Supplements of Keto Acids in Patients with Chronic Renal Failure

Vladimír Teplan
Department of Nephrology, Institute for Clinical and Experimental Medicine and Chair of Nephrology, Institute for Postgraduate Medical Education, Prague, Czech Republic

Nefroloji Dergisi 2004;13 (1) 3-7

Chronic renal failure (CRF) is consistently associated with major metabolic disorders. There are two reasons to design and implement a low- protein diet (LPD) for the successful managment of patients with chronic renal failure: 1) to improve uremic symptoms and the metabolic abnormalities associated with renal insufficiency; and 2) to slow the loss of residual renal function. The former reason has been standard clinical practice for more than 130 years ago while the latter is more controversial (1). Controversy about the efficacy of the latter reason is based principally on results of the U.S., NIH-sponsored MDRD Study but there are several reasons why this study can not be accepted as the "last word" about the efficacy of LPD in slowing the loss of the remaining kidney function (2, 3). Even though a LPD does improve metabolism with little or no risk, properly designed diets are not systematically prescribed in many nephrological units and questions are raised about its safety in reviews (4). On the other hand, a systematic examination of the available literature and several meta- analyses have shown this "simple" type of intervention can slow the progression of renal failure and exert other positive effects (3, 5-8). In accordance with criteria of Evidence Based Medicine LPDs have to be regarded a type A recommendation for both non-diabetic and diabetic patients with CRF.

The major effects of LPDs is to correct metabolic abnormalities and to delay the time until dialysis has to be started. This is not a trivial period of time (9, 10) and viewed from a worldwide public health point of view, LPDs are desirable given the increasing costs of dialysis therapy and the risk of death after patients begin dialysis. On average beginning dialysis therapy can be delayed more than one year (9-11). There also is abundant evidence that LPDs are associated with an improvement of a broad range of signs and symptoms of uremic syndrome, including amelioration of hyperparathyreoidism, increased insulin sensitivity, reduced incidence of metabolic acidosis, reduced proteinuria, improved management of hypertension and last but not least an improvement in subjective well being (1, 9-12).

Initially, supplements of amino acids and of keto acids (KA), the nitrogen free amino acid analogues respectively, were introduced so that protein intake could be reduced to minimal amounts in order to augment the positive effects exerted by LPDs while avoiding the development of malnutrition - the only real potential complication of LPDs. If KA are used an even lower protein intake of as low as 0.3 g/kg BW/day can be achieved without increasing the dangers of malnutrition (9, 10). KA are the nitrogen free analogues of amino acids, and are transaminated to form the respective amino acid in the body. This improves nitrogen balance at a lower nitrogen intake because essential amino acid requirements are met with a lower nitrogen intake with reduced waste product formation and relief of the symptoms of uremia while maintaining good nutrition.

The keto amino acid therapy contains a dietary protein restriction as well as a supplementation of keto and amino acids essential for patients with CRF. Keto acids are the nitrogen-free analogs of amino acids, which can be converted (transaminated) in the human body into the corresponding amino acids by about 70%.

Keto acids not only substitute for their respective amino acid and maintain nitrogen balance but also exert other desirable properties:

1. The saving of nitrogen due to the transfer of the amino group to the keto acid is associated with a direct inhibition of ureagenesis. The inhibition is related

Yazışma adresi: Prof. Dr. Vladim r Teplan, DSc.
Institute for Clinical and Experimental Medicine Videnska 1958/9
140 21 Prague 4, Czech Republic
e-mail: vladimir.teplan@medicon.cz

to the increased activity of branched-chain amino acid transferase resulting in less availability of the ramified keto acid for oxidative decarboxylation.

2. Keto acids have the ability to stimulate protein synthesis and inhibit protein degradation. Especially ketoleucine, and perhaps leucine can increase protein synthesis by inducing an increased aggregation of polyribosomes. Furthermore, ketoleucine stimulates the amino transferase activity.

