Chapter 10

Nutritional Status Disorders in Chronic Kidney Disease: Practical Aspects (Systematic Review)

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http://dx.doi.org/10.5772/intechopen.69297

Abstract

Despite the significant achievements in the management of chronic kidney disease (CKD) patients, the mortality rate of these patients still remains high. Nutritional status disorders (NSD) are considered now as one of the prognostic risk factors not only for dialysis but also for predialysis CKD stages. Since the publication of KDIGO 2012 guidelines for CKD patient's management, there has been some significant advancement in our understanding of main NSD mechanisms in CKD, including different nosological group patients (first, in diabetic and systemic diseases patients). At the same time, there is still an urgent need for randomized trials for better-informed decisions and future optimization of CKD patients' care. This chapter provides the current data on all aspects of NSD in CKD: etiology, diagnosis, prevention, and treatment approaches, as well as on risk factors of NSD at predialysis stages and in chronic hemodialysis patients. Considerable attention was devoted to the diagnosis and differential diagnosis of NSD in CKD patients. It was determined that the overall strategy for dietary treatment contributed to improving the life quality of patients and slowing down of CKD progression. The review is written based on the published results of clinical studies performed on the position of evidence-based medicine.

Keywords: chronic kidney disease, nutrition status disorders, protein energy wasting, Klotho

1. Introduction

One of the actual problems of nephrology is to improve quality of life and overall survival of patients with chronic kidney disease (CKD), the prevalence of which is steadily growing throughout the world. Therefore, the retardation of CKD progression and prevention of its complications, as well as the delay of renal replacement therapy (RRT) onset, are the primary medical and social-economical goal [1–3].

The rate of renal failure progression depends on a range of factors, and among them, nutritional status disorders (NSD) have the important prognostic value [2, 3]. Early detection of NSD requires a further in-depth examination of a patient to identify the potential cause (or causes) of NSD. NSD develops 2.5 times more often in patients with systemic disease that is caused by both the underlying disease activity (increased levels of inflammatory cytokines) and duration of corticosteroid therapy in addition to the general CKD risk factors [4]. NSD at predialysis CKD stages is found mainly to occur in diabetes mellitus, in patients with severe anemia (hemoglobin <100 g/l) or with high proteinuria (more than 2.5 g/day), as well as in patients who eat low-calorie nutrition (less than 30 kcal/kg/day) [1, 2, 5].

Low-protein diet (LPD) is considered now as more optimal for CKD patients. LPD, reducing glomerular hypertension, favors decreasing proteinuria as well as hemodynamic damage of renal glomeruli and thus contributing to a slowdown of CKD progression [2, 6, 7]. The influence of LPD on CKD progression is more expressed in case of diabetic nephropathy (DN). The annual rate of glomerular filtration rate (GFR) decline in patients who follow LPD and slow down by 1.5–2 times compared with standard diet, and outcome to the end-stage of CKD is observed less often almost by three times [5, 7]. Renal protective effects of LPD are connected with its hemodynamic and metabolic abilities. The adjustment of protein and phosphorus contents in the diet in accordance with patient's residual renal function contributes to reducing hemodynamic load to the residual nephrons, in addition to the decreasing of uremic intoxication. As a result, the glomerular hypertrophy process as well as the renin-angiotensin-aldosterone system (RAAS) activation decreases, intraglomerular autoregulation normalizes, and intraglomerular and systemic hypertension reduces. LPD also partially corrects such unfavorable uremic, metabolic, and endocrine complications, such as hypoalbuminemia, dyslipidemia, anemia, hyperphosphatemia with parathyroid glands hyperplasia, and thereby it helps to reduce the risk of uremic hyperparathyroidism, vascular calcification, and atherosclerosis [2, 8, 9]. LPD in combination with ketoanalogs of essential amino acids enhances also antihypertensive and antiproteinuric effects of angiotensin receptor blockers (ARB), corrective action of erythropoietins in anemia, effects of synthetic vitamin D analogs and calcimimetics on hyperparathyroidism symptoms, and hypolipidemic effect of statins [4, 10, 11].

It was found that the mortality rate of dialysis patients is inversely related to the amount of protein intake (protein quota), body mass index, and serum albumin [1, 12].

Improvement of the approaches to the early diagnosis, treatment, and prevention of NSD in CKD patients is an important strategy to reduce cardiovascular (CV) and overall mortality, to increase quality of life, as well as to reduce the cost of hospital and RRT treatment [1, 13].

http://dx.doi.org/10.5772/intechopen.69297

The review was written based on the published results of clinical studies performed on the position of evidence-based medicine. It is intended not only for nephrologists but also for internists, cardiologists, and endocrinologists.

2. Methods

Literature searches were made of 10 major databases among which were PubMed, Medline, Embase, Cochrane Library, CINAHL, and e-library. The search was carried out to find all articles relevant to CKD and Nutrition Status Disorders. This search encompassed original articles, systematic reviews, and meta-analyses. There was no language restriction.

2.1. Agreed criteria for article inclusion in the review

Articles should be full-text. Brief publications and abstracts were not included:

- Research should include at least 20 patients in each group. The minimum mean duration of a study was 6 months.
- Analyzed literature over past 15 years.
- The article has the detailed research protocol for assessing its quality.
- Patients examination must meet KDIGO 2012 guidelines.
- Randomized controlled trials.
- Retrospective nonrandomized trials.

3. Nutritional status disorders in chronic kidney disease patients

The International Society of Renal Nutrition and Metabolism (ISRNM) [14] recommended the term "Protein-energy wasting (PEW)" to describe the state of decreased body stores of protein and energy in CKD patients and proposed a common nomenclature and diagnostic criteria for these alterations in the context of CKD.

