Seminars in Dialysis



# Do Ketoanalogues Still Have a Role in Delaying Dialysis Initiation in CKD Predialysis Patients?

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## ABSTRACT

Early versus later start of dialysis is still a matter of debate. Low-protein diets have been used for many decades to delay dialysis initiation. Protein-restricted diets (0.3–0.6 g protein/kg/day) supplemented with essential amino acids and ketoanalogues (sVLPD) can be offered, in association with pharmacological treatment, to motivated stage 4–5 chronic kidney disease (CKD) patients not having severe comorbid conditions; they probably represent 30–40% of the concerned population. A satisfactory adherence to such dietary prescription is observed in approximately 50% of the patients. While the results of the studies on the effects of this diet on the rate of progression of renal failure remain inconclusive, they are highly significant when initiation of dialysis is the primary outcome. The correction of uremic symptoms allows for initiation of dialysis treatment at a level of residual renal function lower than that usually recommended. Most of the CKD-associated complications of cardiovascular and metabolic origin, which hamper both lifespan and quality of life, are positively influenced by the diet. Lastly, with regular monitoring jointly assumed by physicians and dietitians, nutritional status is well preserved as confirmed by a very low mortality rate and by the absence of detrimental effect on the long-term outcome of patients once renal replacement therapy is initiated. On account of its feasibility, efficacy and safety, sVLPD deserves a place in the management of selected patients to safely delay the time needed for dialysis.

For the nephrologist who is in charge of the chronic kidney disease (CKD) patient, and for the patient himself, one the main therapeutic objectives is to delay the time needed for dialysis both by correcting uremic signs and symptoms and possibly by attenuating the progression of renal failure.

At the same time, the medical survey will also aim at maintaining satisfactory nutritional status while forestalling the development of CKD-associated complications, particularly of cardiovascular (CV) and metabolic origin, which hamper both life span and quality of life.

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers are proposed as first-line treatment to achieve some of these targets, particularly progression of renal failure and CV complications. In addition to the drug therapy, a reduction in protein intake is recommended, and careful planning of a low-protein diet (LPD) can, in and of itself, attain all the above-mentioned objectives and therefore can be a valuable partner for the inhibitors of the renin-angiotensin-aldosterone system (Table 1). As a matter of fact, it was shown over 140 years ago that reduced protein intake had beneficial effects on the uremic syndrome, most of

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**TABLE 1. Beneficial effects of Keto/amino acid-supplemented protein-restricted diets**

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| Delay the time to dialysis |
| May slow progression of glomerular filtration rate decline |
| Decreases uremic toxins |
| Better blood pressure control |
| Reduces proteinuria |
| Improves insulin sensitivity |
| Improves lipid profile, oxidative and inflammatory status |
| Improves calcium-phosphate metabolism |
| Correction of metabolic acidosis |
| Prevents malnutrition |

the symptoms of which are caused by the accumulation of metabolic products of dietary protein and also of phosphates and fixed acids. It was also shown more recently that changes in dietary protein intake could strongly influence the rate of loss of renal function, at least in some animal models (1).

Besides the conventional LPD (which provides 0.6–0.8 g protein/kg/day), a very low-protein diet supplemented (sVLPD) with essential amino acids (EAA) or calcium salts of their nitrogen-free ketoanalogs (KA) as well as with water-soluble vitamins, calcium carbonate and iron, has been proposed to treat CKD patients. This supplement allows further reduction in dietary protein to 0.3 g protein/kg/day while providing adequate amount of EAA and a neutral nitrogen balance due to a reduction in urea nitrogen appearance. Adaptive response to a low-protein diet is maintained in CKD patients (2).

