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Practical aspects of a low-protein diet

ABSTRACT

The updated 2020 Kidney Disease Outcome Quality Initiative (KDOQI) guidelines resulted in an increased interest in the use of a low-protein diet in patients with chronic kidney disease. In Poland, from March 2021, patients can be enrolled, provided that they meet certain criteria, in the therapeutic program including the use of a low-protein diet and ketonanalogues of amino acids. However, it is very important to properly educate medical personnel and patients so that the KDOQI recommendations are implemented in clinical practice and bring benefits by slowing progression of chronic kidney disease.

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Key words: low-protein diet, ketoanalogues, drug program

INTRODUCTION

The 2020 Kidney Disease Outcome Quality Initiative (KDOQI) dietary guidelines recommend protein reduction in patients with stages 3 to 5 chronic kidney disease (CKD) provided that they are metabolically stable, do not show characteristics of inflammation or unintentional weight loss or do not require hospitalization. The purpose of such a procedure is to delay progression of CKD and improve the quality of life [1]. In Poland, since March 2021, those guidelines have been implemented as part of the *Kidney Diseases* drug program (the program includes implementation of a low-protein diet of 0.4–0.6 g protein/kg body weight/day and ketoaminoacids). Throughout the program, the participating centers have gained quite a lot of experience, which can be used to make the program more accessible to patients and physicians. Despite highly reliable scientific evidence (1A), low-protein diets (LPD) are still not recommended by many nephrologists. Nephrologists and nutritionists should be familiar with indications, contraindications, mechanisms of action, dosage, side effects, and special warnings regarding the use of low-protein diets. Despite the indications and contraindications specified in the drug program, in practice, there are many questions and concerns about the safety and effectiveness of such a therapy. In everyday practice, it turns out that not all parameters selected for qualification/disqualification and monitoring of patients during the program are easily accessible in each healthcare center, some of those that were selected for clinical trials are, in turn, not very useful in everyday practice. In addition, education of patients and accurate presentation of the benefits and risks of long-term use of the low-protein diet and ketoanalogues of amino acids is worth emphasizing. The patient must know that it is an element of comprehensive therapy; they should be able to use modern drugs that slow down the progression of chronic kidney disease and must be informed that despite applied nephroprotection, the disease will continue to proceed.

MALNUTRITION

There is a consensus that people qualified for a low-protein diet must have a good nutritional status. The exclusion of malnutrition is based on several basic methods: anthropometric, biochemical, clinical, and dietary.

For many years, the SGA method (subjective assessment of nutritional status) and its variations, whose usefulness has been proven in scientific studies [2], have been used in nephrology patients. In 2008, the ISRNM (International Society of Renal Nutrition and

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Metabolism) proposed extensive criteria for diagnosis of malnutrition in CKD patients [3]. However, most researchers indicate that there is no clearly superior diagnostic malnutrition index. In addition to SGA, the usefulness of serum albumin [4] has also been proven. Low serum albumin correlates significantly with a risk of progression of chronic kidney disease and death due to cardiovascular sequelae. In addition, the relationship between serum albumin and inflammation is also known in CKD patients, and it is referred to as MIA syndrome [5].

Recommendations for assessing nutritional status during the period of conservative treatment according to NKF K/DOQI (Kidney Diseases Outcome Quality Initiative Guideline 23. Panels of Nutritional Measures for Nondialyzed Patients — GFR 20 mL/min) included regular checking for serum albumin, body weight measurement, SGA (Subjective Global Assessment), nPNA (normalized Protein Nitrogen Appearance) calculation, or dietary history taking. As a consequence, SGA and albumin are most often used to assess nutritional status in CKD patients.

The indicator that is used in the assessment of nutritional status in practice is BMI. However, it is often criticized as unreliable in assessment of malnutrition, especially in patients with fluid overload, where BMI may be overestimated. In the population with renal impairment, there is a high risk of death with low BMI (< 18.5 kg/m^2), while higher BMI in end-stage renal disease dialysis patients indicates better prognosis, even if it indicates overweight or obesity [6].

Other nutritional status indicators in CKD patients have less proven usefulness in assessment of malnutrition because metabolic disorders found in chronic kidney disease significantly affect many biochemical parameters, e.g. serum transferrin level, total number of lymphocytes or lipids.