3.1. Prevalence PEW in CKD

PEW was traditionally considered for a long time as the problem of patients who receive RRT. Meanwhile, the results of epidemiological studies conducted for recent years have convincingly demonstrated that nutritional status disorders appear to be revealed much earlier, before dialysis treatment starting, from stages 3B–4 CKD, and impact on prognosis of patients on dialysis [1, 2, 12, 13, 15]. The incidence of PEW depends on the stage of CKD (**Table 1**): among CKD patients with a glomerular filtration rate (GFR) of 44–30 ml/min/1.73m^2, PEW is detected in 4.2% of cases in average, whereas in CKD patients with GFR of 29-15 ml/min/1.73m^2 in 21.3%, and almost all patients with end-stage of CKD have PEW [1, 2, 7, 13, 15, 16].

CKD stage	Description	GFR, ml/min/1.73 m^2	Incidence of PEW
1	Kidney damage with normal or increased GFR	≥90	No
2	Kidney damage with mildly decreased GFR	89–60	No
3		59–30	
3a	Mild-to-moderate decrease in GFR	59–45	No
3b	Moderate-to-severe decrease in GFR	44–30	4.2%
4	Severely decreased GFR	29–15	21.3%
5	End-stage of renal failure	<15 or RRT onset	74.5%

GFR: glomerular filtration rate, is calculated by CKD-EPI creatinine equation (2009); PEW: protein-energy wasting; and RRT: renal replacement therapy.

Table 1. Incidence of PEW depending on CKD stage.

At the predialysis stages, PEW is typical for patients with DN because of insulin deficiency or insulin resistance, accelerating protein catabolism, as well as due to a high incidence of infectious complications, diabetic neuropathy of gastrointestinal tract with malabsorption, [1, 5, 15, 17]; for patients with systemic diseases; high proteinuria (more than 2.5 g/day); severe anemia (hemoglobin <100 g/L); for those who receive prolonged corticosteroid therapy (more than 6 months); for patients who eat low-calorie foods (less than 30 kcal/kg/day) [1, 2, 4, 15].

3.2. Etiology and pathogenesis

In contrast to the end products of fat and carbohydrate metabolism (CO_2 and H_2O) that are excreted through the lungs and skin, the products of protein metabolism can be excreted only by kidneys [7, 16].

Qualitative protein food composition is very important because the absence or deficiency of at least one of any essential amino acid (EAA) may be a limiting factor for protein biosynthesis in the body. Even when the dietary intake provides all amino acids, the body may suffer from a protein deficiency if the absorption of any amino acid decreases in the intestine, or when it breaks up more than usual under the influence of gut microbiota. In these cases, limited protein synthesis will occur or the body will compensate for the lack of amino acid required for protein biosynthesis by breaking down its own proteins [9, 18]. Changes in protein metabolism in uremia are closely related to amino acid metabolism disturbance. Due to a decrease in the metabolically active mass of the kidneys, the deficiency of the enzymes synthesized in the kidneys, which are necessary for the formation of amino acids, develops [9, 13]. Decrease in plasma concentration of EAA can also be largely due to acidosis [15, 17].

The degree of protein and amino acids assimilation from food also depends on the quantitative and qualitative composition of carbohydrates and lipids. Experimental and clinical data indicate that a diet with insufficient fat and low-calorie diet contribute to the increased oxidation of amino acids, intensified degradation, and, partly, even protein synthesis [7, 18]. Protein metabolism, in turn, is closely integrated with the exchange of carbohydrates, lipids, and nucleic acids through amino acids or α-ketoacids (α-ketoglutarate, oxaloacetate, and pyruvate). Thus, aspartic acid or

alanine through the transamination way is reversibly converted to pyruvate oxaloacetate, which are subsequently directly included in the carbohydrate metabolism. An inverse relationship was found between the leptin concentration and the nutritional status (NS) parameters and a direct relationship with the leptin of the C-reactive protein (CRP) [19].

Proteins (and consequently, amino acids as products of their hydrolysis) are directly involved in the biosynthesis of a number of hormones and other biologically active compounds that regulate metabolic processes in the body. With insufficient intake of protein from food, the protein from its own pool disintegrate into free amino acids, which ensure the synthesis of the necessary cytoplasmic fractions of protein, enzymes, hormones, and other biologically active compounds [16, 18].

PEW in CKD can also be exacerbated by eating mostly plant proteins of low biological value and low-calorie diet. This increases the insulin secretion, which inhibits lipolysis and mobilization of skeletal muscle proteins. These disturbances lead to that the levels of amino acids in the blood drop the levels of amino acids in the blood drop, the synthesis of albumin and other proteins decreases, leading to hypoalbuminemia. The adaptation mechanism includes hormonal changes. These changes help mobilize free fatty acids from adipose tissue and amino acids from the muscles. Gluconeogenesis and oxidation of amino acids provide the energy that is necessary for the organism-sustaining processes, as a result, protein synthesis is inhibited, metabolism is slowed down, and muscle mass and body fat stores decrease [1, 6, 9].

An important role in the development of PEW is assigned to cytokines and chemokines, which begin to accumulate in the blood of patients as the stage of CKD progresses. Cytokines, suppressing appetite, cause loss of body weight [13, 18]. Patients with CKD, stages 4–5, are prone to negative nitrogen balance and hypercatabolism due to anorexia, inhibition of protein and amino acid synthesis, and the deficiency of vitamins and microelements [1, 16].