## Management and Monitoring of Patients on sVLPD

sVLPD provides 0.3–0.5 g protein/kg BW/day with high percentage from plant sources (Table 2). The energy supply (30–35 kcal/kg/day) is mainly provided by carbohydrates (65%), lipids and protein accounting for 30% and 5% of the total energy intake, respectively. The supplementation with a mixture of EAA and KA prevents the need for a high amount of protein of high biological value and allows the patient to benefit from a greater variety and better palatability of foods from which to choose. In nephrotic patients, the dietary protein intake can be increased by 1.5 g of protein of high biologic value for each gram of urinary protein above 3 g/day.

**TABLE 2. Components of Keto/amino Acid-Supplemented protein-restricted diets**

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|---|
| 0.3/0.4 to 0.6 g protein/kg body weight/day depending on the stage of chronic kidney disease (3–5) |
| Keto/amino acid supplementation (Ketosteril®; Fresenius Kabi, Germany, Alfa-Kappa®; Fresenius Kabi Italia S.r.l.): 1 tablet/5-kg body weight/day (0.1 g/kg body weight/day) |
| Energy: 30–35 kcal/kg body weight/day |
| Phosphate: 5–7 mg/kg body weight/day |
| Sodium: <2 g/day |
| Vitamins and trace elements (e.g., iron) |

sVLPD is proposed for stage 4–5 CKD patients excluding those with severe comorbid conditions predisposed to a potential hypercatabolic status. Patients who obviously could not adapt to the diet and/or to close monitoring should also be excluded. In these circumstances, sVLPD may be proposed to approximately 30–40% of stage 4–5 CKD patients (3).

Such dietary treatment needs frequent clinical follow-up jointly assumed by a physician and a dietitian. A close clinical monitoring program permits a better control of blood pressure and of the nutritional adequacy of the diet and allows for checking compliance with the dietary prescription. More than 20 years ago, Bergström et al. (4) stressed the importance of a regular predialysis survey on the outcome of the patients, which was confirmed later on by several other studies (5).

In uncomplicated patients, without superimposed catabolic factors, protein intake can be estimated by monitoring nitrogen intake, which equals urinary urea nitrogen excretion plus nonurea nitrogen excretion; the latter does not vary with protein intake and averages 0.031 g/kg body weight/day (6). Food diaries or diet recall assesses energy intake. Diet adherence, which is the cornerstone of the efficacy of the treatment, is defined as an actual intake, should not differ by more than 20% from the prescribed intake. Even in carefully selected and motivated patients, satisfactory compliance is seen 40% and 60% (7). The Modification of Diet in Renal Disease (MDRD) Study has confirmed that the rate of compliance was similar in patients on sVLPD and on conventional LPD (8).

## Does sVLPD Defer Time of End-Stage Renal Disease (ESRD)?

### Effect on Progression of Renal Failure

The effect of such dietary treatment on the progression of renal failure is of interest on both experimental and clinical grounds. Beneficial effect of sVLPD have been reported on the preservation of renal function in several, but not all, animal models of CKD, mainly through the prevention of the adaptive increase in glomerular capillary pressure, which occurs in CKD, leading to progressive glomerular sclerosis (9). A direct anti-inflammatory action of dietary protein restriction has also been put forward in experimental models (10). In several clinical trials, it has been shown that sVLPD had favorable effects on two of the main factors of progression of renal failure: hypertension and proteinuria.

However, despite these promising experimental and clinical findings, the different analyses of the results from the largest and most comprehensive study that assessed the effects of protein restriction on the progression of renal failure, the MDRD

Study, were at best inconclusive (11,12). These disappointing results were indirectly confirmed by Kasiske et al. who, analyzing the results of 13 randomized, controlled trials (*n*: 1919 patients) observed that, compared with no dietary restriction, low-protein intake reduced the rate of decline in glomerular filtration rate (GFR) by only 7%: 0.53 ml/min/year (13).