3. Administration of keto acids may lead to a partial correction of the amino acid profile in uremic patients, which is also favoured by the simultaneous correction of metabolic acidosis due to the reduced alimentary intake of sulphur-containing amino acids. In addition, the decrease in urinary protein excretion due to amino/keto acid supplemented protein-restricted diets contributes to the rise in serum albumin and the maintenance of various indices of nutritional status within the normal range. Compared to other amino acids, keto acids lack a stimulating effect on the hyperfiltration of the kidney. Following the supply of keto acids of branched chain amino acids (BCAA) during a protein-restricted diet, the pancreatic glucagon stimulation and the subsequent glucagon-induced hepatic cAMP secretion that is typical for amino acids is missing. Metabolic acidosis results from impaired excretion of hydrogen ions. A large proportion of the hydrogen ions come from the metabolism of sulphur-containing amino acids. This acidosis has several deleterious effects, namely on protein metabolism, glucose tolerance and bone metabolism. Only strict reduction or suppression of protein of animal origin is susceptible to correct metabolic acidosis. Since metabolic acidosis increases the degradation of branched- chain amino acids and protein catabolism, and suppresses albumin synthesis, the control of this disorder is especially important in patients with a reduced protein intake. Protein-restricted diets which do not contain proteins of animal origin reduce phosphorus intake, and the presence of calcium (calcium salts of the ketoanalogues in Ketosteril®), has additional beneficial effects on calcium/phosphate metabolism and secondary hyperparathyroidism. The keto amino acid therapy is able to correct most of the disorders of carbohydrate metabolism observed in uremia. Beneficial effects include the improvement in tissue sensitivity to insulin reduction in circulating insulin levels in relation to an increase in the metabolic clearance rate of insulin and improved inhibitory action of insulin on endogenous glucose production. The lowering of insulin resistance, reduction of hyperinsulinemia and increase in energy production rate in patients on a keto amino acid therapy make it a therapeutic arm remarkably well adapted for the treatment of uremic patients, especially the growing group of obese non-insulin dependent diabetics with CRF. The keto amino acid therapy has benefical effects on the correction of lipid disorders, especially with respect to an decrease in triglyceride levels and an increase HDL-cholesterol levels. These results are important because of the accelerated atherosclerosis commonly seen in uremia. Dietary regime, used in the Institute for Clinical and Experimental Medicine, Department of Nephrology, Prague, contains 0.6 g protein, 1.3 g lipids, 4.9 g carbohydrate and 140 kJ energy /kg body weight/day supplemented with 100 mg Ketosteril®/kg body weight/day. Besides a sufficient energy intake and the amount of protein intake also the ratio of animal/vegetable protein (preferentially 1:1) seems to be important in low protein diet supplemented with Ketosteril®. In Czech Republic, many patients do not accept a strict very low protein diet (0.3 g protein/kg body weight/day) supplemented with Ketosteril®, which is mainly composed of vegetarian food.

Supplements of essential amino acids have largely been abandoned in dietary therapy of patients with CRF because of the concerns cited and they appear to have only limited advantages. If an essential amino acid supplement is given, a nitrogen poor preparation is preferred. In a direct comparison between KA and essential amino acids, Masud and coworkers showed that KA are equally or slightly more effective in maintaining nitrogen equilibrium (13). In a cross over study comparing supplements of essential amino acids and of keto acids the rate of progression of renal failure was slower during KAs (14). It should be noted that not all essential amino acids are given as nitrogen-free analogues as certain essential amino acids can- not be transaminated in the organism, such as lysine and threonine.