In acute and chronic infections or immune inflammations, there are effects of tumor necrosis factor α (TNF α), interleukin 2 and 6 (IL-2 and IL-6), etc., which also contribute to the development of hypoalbuminemia and worsen the prognosis [1, 20].

At the same time, in chronic renal failure patients who ignore the use of protein restricted diet and consume protein in the amounts greater than recommended for their stage of CKD, progressively increased levels of glycation products are observed, which trigger a complex cascade of reactions involving the generation of active forms of oxygen. Amino acids, proteins, carbohydrates, and lipids (primarily unsaturated fatty acids both free and in the composition of phospholipids) are subjected to reactions of free radical oxidation involving reactive oxygen species [1, 16]. Acidosis, induced by uncontrolled protein intake, leads to suppression of amino acid synthesis, increases their decarboxylation in muscles, and reduces albumin synthesis [17].

3.3. Classification

In clinical practice in the predialysis patient population, PEW is divided into three degrees: mild, moderate, and severe [1, 14, 21]. The degree of PEW is established by determining the ratio of body weight/recommended body weight × 100%. A decreased ratio down to 80% means a mild degree of nutritional disorder, a decrease from 80–70%—moderate, and less than 70%—severe nutrition disorder.

3.4. Clinical presentation

Complaints depending on the underlying pathology that caused signs of PEW: a weight loss over the past 6 months, poor appetite, in case of severe PEW—refusal to eat, vomiting, nausea, bloating, diarrhea, constipation, abdominal pain, edema, cramps, cough, shortness of breath, prolonged fever, anxiety, dry skin, hair loss, deformation of the nails, and weakness.

Medical history allows to identify the *kidney disease*, which has led to the development of PEW.

3.4.1. Physical examination

Assessment of nutritional status is carried out on a four- or seven-point scale. A seven-point scale evaluation is considered more reliable [14, 21, 22].

The following basic criteria are important:

- The dynamics of the patient's weight since the last examination (usually for 6 months).
- The protein quota intake and calorie content of food calculated according to a 3-day food diary; the presence of symptoms of gastrointestinal dysfunction.
- The status of the patient's fat and muscle mass bases on a visual examination (shoulder line, the contouring of clavicles, shoulder blades, and ribs) and palpation (the thickness of the fat fold above the biceps and triceps, muscular mass of the triceps, and muscles between the thumb and index finger). To objectify the data, the caliper can be used to measure the fat fold thickness in several places (subscapular region, above the biceps, triceps, and iliac crest) and the shoulder circumference in the middle third.

Familiarity with the anamnesis and physical examination reveals the **clinical picture of PEW** [1, 13, 14, 21]:

- Decrease in the body weight by 10% over the last 6 months and shorter period; poor appetite.
- Reduced subcutaneous tissue.
- Possible apathy, fast fatigue, decreased taste, and slowing of peristalsis.
- Subjective assessment (according to seven-point scale) ≤ 5 points.
- Basal metabolic rate and body temperature are lowered due to decreased levels of triiodothyronine (T_3) below 3.5 pg/ml and loss of the heat-insulating function of the subcutaneous tissue.

3.4.1.1. Mild-to-moderate PEW

Symptoms of nutritional disorders are characterized by a decrease in the body weight (by 3–5% per month) and a progressive decrease in appetite with the development of anorexia. The thickness of the skin-fat fold (SFFT) above the triceps muscle of the shoulder as well as a muscular mass in the shoulder region is reduced. The blood levels of albumin, prealbumin, transferrin, and triiodothyronine (T3) decrease. Lymphopenia and impaired glucose tolerance may develop.

http://dx.doi.org/10.5772/intechopen.69297

3.4.1.2. Severe PEW

It is accompanied by more pronounced changes in clinical and laboratory parameters. Physical examination reveals the intercostal depression, atrophy of the temporal muscles, and muscles of the extremities. Subcutaneous fat tissue is atrophied or absent. Apathy, rapid fatigue, and a feeling of cold are often symptoms of hypovitaminosis (vitamins B, C, folic acid, D_3 and B_{12}, and PP); deficiency of trace elements (iron, zinc, copper, and selenium), calcium, arginine and L-carnitine are added symptoms; and signs of oxidative stress, aggravating renal anemia, cardiomyopathy, myopathy, encephalopathy, and hypertension also accompany. There may be atrophy of intestinal villi and increased growth of microflora in the small intestine.

3.5. Diagnosis

Diagnostic challenges with PEW arise from a variety of causes and also because the body weight of patients changes a little due to sodium and water retention and decrease only at the last stage of CKD [1, 7, 21, 22].

3.5.1. Anthropometric methods of assessment

Anthropometric methods include determination of body mass index and evaluation of muscle and fat mass of the body [1, 14, 21]. The body mass index (BMI) (Quetelet index, kg/m^2) is calculated by the formula: BMI = $M/L2$, where M is the body weight in kilograms and L is the height of a person measured in meters and squared.

Measurement of the SFFT by a caliper at 4 points (subscapular region, above the biceps, triceps, and iliac crest) allows to calculate the proportion of fat component as a percentage of the total body weight, which is 15–16% in healthy men and 25% in women. If the SFFT is reduced by more than 10% from the normal value, it indicates a predominant *energy insufficiency* [1, 14, 22].