### Effect on The Uremic Syndrome

These results are in contrast with the reported effects of sVLPD on the uremic syndrome, which clearly delay the time until dialysis is required. The dramatic reduction in serum urea nitrogen concentration associated with the improvement of most of the manifestations of the uremic state allows patients on sVLPD to start dialysis treatment at a level of residual function lower than usually recommended (3,14). Walser et al. have estimated that, in part by delaying the occurrence of uremic symptoms, sVLPD prolonged the interval to renal death by a median of 1 year after patients reach a GFR level of 10 ml/min in nondiabetics and 15 ml/min in diabetics (15). Several meta-analyses have shown the benefits of LPD and/or sVLPD on the risk of renal failure and deaths. In a meta-analysis analyzing 5 trials including the MDRD Study, Pedrini et al. reported for a mean follow-up of 18–36 months, a significant reduction (RR = 0.67) of this risk (16). In two successive meta-analyses, Fouque et al. have also shown that there was a 39% reduction in the number of renal deaths in patients on LPD or sVLPD (17).

The indisputable effect of sVLPD on uremic symptoms explains the differences in the conclusions reported between the meta-analyses according to the key outcome measures: debatable for the loss of renal function, highly significant when onset of dialysis or death was the primary outcome.

Late dialysis initiation in CKD (as in failed transplant patients) could be safely considered until the patient is symptomatic (18). Delay in the time to dialysis is probably the most important consideration for the patient. Supplemented VLPD is a valuable option to attain this goal in many patients and also presents some additional advantages considering vascular or metabolic complications of CKD.

## Effects of sVLPD on Complications of CKD

Cardiovascular diseases and metabolic disorders are the main complications of CKD; they are tightly intertwined, in that most of the metabolic disorders contribute more or less directly to the development of CV complications.

### Cardiovascular Complications

Cardiovascular disease is the main cause of morbidity and mortality in CKD patients, accounting for about 50% of the deaths of dialysis patients. High CV risk is present from the very early stages of renal insufficiency and increases with declining renal function; the risk of death linked to CV events is estimated to be 15 times higher than that of progression to ESRD. sVLPD with its important vegetarian component limits the intake not only of protein but also of salt and phosphates, all characteristics liable to ameliorate traditional and nontraditional CV risk factors through different pathways (19,20).

### Control of Blood Pressure

In a prospective nonrandomized study concerning 110 stage 4–5 CKD patients, Bellizzi et al. have observed that sVLPD induced a significant decrease in blood pressure levels associated with a concurrent reduction in the antihypertensive treatment (21). Several mechanisms have been put forward to explain this result: increased plasma concentration of the branched chain amino acids which have a vasodilator effect, shift from a usual meat-based diet to a vegetarian diet, which results in significant reduction in blood pressure in subjects with normal renal function (22), or more simply, the salt restriction associated with sVLPD could have played a leading role in the reduction in blood pressure levels (23).

### Reduction in Proteinuria

Besides its well known role as a marker of CKD and as a risk factor of progression of CKD, proteinuria is linked by a dose–response relationship with CV risk both in the general population (24) and in patients with nephropathy (25), so that proteinuria should be considered as one of the main targets for both renal and CV protective treatments.

Actually, in numerous studies, a positive relationship was observed in patients on ACEI or angiotensin II receptor blockers between the reduction in proteinuria and the reduction in CV risk, independent of the effects on blood pressure. Proteinuria-reducing effects of sVLPD are similar to those reported with the drugs: after an initial decline from the first week, the greatest improvement in proteinuria is achieved within 3 months with a mean reduction ranging between 20% and 47%. (26,27). It is likely that the effects of sVLPD on CV outcome are also similar to those observed with drugs. However, as antagonists of the renin angiotensin system and sVLPD exert their proteinuria-reducing effect via a different mechanism: postglomerular vasodilation for the first and preglomerular vasoconstriction for the latter, their association results in additive benefits and is justified to reduce proteinuria to its lowest achievable level (28,29).

### Metabolic Complications

sVLPD reduces uremic signs and symptoms either by a direct effect on some metabolic disorders (such

as metabolic acidosis or calcium-phosphate metabolism disorders) or by the reduced production of by-products of protein metabolism that behave as metabolic inhibitors.