Numerous reports have provided evidence of the benefits of LPDs and shown that these benefits can be augmented by KA (1, 15, 16). For sure some of these benefits are attributable to a lower intake of protein (and hence, a reduced tendency to form waste products). During the last decade, however, there is evidence that KA supplements might exert specific effects beyond those attributed to the reduced nitrogen intake and amelioration of protein balance. The proven and proposed effects of LPDs and or supplemented diets are summarized in **Table 1.**

Table I. Proven and potential beneficial effect of keto acid supplements in patients with chronic renal failure on a low protein diet

Preservation of nitrogen balance
Reduction of "uremic intoxication"
Retardation of progression of renal failure
Reduction of proteinuria and amino aciduria
Amelioration of metabolic acidosis
Improvement of nutritional status
Reduction of growth retardation in CRF children
Increases in plasma concentrations of essential amino acids
Improvement of plasma protein concentrations (albumin) Improvement of glucose metabolism and insulin sensitivity Improvement in lipid metabolism
Reduction of hyperphosphatemia
Amelioration of hyperparathyreoidsim
Decrease in oxygen radical generation Improvement of tubular functions
Reduction in blood pressure (?)
Reduction in NO-metabolite formation (?)

An especially interesting benefit of KA supplements is found in the observation that the KA of leucine (a-ketoisocaproate) exerts a pharmacologic effect on protein metabolism by suppressing protein catabolism in skeletal muscle (there is no change in the rate of protein synthesis (17).

KA supplements also help to ameliorate hyperparathyreodism (18). The KA supplements are phosphate free and so help to reduce phosphate intake and this may be one mechanism that accounts for the reduction in progression of renal insufficiency in CRF. Notably, KA are often provided as calcium salts thereby raising calcium intake and promoting the binding of phosphate in the intestine to increase phosphate excretion. In fact, α-ketoglutarate and ketovaline have been assessed as alternative phosphate binders.

Studies by the group of Teplan from Prague (19) and (20) illustrate that KA supplements can have benefits that are far beyond these "classical" effects. In contrast to amino acids, KA do not exert change renal hemodynamics, nor induce hyperfiltration. This might also explain their more pronounced influence on reducing proteinuria (although it is well known that any LPD will reduce proteinuria in comparison to excess dietary protein). KA can also benefit tubular functions: despite increases in plasma concentrations of branched-chain amino acids, the losses of amino acids in the urine were reduced by the KA supplements. Furthermore, NO-metabolite excretion was lower during KA supplementation potentially reflecting a reduced hemodynamic stress within the kidneys.

Metabolic effects of KA supplements are not confined to improvements in protein metabolism: there are benefcial effects on glucose tolerance, insulin sensitivity leading to a decrease in insulin requirements in diabetic patients (21). As noted by others, Teplan et al. found a remarkable effect of KA supplements on plasma lipids (20, 22); there was a mild yet significant decrease in total cholesterol and LDL-cholesterol whereas HDL-cholesterol levels increased. Furthermore, a dramatic fall in plasma triglycerides by 50% was seen. Finally, there is reduced serum concentrations of free radicals with KA supplemented diets (20, 23) and this response might contribute to the preservation of renal function, together with improvements in lipid metabolism to retardation of progression of atherosclerosis and improvement of other physiologic functions such as immunocompetence.

Obviously, the effects of KA will not be apparent if protein intake is too liberal (24). However the optimal extent of the reduction of protein intake is not known. Usually it was assumed that KA are only beneficial when a very low protein diet of about 0.3 g/kg/day is prescribed. Interestingly, our studies would suggest that in part the beneficial effects can be seen when only a moderate reduction of protein intake to about 0.6 to 0.7 g/kg/day is instituted and obviously, this fact would present a major advantage in terms of compliance with the diet.

Given the accumulated evidence cited, it is distressing that fewer that 50% of nephrology units in industrialized countries regularly prescribe low protein diets and even a much lower number is using KA supplements. The reasons why this cheap therapeutic modality with proven efficiency is so little used is mystifying. Among the reasons, is the possibility that the financial incentive of having a patient on hemodialysis is very important in many countries. There also is the possibility that the need for education of the patient and his/her family is time consuming and will require a therapeutic partnership between a motivated patient and a devoted nephrologist and renal dieticians but even if the patient is sent to dialysis, he/she will still have to learn about dietary and fluid restrictions. In short, this should not be a major impediment. The Hungarian Ke-

tosteril study published in 2001 underlines that this is feasible in large groups of patients (25).

On the other hand, two recent reports emphasize that a low-protein diet regimen can produce a pronounced delay in the time until dialys is or transplantation are required (9, 10).