The amount of fat in the body (fat mass) can be calculated by the formula: $D = d \times S \times K$, where D is fat mass (kg); d is the average thickness of the subcutaneous fat layer together with the skin (sm) = $(d_1 + d_2 + d_3 + d_4)/8$, where d_1 is above the triceps; d_2 is above the biceps; d_3 is above the shoulder blade; d_4 is on the abdomen; S is the surface of the body = $M^{0.425} \times P^{0.725} \times 71.84 \times 10^{-4}$, where M is the weight (kg), P is height (sm), and K is a constant equal to 1.3.

About the muscle mass, it can be indirectly judged by the formula: SMV (sm) = SC (sm) – 0.314 × SFFT (mm), where SMV is the shoulder muscles volume; SC is shoulder circumference at mid-shoulder level; and SFFT is the skin-fat fold thickness above the triceps at the point of shoulder circumference measurement. Deficiency of SMV, exceeding 10%, is typical for *protein deficiency*.

For dialysis PEW, a combination of muscle deficiency with a decreased volume of adipose tissue is typical. Assessment of anthropometric parameters should be performed in all patients with CKD once every 3 months.

Anthropometric criteria of PEW are BMI <18.5 kg/m^2; SFFT in men <9.5 mm, in women <13 mm; SMV in men <23 cm, in women <21 cm. At the same time, SFFT is a reflection of body fat reserves, and SMV is an indicator of the peripheral protein pool.

3.5.2. Laboratory diagnostics

For the diagnose of impairments in the synthesis of visceral proteins, the determination of the content of albumin, transferrin, and lymphocytes number in the blood, as well as of the level and spectrum of essential amino acids, is used [1, 14, 21]. The serum albumin level only is insufficient for the decision about NS in CKD patients, since its level depends on the intravascular volume and the half-life period of albumin is approximately 21 days [14]. Therefore, a decrease in the albumin serum level is a relatively a late marker of PEW. It should be taken into account that the decrease in serum albumin level may be due to the other causes, in addition to PEW. Infections, injuries, and surgical interventions, associated with blood and plasma loses; a high level of proteinuria; and disturbances of the protein-synthetic function of the liver can cause a rapid and significant decrease in serum albumin level [14]. On the other hand, prolonged and persistent decrease in serum albumin level regardless of its cause always leads to PEW in CKD patients [1, 14]. Hypoalbuminemia is closely associated with an increase in concomitant diseases, hospitalizations, and the mortality rate of CKD patients [1, 3, 20, 23].

The association of hypoalbuminemia with inflammatory process may be established using the ratio of the levels of albumin and C-reactive protein in serum [1, 4, 13, 14].

An important diagnostic marker of PEW is also a low serum level of transferrin in the blood and is representative of the fraction of beta-globulin; its decrease is observed at an earlier stage of protein metabolism disturbance than changes in albumin levels (lifetime of transferrin is 7–8 days). However, the concentration of transferrin may increase the iron deficiency usually accompanying PEW, which should be taken into account in determining the severity of PEW [1, 14, 21].

More accurate markers of the visceral protein pool status are both short-lived transport proteins—prealbumin (lifespan is 2 days) and retino-binding protein (lifespan is 10–12 h). The prealbumin level below 0.3 g/l is associated with an increased risk of death and correlates with other indicators of PEW [13, 14, 16]. Their content in serum decreases earlier in the case of protein deficiency in the diet, although it can quickly decrease due to intercurrent diseases [14].

The degree of PEW correlates with the content of lymphocytes in blood [14, 15]. Therefore, the absolute number of lymphocytes in the blood can be used to judge the severity of PEW in patients with CKD: absolute number of lymphocytes = % of lymphocytes × number of white blood cells/100.

The laboratory signs of PEW are serum albumin <35 g/l; serum transferrin <180 mg/dl; and absolute number of blood lymphocytes <1800

The study of serum protein counts and the absolute number of lymphocytes should be carried out once every 3 months, and if necessary—once every 1.5 months [1, 14].

3.5.3. Instrumental diagnostics

From the instrumental methods for the main body components assessing, the method of 2-hour bioimpedanceometry is most often used in practical work in connection with the ability to quantitatively determine not only fatty tissue and muscle mass of the body but also the

distribution of fluid in the body [22, 24]. Complex instrumental methods for analyzing NS of the body (neutron activation analysis, two-photon X-ray absorptiometry, etc.) are not widely available due to high cost.

Bioimpedansometry measures the volume of the total fluid and the proportion of extracellular and cellular fluids separately, allows to establish a nonfat body mass and a "dry weight," and thus contributes to the selection of an effective mode of HD and ultrafiltration as well as the value of the protein quota.

DEXA is a noninvasive method for assessing the condition of the three main body components (fatty tissue, muscle mass, bone mass, and bone mineral density). The state of hyperhydration of dialysis patients practically does not affect the accuracy of DEXA. The principle of the DEXA method is the scanning of a body in a rectilinear section with the help of two beams of photons emitted by an X-ray source. Different tissues (fat, muscle, and bone) absorb X-rays in varying degrees. The composition of the body is calculated from the ratio of the natural logarithms of the absorbed and unabsorbed beams [14, 22].

Fresenius Medical Care (Germany) company has developed a device that allows to determine the individual fluid balance and body composition of the patient—the Body Composition Monitor (BCM). The BCM can be used in patients with CKD, regardless of patient's treatment. The measurement is based on the bioimpedance spectroscopy technology, which allows to calculate the volume of body water (total, intra-, and extracellular), as well as muscle and fat mass of the body (**Table 2**). Since the total body water (TBW) index is equivalent to the urea volume distribution (V), it is not necessary to spend working time for calculating urea kinetic modeling and calculating TBW based on anthropometric parameters. Indicator V can be used to calculate the dose of dialysis [22].