### Amelioration of Insulin Resistance

Besides its role in the pathogenesis of protein energy wasting, insulin resistance is also an independent predictor of CV mortality, which is present from the early stages of chronic renal failure. A beneficial effect on glucose tolerance and insulin sensitivity demonstrated by clamp studies is observed after 3 months on sVLPD (30). The lowered production and accumulation of metabolic products of dietary protein, which behave as insulin inhibitors, might be responsible for the reduction in hyperinsulinism and its CV consequences.

### Improvement of Lipid Profile, Oxidative and Inflammatory Status

The dramatic reduction in protein intake of animal origin in sVLPD is associated with a concomitant reduction in the intake of saturated fatty acids and an improvement of serum lipid profile: reduction in serum triglycerides and increase in the Apo A1/Apo B ratio (31). In response to amelioration of proteinuria, there is a correlated reduction in total and low-density lipoprotein cholesterol also favored by a high percentage of protein of vegetable origin (32). Oxidative status is also improved by sVLPD because this diet contains a wide range of antioxidant-rich foods: antioxidant vitamins and carotenoid, capable of reducing oxidative stress. Compared with patients on conventional LPD, patients on sVLPD showed an improvement of their lipid profile and a reduced oxidative stress with a reduced acute phase response (33). Ketoacid supplementation in patients with CKD administered erythropoietin potentiates the beneficial effect on metabolism of proteins, amino acids, and lipids (34).

### Correction of Calcium-Phosphate Metabolism Disorders

Hyperphosphatemia is an independent risk factor for mortality in CKD patients in relation with vascular calcifications and cardiac damage. Hyperphosphatemia results from a positive phosphorus balance despite compensatory secondary hyperparathyroidism and increase in fibroblast growth factor 23 (FGF 23). A recent study has shown that sVLPD reduced both hyperphosphatemia and FGF 23 serum levels (35). This is an important point as FGF 23 concentrations, which are several times higher than normal in CKD patients, are independently associated with CV events and all-cause deaths. Another study from the same group has just shown that phosphate was a strong modifier of the antiproteinuric effect of sVLPD, the fall in proteinuria in response to sVLPD being negatively correlated with serum phosphorus level, which can partly explain the association of high serum phosphate levels with more rapid progression of CKD (36).

The overall effect of sVLPD on calcium-phosphate abnormalities is a good illustration of the complementary actions of the different components of sVLPD. Such diet provides a very low phosphorus load, not exceeding 7–9 mg/kg/day because dietary phosphorus parallels dietary protein intake, and prevents a positive phosphorus balance with its vascular and bony consequences. Increased vegetable proportions of the diet also plays a role because bioavailability of phosphorus varies widely according to sources: while intestinal absorption of phosphorus from a meat-source reaches 80%, intestinal absorption of phosphorus from plant-based protein, mostly in a complex form of phytic acid, does not exceed 30–40% because lack of phytase in humans, which facilitates the control of serum phosphorus and of FGF 23 (37,38). Lastly, ketoanalogues, which are given as calcium salts, each tablet providing 50 mg of calcium, have a hypophosphatemic effect due to the formation of insoluble calcium-phosphate in the intestine (39).

### Correction of Metabolic Acidosis

Metabolic acidosis, quite common in CKD patients, accelerates protein catabolism, decreases albumin synthesis, favors loss of fat-free mass and, possibly, the progression of CKD; conversely, correction of acidosis is associated with better survival and renal outcomes (40). It has been recently shown that oral alkali supplementation and a diet rich in fruits and vegetables were equally effective at controlling metabolic acidosis and some of its renal consequences (41). While acidosis is worsened by animal-protein diet, which implicates a high production of fixed acids, vegetarian foods, which contain higher amounts of metabolizable organic anions and lower amounts of sulfur-containing amino acids, tend to yield an alkaline load and to limit acidosis. In a recent observational cross-sectional study concerning nearly 3000 patients with various CKD stages, it was observed that the percent plant protein of total protein intake was correlated with serum bicarbonate levels regardless of CKD stages or total protein intake (38). The beneficial effect of sVLPD on metabolic acidosis of CKD patients is explained by the reduction in meat consumption and the higher percentage of protein intake from plant sources in the diet (3,42).