Malnutrition affects immunity, which in laboratory tests is expressed by a decrease in the absolute blood count of lymphocytes. Values below 800/mm^3 may indicate both impaired nutritional status and immunity. Lymphocytopenia in adults (< 1.5 × 10^9/L) may be associated with diseases and conditions such as connective tissue disease (e.g. systemic lupus erythematosus); glucocorticoid therapy, which should be included in the interpretation in people with various underlying causes of CKD. In publications, a reduced total number of lymphocytes was considered a factor for poor prognosis and occurrence of postoperative complications, for example, in a group of oncology patients [7]. In the study by Polish researchers assessing the relationship between total lymphocyte count and prognosis in hospitalized patients, it was shown in a large group of patients that a small total number of lymphocytes is associated with a higher risk of death during hospital stay re-admission within 14 or 30 days. and a longer stay at the hospital, and also with a higher risk associated with a deterioration of the nutritional status [8]. There is a lack of studies indicating a close correlation between malnutrition characteristics for CKD patients and the lymphocyte count.

DIET ASSESSMENT

Before qualification for and implementation of a low-protein diet, it is necessary to assess the intake of each nutrient. This is the first step for further modification of diet, i.e. gradual reduction of protein intake — some recommend reduction by 0.2 g until recommended 0.6 or below [9].

Dietary assessment by a nutritionist is usually based on the analysis of the so-called diet diary or information on current intake based on listing food products for at least 3 days. Computer programs make it possible to calculate how much protein, calories, and other ingredients the patient consumes. The credibility of those records depends, of course, on the patient's education and motivation, but the dietary intake calculated is considered reliable [10].

If there is no possibility of dietary evaluation by a nutritionist, or there are concerns that the patient does not follow the diet, it is recommended to verify the diet by calculating the weight-normalized PNA index. It requires 24-hour urine collection, measurement of urea nitrogen excretion, and nPNA calculation, which in a patient with a neutral nitrogen balance should correspond to the daily protein intake (DPI) [11].

In the drug program, nPNA was treated as a fixed element of a monthly evaluation; however, it should be noted that 24-hour urine collection and measurement of urea nitrogen excretion (BUN) may be distorted. NKF DOQI guidelines indicate a small number of studies on the use of PNA for protein intake evaluation, but several studies assessed the use of PCR/PNA to determine protein in-

take in CKD patients and found significant correlations with dietary intake evaluation by a dietician. However, it should be noted that PNA overestimated protein intake when the daily protein intake was < 1 g/kg [12–14]. It is worth noting that another advantage of the patient's cooperation with the dietician in measuring DPI is analyzing the patient's diet by both parties, which creates the opportunity to correct ongoing mistakes and broaden the patient's knowledge about compliance with the low-protein diet.

PROTEINURIA

Both Polish and global guidelines emphasize that the efficacy and safety of a low-protein diet depend on the patient's metabolic condition, therefore, exclusion of inflammation, hypercatabolism, or accompanying diseases that increase catabolism is necessary before qualification for a low-protein diet. Proteinuria > 5 g/day is a condition that, according to the guidelines, requires an increase in the supply of protein in the diet [15]. On the other hand, proteinuria has been identified as one of the most important and independent risk factors for progression of CKD, and any attempt to lower proteinuria to a minimum seems profitable. Studies indicate that in nephrotic syndrome (when GFR is < 60 mL/min), the LPD may reduce proteinuria.

GLOMERULAR FILTRATION

One of the criteria qualifying patients for the B.113 drug program is as follows: "Reduction of eGFR < 2 mL/min within the last 6 months prior to qualification". For the estimation of the glomerular filtration rate (eGFR), it is recommended to use the MDRD formula (Modification of Diet in Renal Disease Study Group) [16]. This is justified in this clinical situation because, in the target group of the program, i.e. in patients with stages 4 and 5 CKD, this formula is characterized by a relatively better agreement between the measured and estimated GFR compared to other formulas such as CKD-EPI (*Chronic Kidney Disease Epidemiology Collaboration formula*) [17]. It should be noted that an estimate of a decrease in GFR over a short period of 6 months may be burdened with a significant error, resulting in an unintended exclusion of patients who would benefit from the program. The nonlinearity of the loss of GFR or its daily fluctuations can pose a real threat since obtaining the proposed precision of the calculation (< 2 mL/min) in practice requires repeated measurements over consecutive days and an extension of the observation period. This is for many reasons impractical, costly, and unnecessary in everyday clinical practice. Moreover, serum creatinine, which is the basis for the calculation, depends on the amount of protein consumed and may fluctuate during the introduction of a low-protein diet independently of GFR [18]. It should also be remembered that the final GFR value is influenced by many other physiological and pathological factors, e.g. physical activity, glucose level, drugs, and hydration status [17].

