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VIA MEDICA

Low-protein diets and ketoanalogues of amino acids in the treatment of chronic kidney disease — position of the Executive Board of the Polish Society of Nephrology

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ABSTRACT

The NKF DOQI (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative) recommendations from 2020 advice the use in patients with chronic kidney disease (CKD) 3–5 without diabetes, in a stable metabolic state and under strict medical care, a diet with a protein amount of 0.55–0.6 g/kg/day The use of low-protein with or without ketoanalogues of amino acid reduces the risk of end-stage renal disease. The constantly growing number of patients with advanced chronic kidney disease, the high costs of dialysis therapy and the lack of beneficial effects of early qualification for dialysis on the prognosis of patients cause a renewed interest in the use of low-protein diets with the hope of prolongation conservative treatment.
The position of the Polish Society of Nephrology, based on global recommendations and current scientific research results, recommends the use of low-protein diets and amino acid ketanalogues in patients with CKD as part of conservative treatment in a group of patients in good clinical condition, who have no contraindications for this type of proceeding.

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Key words: low-protein diets, chronic kidney disease, conservative treatment, ketoanalogues of amino acid

INTRODUCTION

According to the 2020 recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF DOQI), a diet with the protein content of 0.55–0.6 g/kg/day is advised for non-diabetic, metabolically stable patients with stage 3–5 chronic kidney disease (CKD) remaining under strict medical care. A low-protein diet with or without amino acid ketoanalogues reduces the risk of end-stage renal disease [1].

According to the guidelines of the European Society of Clinical Nutrition and Metabolism (ESPEN), a diet containing 0.6 g of protein/kg/day is recommended for patients with chronic kidney disease stage 3b [2, 3]. The 2012 Consensus Statement [4], based on the studies demonstrating the benefits of low protein diets in the advanced stages of the disease (CKD stages 3–5), recommends the use of diets with reduced protein and ketoamino acid (KA) content. Limiting the supply of proteins (0,6 g/kg/day or < 0.6 g/kg/day with KA sup-

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plementation) reduces the serum urea level while simultaneously:
— reducing the phosphate levels;
— reducing metabolic acidosis;
— reducing hyperkalemia;
— increasing insulin sensitivity;
— improving the lipid profile;
— slowing down CKD progression [5, 6].

The main concerns regarding the low-protein diet (LPD) are its safety and practical implementation OR applicability. According to a common belief, the diet is very difficult for the patients and may lead to protein/energy malnutrition. Thanks to the increasing availability of dietary consultations in recent years, more widespread use of low-protein diets have become possible.

The continuously growing number of patients with advanced chronic kidney disease, the high costs of dialysis therapy, and the lack of beneficial effects of early qualification for dialysis on the patients' prognosis have caused a renewed interest in the use of low-protein diets, in the hope of prolonging the conservative treatment phase, particularly in clinically and metabolically stable patients with stage 3b-5 CKD [7–11].

For these reasons, the Working Group of the Polish Society of Nephrology (PTN) and the Management Board of the PTN consider it appropriate to present their position on the use of low protein diet and amino acid ketoanalogues.

POSITION 1

A low-protein diet, i.e. a diet with a protein content of 0.6 g /kg/day or < 0.6 g/kg/day with amino acid ketoanalogue supplementation, extends the conservative treatment phase and improves patient survival after initiating dialysis treatment.

COMMENT

In patients with CKD, a diet with the protein content being restricted to 0.6 g/kg/day or less than 0.6 g/kg of due body weight/day with amino acid ketoanalogue supplementation (sVLPD, supplemented Very Low-Protein Diet) slows down the disease progression. It delays kidney replacement therapy by as much as several months [12–14]. sVLPD also results in a ca. 30% extension of the conservative treatment period compared to no diet [15–17]. Studies included mainly stage 3b, 4, or 5 CKD patients.

In a retrospective study, Fouque et al. analyzed the fate of patients on sVLPD to find that the risk of death after the onset of dialysis therapy was statistically significantly lower for patients on a low-protein diet compared to other patients [18].

POSITION 2

The risk of malnutrition when using a low-protein diet supplemented with amino acid ketoanalogues is low provided that nutrition status is regularly monitored.

COMMENT

Low-protein or very low-protein diets (protein content of 0.3–0.6 g/kg/day) may result in a risk of protein-energy malnutrition. For this reason, it is necessary to monitor patients' nutritional status both before and throughout the entire dietary treatment. Constant supervision by a dietitian is also required to ensure compliance with the protein and energy intake instructions.

The additional KA supplementation is intended, among other factors, to prevent systemic protein shortages and supply amino acids (leucine, isoleucine, valine) required to maintain the correct muscle mass. No signs of malnutrition were observed due to diet and KA supplementation [13, 19].

When qualifying patients for LPD, the patient's nutritional status should be assessed as per the recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative [1] and the Polish Society of Nephrology [26]. Regarding the diagnosis of malnutrition, the above recommendations suggest evaluating unintentional body weight loss, calculation of BMI, serum albumin levels, normalized protein nitrogen appearance (nPNA), or the protein and energy intake being assessed by a dietitian.

Malnourished patients, i.e. patients with hypoalbuminemia and/or unintentional body weight loss, and patients with low BMI, require an increased supply of proteins and energy with the diet or oral nutritional supplements as the first intervention.

POSITION 3

Proper use of a low-protein diet supplemented with ketoanalogues of amino acids requires appropriate monitoring of biochemical parameters and diet compliance (as well as co-operation between the patient, the nephrologist, and dietitian).

