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) 2020 Clinical Practice Guidelines for Nutrition issued in association with the Academy of Nutrition and Dietetics strongly recommended rigorous protein restriction (Grade 1A). The guideline defines an LPD as an intake of 0.55–0.60g/kg of dietary protein and a very-low protein diet (VLPD) as 0.28–0.43 g/kg protein intake. The guidelines recommend practising these nutritional regimens under close clinical supervision, preferentially by a dietician, to mitigate any potential risk associated with decreased nutrient intake.

In practice, several options for LPD are available in CKD population: conventional LPD with protein intake 0.6g/kg/day, supplemented LPD (sLPD) with added 1 tablet of ketoanalogues per 10kg dry body weight, and vegetarian very low protein diets (sVLPD/keto-diet, KD) with 0.3-0.4g/kg/day plant-based proteins intake supplemented with essential amino-acids and ketoanalogues at 1 tablet/5kg dry body weight.

Evidence on the efficacy and safety of protein restriction in CKD

Among others, the work by Garneata et al., examined the efficacy and safety of ketoanalogue-supplemented vegetarian VLPD compared with conventional LPD in the non-diabetic advanced CKD population. This prospective, randomised, controlled trial initially assessed over fourteen hundred patients with CKD stage 4, of whom only 207 met the criteria to be randomised to one of the dietary regimens which they pursued in the following 15 months. The results showed that all patients achieved prescribed energy intake and no significant changes in nutritional parameters in either group were noted. Compliance with the dietary regimen was good, and the dropout rate was only 3%. Also, no adverse reactions were observed related to the prescribed supplements. Supplemented VLPD was associated with less reduction in eGFR and less need to initiate dialysis in this research. Thus, the authors concluded that VLPD supplemented with ketoanalogues was nutritionally safe and possibly even able to postpone dialysis in some patients, with more pronounced results in patients with more advanced CKD. Compared to certain

other interventions in internal medicine, such as curing peptic ulcers with antibiotics or preventing heart attacks with statins, a ketoanalogue-supplemented diet appears to be substantially more efficient in delaying the need for dialysis (Figure 1).

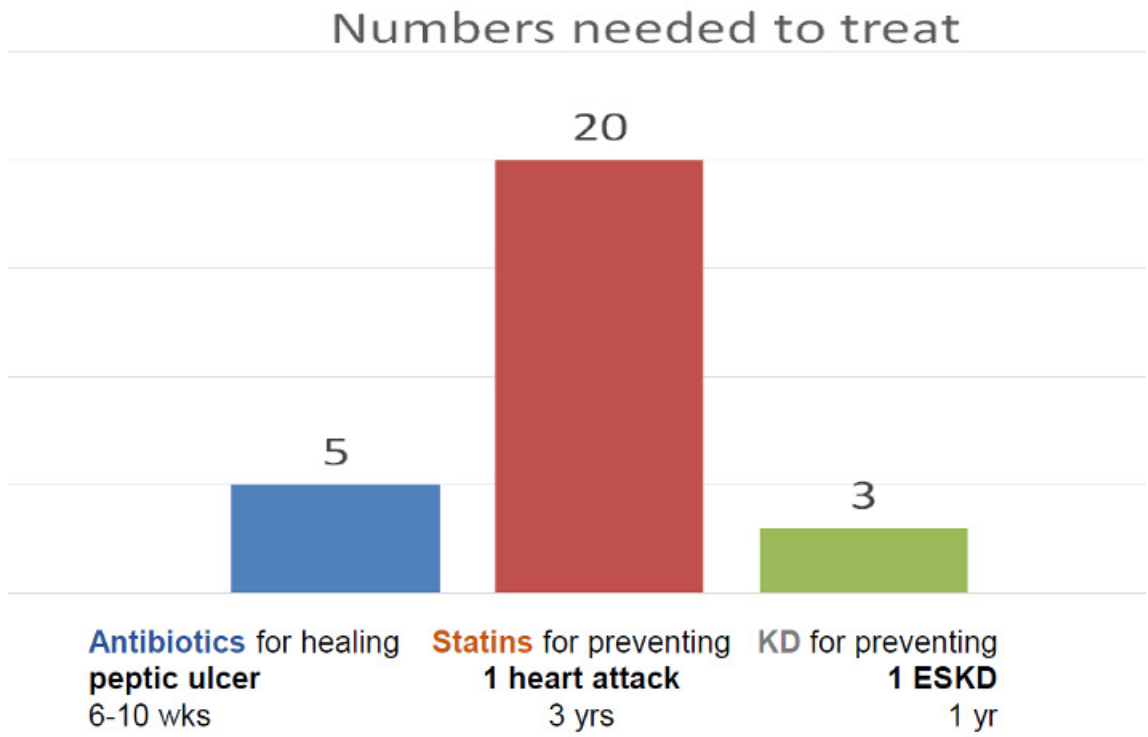

Figure 1.
Effectiveness of keto-supplemented vegetarian VLPD (KD) in preventing end-stage kidney disease (ESKD) compared to certain other interventions