In addition to the anthropometric (BMI, SFFT, and SMV) and laboratory (albumin, transferrin, and absolute number of lymphocytes) indicators of NS, the evaluation of protein

Parameter	Gender	Age	Normal range
BMI, kg/m^2			19.5 ± 0.33 (23–18.4)
Body fat mass, %	M	20–39	12.9 ± 0.65 (19.9–8.0)
		40–59	18.1 ± 0.41(21.9–11.0)
		60–79	20.7 ± 0.66 (24.9–13.0)
	F	20–39	29.1 ± 0.44 (32.9–21.0)
		40–59	26.4 ± 0.51 (33.9–2.30)
		60–79	27.8 ± 0.35 (35.9–24.0)
Body muscles mass, %	M	18–39	35.4 ± 0.75 (39.3–33.3)
		40–59	37.1 ± 0.85 (39.1–31.1)
		60–80	34.6 ± 0.31 (38.9–32.9)
	F	18–39	26.2 ± 0.45 (30.3–24.3)
		40–59	27.1 ± 0.65 (30.1–24.1)
		60–80	27.3 ± 0.55 (29.9–23.9)

BMI: body mass index; M: male; F: female; and BIA: bioimpedance analysis.

Table 2. Normal range of nutritional status parameters according to BIA.

intake and calorie content of food assessed according to a three-day food diary is needed [22, 25].

Integrated assessment of nutritional status can be performed also using the malnutrition inflammation score (MIS) scale. It allows to analyze anthropometric data (BMI, dry weight dynamics, body fat, and muscle mass), gastrointestinal symptoms, dialysis time, laboratory data (albumin and blood transferrin), hospitalization rates, and the risk of lethality on dialysis [14, 22].

All patients with an identified PEW should be given anthropometric measurements (or bioelectrical impedance analysis), a clinical and biochemical blood test, and a general urinalysis at least one time per 1.5 months, an analysis of protein intake and calorie content on a 3-day food diary for at least one time in 3 months [1, 15, 21].

3.6. Differential diagnosis

PEW should be differentiated with a malabsorption syndrome, given a number of common manifestations (progressive decrease in BMI and blood albumin). In contrast to malabsorption, chronic diarrhea with steatorrhea and creatoria is not typical for PEW; while there is pronounced increase in serum CRP and TNF-α, calcification of the arteries [1, 14, 20] is found [1, 14, 20].

According to the WHO, the diagnostic sign of PEW is a decrease in the mental and physical performance of patients, identified as a decrease in the quality of life when determining the psychosomatic status according to the standard questionnaires of Kidney Disease Quality of life short form (KDQOL-SF) [1].

3.7. Prognosis

Disorders of nutritional status are of great prognostic importance, since they significantly impact on the survival and level of rehabilitation of these patients. According to a single-site study [23], the mortality rate during the first year on dialysis therapy was 1% in patients with a serum albumin level > 38 g/l at the moment of admission to HD treatment, and 30% for patients in whom the serum albumin did not exceed 30 g/l.

3.8. Possibilities for PEW correction in CKD: goals and approaches

In CKD patients at the predialysis stage with PEW, the main goal of the treatment is to eliminate the factors contributing to the progression of nutritional disorders and to achieve the stabilization of renal failure [1, 14, 21]. The main aim of the diet is to inhibit glomerular hypertrophy and intraglomerular hypertension, to reduce the traffic load to tubules, to decrease cytokines and uremic toxins production: (TGF-β, ATII, oxygen radicals, TIMP (tissue inhibitor matrix metalloproteinases), indoxyl sulfate, guanidine, phosphates, oxalic acid, NO, etc.)

In most patients with CKD and systemic disease (systemic lupus erythematosus, and systemic vasculitis) with persistent disease activity, therapy (correction of the diet and hypertension, suppression of disease activity by glucocorticosteroids (GS) and/or cytostatics) can

http://dx.doi.org/10.5772/intechopen.69297

allow to slow the progression of renal failure and eliminates PEW [1, 4]. However, it should be borne in mind that the long-term (more than 6 months) use of CS in CKD patients in predialysis stages can enhance hypercatabolism, promote the development or aggravation of an existing PEW, and therefore careful and regular monitoring of anthropometric indices and serum albumin level is required for these patients [1, 13, 14].

LPD with a protein content of 0.6 g/kg body weight/day should be carefully balanced both in essential amino acid contents and in calories (at least 34 kcal/kg of ideal body weight/day). This requirement must be strictly observed in patients with 4–5 stages of CKD with digestive disorders due to uremia and also in patients with stages 3–4 of CKD in systemic diseases with persistent disease activity, long-term treatment with GS [1]. When making a 7-day menu, it is allowed to substitute products for their protein and carbohydrate equivalents, and to replace a portion of the animal protein (0.1 g/kg body weight/day or more) with a high-purity soybean protein (equivalent amount) in the LPD [1, 14, 21, 26].

It is promising to use highly purified soy protein SUPRO-760 (DuPont Protein Technologies USA) [1, 13, 14]. Protein "SUPRO" is a protein of high quality, fully digested by the body (adjusted amino acid coefficient of protein digestion—1.0). It is prescribed as an additive to food at the rate of 0.2–0.3 g soy protein per kg body weight per day [1, 14]. When compiling a diet that includes the soy protein SUPRO-760, the total amount of protein in the diet should not exceed 0.7 g/kg of body weight/day, whereas the total caloric value should not be less than 30 kcal/kg body weight/day for patients with 3B-5 stages of CKD [1, 14]. In patients who are committed to the use of predominantly vegetable protein, as well as in patients with anorexia (usually with eGFR <25 ml/min, 1.73 m^2), half the daily amount of animal origin protein in a traditional LPD (0.6 g/kg body weight/day) may be replaced with highly purified soy protein [1, 13, 14]. In most of CKD 4–5 stages, patients with anorexia, when using such diet, dyspeptic phenomena decreased, blood urea nitrogen level decreased, acidosis corrected, and the general condition improved [19].