## Is sVLPD safe?

Chronic kidney disease patients may present with a spontaneous decrease in protein and energy intake, which tend to worsen with the progression of renal failure resulting in protein energy malnutrition at the onset of renal replacement therapy (RRT) in 40–50% of them. In these circumstances, the nutritional safety

of protein-restricted diets, more especially of sVLPD, and their long-term effects on body protein stores have been frequently questioned.

In fact, it has been widely shown that nutritional status was well preserved in patients on sVLPD as evidenced by a regular survey of energy and protein intakes and by the anabolic or anticatabolic effects of ketoanalogues (especially from leucine and isoleucine). In the MDRD Study B, only two of 255 patients reached a "stop point" for malnutrition; mean values for different markers of nutritional status remained within the normal range during the 2.2-year follow-up (8). Other series confirm these results: in a 2-year survey of body composition with DEXA, Chauveau et al. reported that after an initial decrease, lean body mass stabilized at 6 months and then increased significantly from 6 to 24 months; no significant change was observed for total fat mass (43). A recent review analyzing 14 studies, which included 666 patients on sVLPD, confirmed that, in all but two studies, this diet was not associated with deterioration in body composition (44). Fifteen years earlier, Walser had already concluded that "rather than causing malnutrition, sVLPD prevents it" (15). The overall safety of sVLPD is confirmed by a mortality rate of 2.4% per annum in the MDRD Study B. The mortality rate per year at risk was exactly the same in two other series (3,45). Lastly, in a more recent study, no death occurred during a 48-week follow-up (46).

Concerns have also been raised about the outcome of the patients once RRT has begun because of a very low level of residual renal function. It was also feared that once on dialysis, these patients would be unable to change their predialysis dietary habits. In fact, no correlation was observed between the death rate and the duration of predialysis sVLPD (47). It can be concluded (without the prejudice of carrying out of a regular survey) that predialysis sVLPD has no detrimental effect on the short- and long-term outcome of patients once RRT is initiated whatever the treatment: dialysis or renal transplantation (47).

## Considerations in Selected Populations

Safety of sVLPD has also been observed in pregnancy, which remains a hazardous challenge in CKD. A recent study reported the outcome of 12 pregnancies in 11 women with stage 3–4 CKD who received a supplemented diet providing 0.6–0.7 g protein/kg/day. Nutritional status was maintained during the pregnancy and after the delivery even though one-third of the women breastfed their babies. As to the babies, all but one had a normal intrauterine growth and were well at 1 month–7.5 years from delivery (48).

In elderly patients, who represent the most important group requiring RRT, a prospective multicenter study concluded that sVLPD is effective and safe when postponing dialysis in patients older than 70 years (49). A secondary analysis of this study, comparing medical and nonmedical benefits and costs of initiating sVLPD versus dialysis, concluded that sVLPD significantly postponed the onset of maintenance dialysis without negative clinical consequences, but with substantial economic advantages (50), which will be strongly appreciated not only by physicians and their patients but also by the economists of the overburdened healthcare systems.

## Conclusion

A positive answer may be given to the initial question concerning the place of sVLPD in the management of CKD patients; the diet is feasible, safe, and efficacious. With the reservation that regular monitoring of patients is compulsory, sVLPD represents a safe approach to postpone dialysis treatment in patients selected on medical, psychological, and environmental grounds who should a priori adhere to such diet and represent approximately 30–40% of the concerned population. Feasibility of the prescription is confirmed by a long-term satisfactory adherence to the diet, which is observed in approximately 50% of patients. sVLPD effectively defers the initiation of dialysis—possibly by slowing down the rate of progression of renal failure and definitively by reducing uremic signs and symptoms.

### Conflict of Interest

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