The yet unpublished data from a follow-up study of this patient cohort also showed a significant survival advantage in patients on supplemented VLPD compared to LPD, which was exclusively associated with nutritional intervention. Furthermore, results from this ten-year follow-up substantiated the long-term compliance to the dietary regimen, preservation of nutritional status, and dialysis deferral.

Implementation of low-protein dietary regimens is especially challenging in patients with diabetes due to the apparent risk of inadequate energy intake and consequent malnutrition. Therefore, data related to the population with diabetic kidney disease are limited. A recently published study by Garneata et al. addressed the issue of efficacy, safety and feasibility of LPD with ketoanalogue supplementation in patients with type 2 diabetes, high-range proteinuria (over 3g/g creatinine) and advanced CKD (eGFR below 30mL/min).

This interventional, prospective, uncontrolled study enrolled 97 out of 452 screened patients who were prescribed mainly vegetarian LPD supplemented with ketoanalogues, along with conventional renoprotective agents. The patients were followed for 12 months during which time only 5 of them dropped out due to noncompliance or pre-emptive kidney transplant. At the end of the follow-up, the diet attenuated both eGFR decline and CKD complications, while proteinuria decreased threefold (Figure 2). Also, there were no side effects to the nutritional intervention in the observed period and, although the initial acceptance rate was low, the long-term adherence was excellent. These results strongly support the efficacy and safety of an LPD as an important tool in managing CKD, including diabetic kidney disease.