MONITORING OF PATIENTS ON A LOW-PROTEIN DIET

Researchers believe that the use of a low-protein diet and KA under the supervision of a nephrologist and nutritionist is safe and does not result in deterioration of the nutritional status. The studies by Garneata et al. [19] and Mocanu et al. [20] showed that serum albumin levels and SGA assessment do not change during 6 months of observation, and the body weight is stable.

Monitoring is intended to control the nutritional status and detect signs of malnutrition, e.g. a decrease in albumin concentration or unintentional weight loss. If the body composition evaluation tools are available, e.g. bioimpedance (BIA), lean body mass should be monitored because in CKD patients the hydration status may mask weight loss or muscle loss.

LABORATORY TESTS

During routine renal care, it is necessary to monitor the function of the kidneys and nutritional status and check for basic metabolic disorders associated with the disease, i.e. serum concentration of potassium, phosphate, calcium, urea, creatinine, uric acid, and proteinuria. In addition, the drug program includes monitoring alkaline phosphatase (ALP) activity, serum glucose, and urinary phosphate excretion.

Serum phosphate control is a key element in CKD management due to the effect of phosphate retention and hyperphosphatemia on several metabolic processes. Because PTH promotes the loss of phosphates, hyperphosphatemia may lead to hyperparathyroidism.

Physiologically, phosphates are excreted with urine by the kidneys depending on the demand. About 90% of phosphates are resorbed in renal tubules, hence tubular disorders may result in excessive loss of phosphates with urine. Urine phosphate excretion measurement is not part of standard care in stages 2 to 5 CKD, and in the case of LPD in metabolically stable patients, it is most commonly correlated with phosphate intake.

The KDIGO guidelines [1] recommend keeping phosphates within normal limits. The recommended phosphate intake ranges from 800 to 1000 mg daily in CKD patients with elevated serum phosphate levels [21]. Phosphates are an integral component of animal-based proteins (1 g of protein contains about 13 mg of phosphorus), so limiting protein intake automatically reduces phosphate intake. As a consequence, the level of parathyroid hormone in the serum is lowered, which is beneficial considering the CKD-MBD. During the low-protein diet based largely on the consumption of plant-based products, normalization of serum phosphate levels can be observed. However, the calcium present in ketoaminoacids helps reduce the dose of calcium carbonate used in many CKD patients [22, 23].

Alkaline phosphatase is an enzyme that is present in many cells of the human body. The enzyme is mainly produced in bones (approximately 50–60%) by osteoblasts (bone-forming cells) as well as in the intestines (30%) and liver (10–20%). Depending on the place of origin, it reaches different concentrations (and different activity). The highest activity is noted in bones, more specifically in bone-forming cells called osteoblasts. High concentrations can also be found in the liver and intestinal epithelial cells, and small activity can be observed in the placenta and kidneys. More than 80% of serum phosphatase is released from the bones and liver.

The measurement of alkaline phosphatase activity is justified when reduced bone turnover in the course of BMD CKD is suspected, accompanied by a decrease in alkaline phosphatase activity, especially its bone fraction. When the alkaline phosphatase activity is reduced, calcimimetics, calcium products, and vitamin D should not be used, nor should parathyroidectomy be performed. High levels of parathyroid hormone and alkaline phosphatase activity strongly support increased bone metabolism due to hyperparathyroidism [15].

CONCLUSIONS

A very low-protein diet combined with aminoacid ketoanalogues gives patients with advanced kidney failure a chance to postpone the initiation of renal replacement therapy, which significantly affects their quality of life as well as makes their therapy cheaper for the healthcare system. The experience gained by the centers participating in the drug program is positive both for the physicians and the patients who were given this additional therapeutic option. However, that experience shows the need to re-evaluate the criteria for patient inclusion in the program to adapt them to the realities of medical practice in nephrological care centers in Poland.

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