In these reports, patients given a low-protein diet supplemented with essential amino acids and/or ketoacids for long periods even after their loss of renal function was sufficiently severe (e.g. creatinine clearance <10 ml/min) to signal a need for dialysis. The delay in the need for dialysis was substantial (>1 year) and the patients maintained body weight and had normal levels of serum albumin and other indices of nutrition.

Keto acids are recommended to be routinely used also during EPO treatment in CRF patients with renal anemia (26).

Finally, it must be stressed that a well-designed LPD is a therapeutic modality among others in the management of patients with CRF; there is the therapy of the underlying disease process leading to renal failure, systematic treatment of hypertension, provision of renoprotective medications such as ACE-inhibitors, strict metabolic control in patients with diabetes mellitus type I and type II, an adapted micronutrient supply, measures to control hyperparathyreodisim, a well timed erythropoietin therapy and last but not least, the correction of metabolic acidosis must be instituted together with dietary interventions. There can be no doubt that within this therapeutic context LPDs and KA supplemented diets have a fixed place in the treatment of patients with CRR

Some important contraindications for the intake of keto acids are an inadequate caloric intake, severe therapy-resistant arterial hypertension with overhydration and a creatinine clearance lower than 5 ml/min/1 .73 m^2.

Other possible indications for a keto acid therapy is the use during dialysis and the treatment of an infrequent dialysis. In dialysis a low protein diet supplemented with keto amino acids with the aim of phosphate binding as well as improvement of the nutritional status and extention of the survival during dialysis.

Another opportunity of treatment is the infrequent dialysis. Generally, the treatment of patients with endstage renal failure is based on the maintenance hemodialysis 3 times a week and a free mixed diet with the only restriction of potassium, sodium and water in some cases. By adding both the detoxifying effects of dialysis and of a keto amino acid therapy, the residual renal function may be maintained and the frequency of dialysis sessions can be reduced. However, this treatment option is only for highly educated and motivated patients with the aim to save residual kidney function, to reduce the number of dialysis sessions, and to increasing the quality of life by creating more freedom for working and travelling.

References

1. Walser M, Mitch WE, Maroni BJ, Kopple JD: Should protein be restricted in predialysis patients? Kidney Int, 1999, 55, pp 771-777
2. Klahr S, Levey AS, Beck GL, Gaggiula AW, Hunsicker L, Kusek JW, Striker G: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med, 1994, 330, pp 877-884
3. Mitch WE: Dietary therapy in uremia: the impact on nutrition and progressive renal failure. Kidney Int, 2000, 57, Suppl 75, pp S38-S43
4. Ruggenenti P Schieppati A, Remuzzi G: Progression, remission, regression of chronic renal diseases. Lancet, 2001, 357, pp 1601-1608
5. Fouque D, Laville M, Boissel JP, Chifflet R, Labeeuw M, Zech PY: Controlled low protein diets in chronic renal insufficiency: meta-analysis. Br Med, 1992, 304, pp 216-220
6. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH: The effect of dietary protein restriction on the progression of diabetic and non-diabetic renal diseases: a meta analysis. Ann Intern Med, 1996, 124, pp 627-632
7. Kasiske BL, Lakatua JDA, Ma JZ, Louis TA: A meta analysis of the effects of dietary protein restriction on the rate of decline of renal function. Am J Kidney Dis., 1998, 31, pp 954-961
8. Fouque D, Wang P Laville M, Boissel JP: Low protein diets delay end-stage renal disease in non diabetic adults with chronic renal failure. Nephrol Dial Transpl, 2000, 15, pp 1986-1992
9. Walser M, Hill S: Can renal replacement be deferred by a supplemented very-low protein diet? J Am Soc Nephrol, 1999, 10, pp 110-116
10. Aparicio M, Chauvenau P, De Precigout V Bouchet J-L, Lasseur C, Combe C: Nutrition and outcome on renal replacement therapy of patients with chronic renal failure treated by a supplemented very low protein diet. J Am Soc Nephrol, 2000, 11, pp 708-716
11. Mitch WE: Are supplements of ketoacids and amino acids useful in treating patients with chronic renal failure. Wien Klin Wochenschr, 2000, 112, pp 863-864
12. Mitch WE, Maroni BJ: Nutritional consideration in the treatment of patients with chronic uremia. Miner Electrolyte Metab, 1998, 24, pp 285-289
13. Masud T, Young WR, Chapman T, Maroni B: Adaptive response to very low protein diets: the first comparison of ketoacids to essential amino acids. Kidney Int, 1994, 45, pp 1182-1192
14. Walser M, Hill S, Ward L: Progression of chronic renal failure on substituting a ketoacid supplement for an amino acid supplement. J Am Soc Nephrol, 1992, 2, pp 1178-1185
15. Teschan PE, Beck GE, Dwyer JT, Greene T, Klahr T, Levey AS, Mitch WE, Snetselaar LG, Steinman TI, Walser M: Effect of a keto acid amino acid - supplemented very low protein diet on the progression of advanced renal disease: a reanalysis of the MDRD feasibility study. Clin Nephrol, 1998, 50, pp 273-283
16. Walser M, Hill SB, Ward L, Magder L: A crossover comparison of