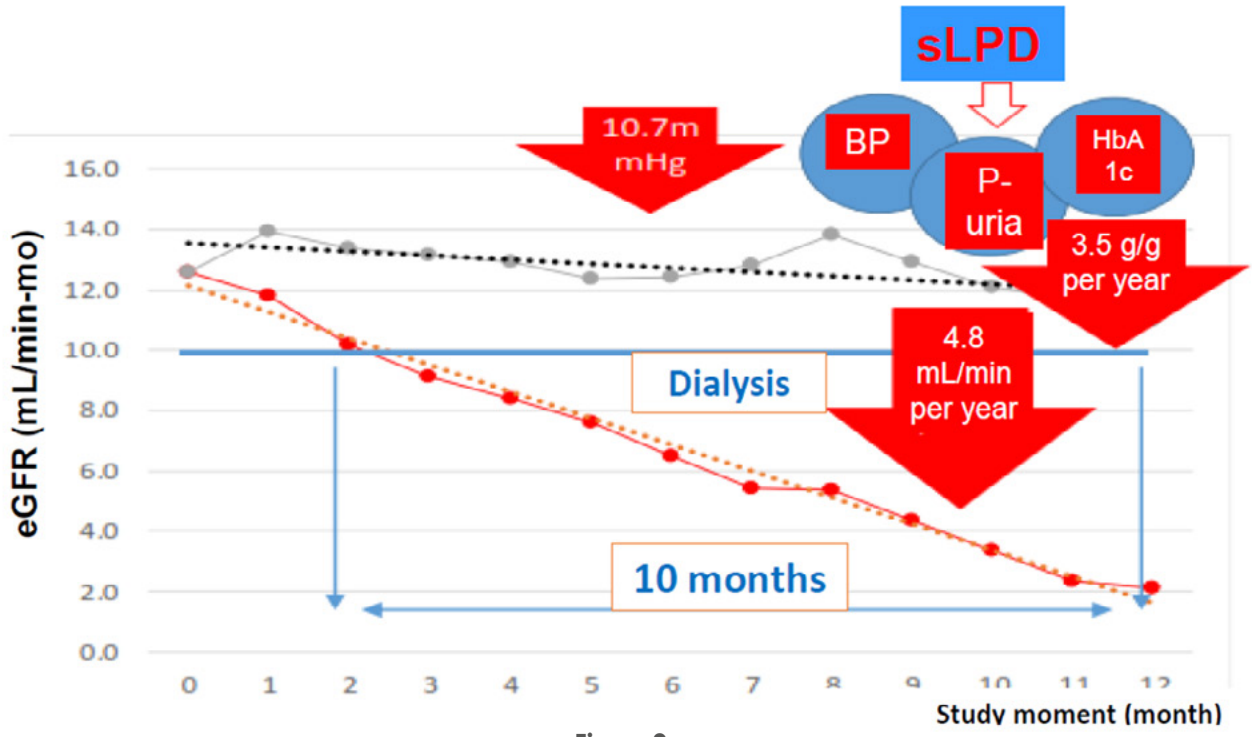

Figure 2.
Effects of LPD with ketoanalogues in patients with advanced diabetic kidney disease

The economic perspective of LPD supplemented with keto-analogues

Renal replacement therapy represents the major part of the economic burden related to CKD. LPDs supplemented with ketoanalogues appear to have the potential to mitigate the rate of renal function decline, but the cost-analyses of this intervention are very limited. A recent literature review based on the following PICOS framework: Population – any stage of CKD, Intervention – any restrictive dietary regimen supplemented with ketoanalogues, Comparators – any restrictive dietary regimen, Outcomes – any healthcare costs, Study types – cost analysis; identified only 5 studies published so far that complied with these criteria. Of those, 2 were poster abstracts and 3 were full-text articles. Four publications originated from Asia and one from Europe. All studies estimated the quality-adjusted life year (QALY) gained and savings attributed to the implementation of LDP or VLPD supplemented with ketoanalogues and unanimously detected notable economic benefits from this intervention. Although scarce, these results support the notion of concurrent benefits of ketoanalogues in both clinical and economic terms. Furthermore, there is unpublished data from a simulation model which compared the cost-effectiveness and budget impact of ketoanalogue-supplemented VLDP and LPD in pre-dialysis CKD patients. The model was based on the clinical outcomes from published literature and country-specific cost data in Spain, Italy, Croatia, Belgium, the Netherlands, Poland and Sweden. These results consistently supported the beneficial economic effect of ketoanalogue supplementation (Figure 3).

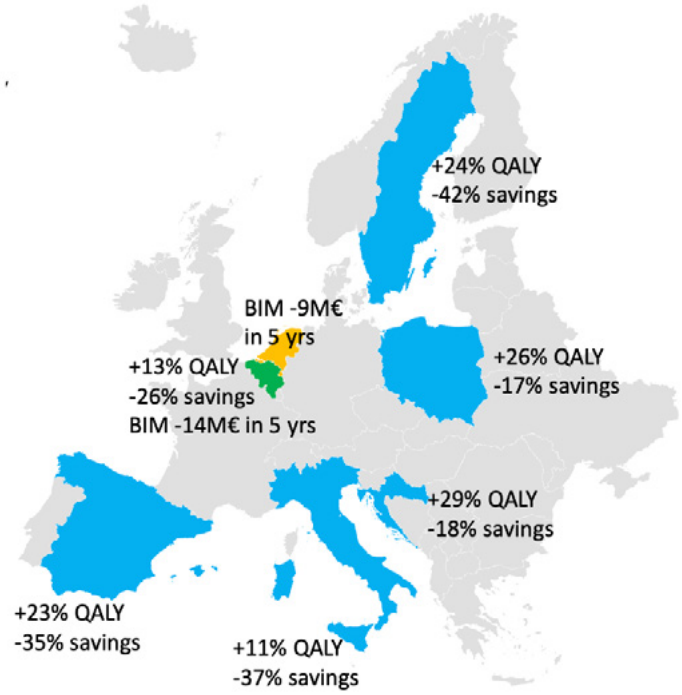

Figure 3.
Results of cost-effectiveness analysis of sVLPD vs. LPD in Europe

Written by Jasna Trbojevic-Stankovic.
The speaker reviewed and approved the content

KEY POINTS

1 CKD is a major source of global healthcare costs. Any intervention delaying the ultimate loss of renal function has the potential to improve patient prognosis and quality of life and reduce economic burden of the disease.

2 The LPD supplemented with ketoanalogues appears effective and safe in postponing kidney function decline in both diabetic and non-diabetic CKD patients.

3 In diabetic kidney disease, LPD with ketoanalogue supplements is associated with better blood pressure control and reduction in proteinuria and the rate of eGFR decline.

4 Data on the economic benefit of this dietary intervention is still limited, but available findings strongly support the implementation of ketoanalogues in suitable CKD patients.

Further readings

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