In the clinical practice of recent years, high-energy nutrient mixtures that are balanced by the essential amino acids content such as Fresubin Renal, manufactured by Fresenius Kabi, Germany, etc., is introduced in the diet of CKD patients to treat the NSD. These specialized mixtures are made on the basis of CKD patients' requirements in protein, fat, carbohydrate, and energy and also enriched with vitamins and minerals.

In the predialysis period of CKD, the use of a low-protein mixture (3 g protein/100 ml) Suplena (Abbott Nutrition, USA), with a minimum amount of potassium, sodium, and phosphorus balanced with a vitamin-mineral complex, is also promising for prevention and treatment of PEW. The energy value of one package of a liquid mixture (237 ml) is 474 kcal [14].

The using of EAA and their α-KA (Ketosteril, Fresenius Kabi) in the LPD allows to maintain the protein balance [1, 6, 10]. EAA and KA are important components of LPD, which prevents the development of PEW, and enhance the beneficial effects of LPD [7, 13]. Ketoanalogues, in contrast to the matched their amino acids, do not contain a nitrogen group; by capturing endogenous nitrogen they are converted into amino acids in the body, and they contribute to the disintegration of urea. The ready-pharmaceutical complex of all EAA and KA in the optimal ratio (ketosteril) provides the need of CKD patients in essential amino

acids with minimal nitrogen administration, correcting amino acid metabolism, and accelerating urea metabolism, reduces the risk of protein hypercatabolism, and negative nitrogen balance when applied diet with protein restriction. This reduces the insulin resistance, uremic dyslipidemia (hypertriglyceridemia), oxidative stress (formation of an active form of oxygen, RO—reactive oxygen). The need of EAA and KA addition to LPD is determined by the CKD stage (**Table 3**) [1, 14].

The use of EAA and KA allows to limit protein intake to the required minimum amount to enhance the positive effects of LPD and at the same time to prevent the development of PEW [6, 11]. With the use of ketoacids, even very low protein intake (up to 0.3 g/kg/day) can be achieved without increasing the risk of PEW developing [1]. In patients who were observed in predialysis stages of CKD who used LPD and received EAA and KA for at least 12 months, there was a significantly lower incidence of NSD and a slower decline in GFR per year than in patients who did not limit the protein content in the diet [4].

In patients with 3B-5 stages of CKD, attachment of PEW can contribute to the development or aggravation of existing arterial hypertension because of decreased synthesis of nitric oxide (NO) due to arginine deficiency. Arginine deficiency in uremia is due to insufficient intake of amino acids with food, as well as a decrease in the formation of arginine from citrulline [16, 18]. CKD patients with PEW need antihypertensive therapy more than other patients. In CKD, ACE inhibitors and ARB have an antihypertensive effect comparable to the effect of calcium channel blockers (CCB), but ACE inhibitors and ARB are more likely, than CCB, have a nephroprotective effect, slowing the progression of renal failure, especially with persistent proteinuria [27]. A "strict" LPD in combination with ACE inhibitors (with predominantly hepatic way of elimination) or ARB in patients with stage 3B-4 CKD and persistent proteinuria more than 1 g/day have a joint effect on proteinuria reduction. The antiproteinuric effect is provided by two components: a

CKD stage	GFR (ml/min/1.73 m^2)	Daily protein intake (g protein/kg body weight/day)	EAA *и* KA
1	≥90	0.8	Not required
2	60–89	0.8	Not required
3A	30–59	0.8	Not required
3B	30–44	0.6/0.7	1 tablet/5 kg of body weight/day
4	15–29	**1.** 0.6 2. 0.3–0.4	1 tablet/5 kg of body weight/day 1 tablet/5 kg of body weight/day
5	>10 to <15 (predialysis)	**1.** 0.6 2. 0.3–0.4	1 tablet/5 kg of body weight/day 1 tablet/5 kg of body weight/day

GFR: glomerular filtration rate is calculated by CKD-EPI creatinine equation; EAA: essential amino acids; and KA: ketoanalogs of amino acids.

Table 3. Essential ketoanalogs and amino acids requirement depending on the diet protein restriction and CKD stage (KDIGO guidelines, 2012).

http://dx.doi.org/10.5772/intechopen.69297

decrease in the preglomerular vasodilation (due to the restriction of protein intake) and postglomerular vasoconstriction (caused by RAAS inhibition), leading to a decrease in intraglomerular hyperfiltration, the main determinant of the tubulointerstitial fibrosis progression [1]. In addition, RAAS blockers in combination with a LPD may affect the maintenance of Klotho products as a cardionephroprotective factor [27, 28]

The cardionephroprotective role of ketoacids and LPD was demonstrated in the experiment after subtotal nephrectomy. There was a decrease in proteinuria, arterial hypertension, and slowing down of left ventricular hypertrophy formation [14]. The retardation of CKD progression is associated with a lesser effect of EAA and KA on intra-glomerular hypertension, as well as with its ability as an additional source of calcium to correct hyperphosphatemia and slow the formation of uremic hyperparathyroidism. LPD in combination with EAA and KA enhances the following positive effects: antihypertensive and antiproteinuric effects of RAAS blockers, the corrective effect of erythropoietin preparations on anemia and of synthetic analogs of vitamin D, calcimimetics on hyperparathyroidism, and also the hypolipidemic effect of statins [1, 13, 14]

At the same time, CKD patients, with combined administration of EAA and active metabolites of vitamin D, due to a possible risk of hypercalcemia should stop taking vitamin D. If hypercalcemia persists, then it is necessary to reduce the dose of EAA to normalize the plasma concentration of calcium [1]. In recent years, the effect of ketosteril on the risk of vascular calcification has not been confirmed [29].