progression of chronic renal failure: k toacids versus amino acids. Kidney Int, 1993, 43, pp 933-939

17. Mitch WE, Clark AS: Specificity of the effect of leucine and its metabolites on protein degradation in skeletal muscle. Biochem J, 1984, 222, pp 579-586
18. Fröhling PT, Kokot F, Schmicker R, Kaschube I, Lindenau K, Vetter K: Influence of keto acids on serum parathyroid hormone levels in patients with chronic renal failure. Clin Nephrol, 1983, 20, pp 212-215
19. Teplan V Schück O, Horácková M, Skibová J, Holecek M: Effect of a keto acid-amino acid supplement on the metabolism and renal elimination of branched-chain amino acids in patients with chronic renal insufficiency on a low protein diet. Wien Klin Wochenschr, 2000, 112, pp 876-881
20. Teplan V Schück O, Votruba M, Poledne R, Kazdová L, Skibová J, Maly J: Metabolic effects of keto acid - amino acid supplementation in patients with chronic renal insufficiency receiving a low-protein diet and recombinant human erythropoietin - A randomized controlled trial. Wien Klin Wochenschr, 2001, 113, pp 661-669
21. Aparicio M, Gin H, Potaux L, Bouchet JL, Morel D, Aubertin J: Effect of a ketoacid diet on glucose tolerance and tissue insulin sensitivity. Kidney Int, 1989, Suppl 27, pp 231-235
22. Bernard S; Fouque D, Laville M, Zech P: Effects of low-protein diet supplemented with ketoacids on plasma lipids in adult chronic renal failure. Miner Electrolyte Metab, 1996, 22, pp 143-146
23. Peuchant E, Delmas-Beauvieux MC, Dubourg L, Thomas MJ, Perromat A, Aparicio M, Clerc M, Combe C: Antioxidant effects of a supplemented very low protein diet in chronic renal failure. Free Radical Biol Med, 1997, 22, pp 313-320
24. Hirschberg R, CohenAH, Kopple JD: Effects of keto acid supplements on renal function and histology in azotemic rats fed high-protein diets. Am J Nephrol, 1988, 8, pp 50-56
25. Zakar G for the Hungarian Ketosteril Cohort Study: The effect of a keto acid supplement on the course of chronic renal failure and nutritional parameters in predialysis patients and patients on regular hemodialysis therapy: The Hungarian Ketosteril Cohort Study. Wien Klin Wochenschr, 2001, 113, pp 688-694
26. Teplan V, Schück O, Knotek A, Hajn_ J, Horá_ková M, Kvapil M: Enhanced effect of erythopoetin and keto acids in chronic renal failure patients: Czech multicentre study (2003) Am J Kidney Diseases 41, 2003, Suppl 1, pp 26-30