COMMENT

A low-protein diet with KA supplementation ensures [1] an adequate supply of proteins in quantities ranging from a minimum of 0.3 to 0.6 g/kg/day [2] the adequate intake of calories, i.e. 30–35 kcal/kg/day, phosphates of 5–7 mg/kg/day, sodium of 2 g/day, [3] an adequate supply of vitamins and elements, e.g. iron. Monitoring a patient on a low-protein diet aims to verify compliance and early detection of potential hypoalbuminemia or excessive body weight loss. It is also necessary to determine the moment to discontinue the conservative treatment and start dialysis therapy [20–24].

The patient should be motivated to adhere to the diet and agree to the proposed treatment [25].

It is advisable to monitor the patient in accordance with the following scheme [26]:

— Monthly medical and dietary counseling visits for the first 3 months followed by medical and dietary counseling visits held every 3 months after that.
— Proposed investigations:
— Daily Protein Intake (DPI) as assessed by the dietitian;
— Compliance with dietary recommendations as assessed by urinary BUN excretion and nPNA calculation;
— Nutritional status assessment, e.g. body weight, BMI, SGA (subjective global assessment), serum albumin levels, lymphocytemia;
— Renal function assessment (determination of eGFR and serum concentrations of creatinine, urea, potassium, sodium, calcium, phosphorus)

nPCR (Protein Catabolic Rate)/nPNA (Protein equivalent of Nitrogen Appearance) = DPI (Daily Protein Intake) nPNA [g/kg/day] = (BUN* [g N/day] + 0.031 × body weight [kg]) × 6.25 / body weight[kg]

*BUN – 24-hour urea nitrogen excretion in urine [g N/day]

POSITION 4

The criteria for qualifying a patient for the low-protein diet with amino acid ketoanalogue supplementation have not been strictly defined. Therefore it is more appropriate to be guided by the lack of contraindications to its use (protein/energy malnutrition, diabetes mellitus, dialysis therapy). The patient should be clinically stable and constantly supervised by a nephrologist [1].

COMMENT

As suggested in the literature, the greatest benefits of dietary therapy + KA are observed in non-diabetic, clinically stable patients with good nutritional status who are motivated to adhere to dietary recommendations [1, 5, 13].

The criteria for qualification to diet + KA supplementation are as:

— followspatient consent;
— no signs of malnutrition;
— CKD stage of 3b–5;
— no dialysis therapy is required;
— availability of dietary consultation.

POSITION 5

Amino acid ketoanalogue supplementation of diet with protein content restricted to 0.6 g/kg/day may be a therapeutic option starting from stage 3b CKD and CKAD (chronic kidney allograft disease). It should be introduced when using a diet with protein content restricted to 0.6 g/kg/day in stage 4 disease but is mandatory when using a diet with protein content restricted to < 0.6 g/kg/day in stage 3b and stage 4 disease.

The European and American guidelines [1–6] recommend introducing 0.6 g/kg/day low-protein diets as early as in stage 3 CKD. Among other factors, regular monitoring of the patient's nutritional status and dietary provision of an adequate supply of energy and exogenous amino acids are required in therapeutic diets, with protein content being restricted to less than 0.8 g/kg/day.

A diet with a protein content of less than 0.6 g/kg/day requires replacing a part of the products that are the source of the plant-derived proteins (cereals, potatoes) with special low protein products (low-protein baked goods and other cereal products). These products must be purchased by the patient. The very low-protein diet is recommended at the earliest stage 4 CKD and should not be used without the amino acid ketoanalogue supplementation.

The most commonly recommended dose of ketoanalogues available as Ketosteril formulation is 1 tablet/5 kg body weight/day in 3 divided doses. One tablet contains 380 mg of pure amino acids, which translates into the patient receiving between 4.5 and 9 g of amino acids per day depending on the body weight.

In the study by Piccoli et al. [27], patients (n = 139) with stage 3–5 CKD received a 0.6 g/kg/day low-protein diet with KA supplementation at the dose of 1 tablet per 10 kg per day for 6 months.

Table 1. Proposed treatment scheme including a low-protein diet and Ketosteril® supplementation depending on kidney function

Stage	GFR (mL/min/1.73 m^2)	Daily protein supply	Ketosteril® supplementation
1	> 90	Normal diet (recommended intake 0,8 g protein/kg bw)	—
2	60–89	Normal diet (recommended intake 0,8 g protein/kg bw)	—
3a	46–59	Normal diet (recommended intake 0,8 g protein/kg bw)	—
3b	45–30	Low-protein diet (0,6 g protein/kg bw)	optionally 1 tablet/5 kg bw/d
4	15–29	Low-protein diet (0,6 g protein/kg bw) Very low-protein diet (0,3 to 0,6 g protein/kg bw)	optionally 1 tablet/5 kg bw/day 1 tablet/5 kg bw/d
5	< 10–15 conservative treatment	Low-protein diet (0,6 g protein/kg bw) Very low-protein diet (0,3 to 0,6 g protein/kg bw)	optionally 1 tablet/5 kg bw/day 1 tablet/5 kg bw/d

* long-term treatment: 1 tablet/5 kg due bw/d (bw = body weight, d = day)

CONCLUSION

One should also keep in mind that end-stage kidney disease is one of the leading causes of increased mortality. CKD has become widespread throughout the globe in recent decades, and the number of patients requiring kidney replacement therapy is likely to double by 2030. Therefore, effective conservative treatment of CKD patients is crucial to prevent end-stage kidney disease.

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