The addition of soy protein in the diet of patients with 3B-5 stages of CKD may also contribute to an antihypertensive effect. According to our data, patients with CKD 3B-5 stages who added soy protein to food achieved more effective correction of hypertension than patients who used milk protein as a food additive [4]. The antihypertensive effect of soy protein is due to the isoflavone in it, genistein (an estrogen of plant origin) that has an anti-inflammatory effect and a protective effect on the vascular endothelium (8 mg of isoflavone is contained in 1 g of soy protein). Soy protein contains more than animal protein, arginine (7.6% vs. 3.7%)—the precursor of NO and glycine (4.2% vs. 1.8%), which inhibit the stress hormone adrenalin and contribute to vasodilation [19, 30].

All patients with PEW to reduce the rate of protein catabolism (PCR) should consume at least 35 kcal/kg of body weight/day [1, 25].

At the same time, in prescribing the caloric content of the diet, in addition to taking into account the age, sex, general condition of the patient, and pathogenetic features of the disease, it is necessary to take into consideration the general regimen of the patient. In persons who comply with bed rest, energy expenditure will be significantly less than that of patients on a general regime. Therefore, the total calorie content of food cannot be the same for all patients [25].

The use of new drug groups, in particular, endothelin-1 receptor agonists, which have an antiproteinuric effect, agents that inhibit fibrogenesis and inflammation such as pyrophenidone and bardoxolone, as well as an inhibitor of aminoguanidine proteins glycation, are discussed [22].

Based on the available literature data, the correction of NSD, especially early, even at the predialysis stage not only improves the quality of life of patients but also contributes to slowing

the progression of CKD and CVE, to prevent PEW at the stage of regular HD [12]. Thus, the correction of NSD becomes an important and obligatory part in the treatment of patients with CKD [1, 14]

3.9. Prophylaxis and dispensary observation

All patients with CKD are advised to consult a dietician, as well as to train in educational programs concerning the need to restrict protein, phosphorus, potassium, and salt in the diet. Primary prevention of NSD in patients with CKD traditionally is the restriction of protein in the diet adequately to the reducing degree of GFR. So if at 2–3A stages of CKD with GFR >45 ml/min/1.73m^2, the recommended daily protein intake is 0.8 g protein/kg/day, then with GFR 44-30 ml/min/1.73m^2, its intake is limited to 0.7–0.6 g/kg body weight/day and 0.6–0.3 g/kg body weight/day when GFR 29-15 ml/min/1.73m^2 [1, 14]. In CKD patients with proteinuria > 3 g/day, the total amount of protein in the daily ration is increased by 1 g protein/g of proteinuria [1, 14, 21, 22].

In a diet with a protein restriction of 0.6 g/ kg body weight, at least 60% should be a protein of animal origin as the most valuable in the content of EAA. Plant protein has a lower biological value, since it does not contain the whole composition of EAA. The exception is the soy protein, which is close to the protein of animal origin in the spectrum of EAA [1, 18, 19, 30].

In a "strict" LPD—0.3 g protein/kg/day—the whole protein could be of plant origin but it is a mandatory requirement to combine this diet with EAA and their α- keto-analogues [6, 11]. However, a strict LPD (but not lower than 0.3 g/kg/day) is permissible only if there are technical and organizational facilities for regular monitoring of nutritional status, and it should be combined with the mandatory intake of EAA and KA.

To ensure that the LPD (0.6–0.3 g protein/kg/day) did not lead to catabolism of the body's own proteins, patients, along with the addition of EAA, should consume at least 35 kcal/kg/day, and only in a background of large amounts of protein (0.8–0.7 g/kg/day) the consumption of 30 kcal/kg/day is sufficient. [25]. High energy value of food should be provided by carbohydrates and fats. [14, 25].

Nutritional value of fats is determined by the presence of fatty unsaturated acids (linoleic and linolenic) in their composition, which are not synthesized by the body, but come from food. The ratio of vegetable oils and animal fats in the diet should be 1:3. Vegetable oil (e.g., sunflower, soybean, corn, and cotton) should be present in the daily diet of the patient [14, 22].

The energy value of food is calculated on the basis of the percentage content of carbohydrates, fats, and proteins in it, and the coefficient of their biological value. The coefficient of biological energy value for carbohydrates is 4 kcal/g, for fats is 9 kcal/g, and for protein is 4 kcal/g. Combining the energy value of the protein, fat, and carbohydrates contained in the products, the caloric value of the entire diet may be calculated [14, 25].

Patients with a purine metabolism disorders (hyperuricemia and hyperuricosuria) should exclude rich broths, by-products—liver, kidneys, heart, tongues, as well as pates, sausages, veal,

pork, smoked products, meat and fish canned food, beans (green peas, beans, French beans, and lentils), cocoa, chocolate, nuts, strong tea and coffee, grapes, raisins, and grape wines [1, 14].

If oxalic acid is impaired (oxaluria, oxalate kidney stones, and oxalosis), in addition to restrictions for patients with elevated uric acid, the consumption of sorrel, spinach, rhubarb, and peppers should also be limited [1, 14, 16].

Contraindications to the administration of LPD in CKD are mainly related to patients with late 5 stage of CKD (**Table 4**).

3.10. Pharmacological support for tolerance to a LPD

Long-term compliance with LPD is difficult due to anorexia as well as the tendency of CKD patients to protein hypercatabolism. The methods that affect anorexia and hypercatabolism in CKD include correction of metabolic acidosis (calcium carbonate, and α-ketoanalogs of EAA), deficiency of iron and erythropoietin, elimination of hyperleptinemia (eicosapentaenoic acid), and hyperparathyroidism (calcitriol, paricalcitol, and cinacalcet) [1, 13, 14, 21].

Treatment with calcium carbonate in the background of protein-intake restriction increases the level of plasma bicarbonate and reduces the protein catabolic rate (PCR) from 1.2 to 1.0 g/day. As a result, protein's catabolism and anorexia that are typical for acidosis are reduced, neutral or positive nitrogen balance is maintained, and parathyroid gland activation is partially inhibited [14].

EAA and KA are important components of LPD, which help to prevent the development of PEW, correct acidosis, and enhance the beneficial effects of LPD [7, 13]. The need of EAA and KA supplementation to LPD is determined by the CKD stage.

The absorption of α-keto acids in the gastrointestinal tract is quick, and their conversion to essential amino acids averages from 30% for valine and up to 70% for phenylalanine. The number of α-keto acids involved in conversion to essential amino acids is inversely proportional

Absolute contradiction	Relative contradiction
• 5 CKD stage with GFR < 10 ml/min and decompensate metabolic acidosis, uremic polyneuropathy, or uncontrolled hypertension • Cachexia (BMI < 18 kg/m^2) • Rapidly progressive glomerulonephritis • Severe nephrotic syndrome • Intolerance to dietary restrictions	• Decompensate diabetes mellitus • Severe hypercatabolism • Bacterial infection (acute, exacerbation of chronic form) • Severe anemia • Noncompliance • Anorexia • Psychopathy, mental disorders, encephalopathy

LPD: low-protein diet; GFR: glomerular filtration rate; BMI: body mass index; CKD: chronic kidney disease.

Table 4. Contraindication to LPD in CKD.

to the daily protein quota in food and directly depends on the caloric content of the diet. Some α-keto acids, e.g., ketoisoleucine, in uremia suppress protein degradation in muscles, allowing to maintain a neutral nitrogen balance in conditions of renal failure in the background of protein restriction [25].

3.11. Consumption of potassium, sodium, and phosphorus in CKD: water regime

At 3B stage CKD daily intake of potassium, phosphorus in the diet should not exceed 3000 mg and 700 mg, respectively, at the 4th stage CKD—potassium intake should be reduced by half. LPD allows to reduce the consumption of phosphorus—when consuming 0.6 g/kg protein, patients receive 500–800 mg of phosphorus a day, and when the protein quota is limited to 0.3 g/kg—250 mg of phosphorus. In case of hyperphosphatemia, it should be limited to a fish (no more than 1 time per week), as well as cereals (except rice) and other foods rich in phosphorus. As an alternative to cereals, artificial sago can be used [1, 14, 26].

In order to correct hyperkalemia, it is recommended to limit the use of dried apricots, figs, bananas, apricots, peaches, and nectarines [1, 14].

Restriction of salt intake (no more than 5 g/day) increases the antiproteinuric effectiveness of RAAS inhibitors. Exceptions include patients with increased sodium excretion in tubular lesions [26].

Most patients with CKD should be recommended a consumption of at least 2 liters of fluid/day and up to 3 liters of fluid/day in hot weather, especially when purine metabolism is disordered, oxalic acid turnover disturbances, urolithiasis, and a tendency to urinary infection [1, 14, 26]

With nephrotic syndrome, as well as in the terminal stage of CKD with a GFR value of less than 15 ml/min, when the patient cannot form more than 1 l urine/day, the fluid intake is corrected by diuresis (300–500 ml to be added to the amount of excreted urine from the previous day) [1].

3.12. Nephroprotective effect of LPD

The nephroprotective effect of LPD is associated with its hemodynamic and metabolic effects. The dietary load of protein and phosphorus, according to the possibilities of the residual function of the kidneys of the patient, in addition to reducing uremic intoxication and lowering the level of urea, creatinine, and uric acid in the blood, reduces the hemodynamic load on the residual nephrons, which slows the progress of glomerular hypertrophy, as well as activation of RAAS, normalizes intraglomerular autoregulation, and reduces intra-glomerular and systemic arterial hypertension [1, 14]. The LPD partially corrects such unfavorable uremic metabolic and endocrine disorders, as hypoalbuminemia, dyslipidemia, insulinoresistance, hyperphosphatemia with parathyroid gland hyperplasia, and anemia, and thereby reduces the risk of uremic hyperparathyroidism, vascular calcification, and atherosclerosis (**Table 5**) [7, 20, 26].

The effect of LPD on CKD advancing is more pronounced in cases of DN. In the background of LPD, the annual incidence of GFR declines by 1.5–2 times, and the outcome in the terminal stage of CKD is observed almost three times less frequently than in the standard diet [5, 7].

Mechanisms of action	Clinical effect
Protein restriction to the level, adapted to residual renal function	Decrease in level of uremic toxins, azotemia, hyperuricemia
Correction of metabolic acidosis	Correction of nutrition status: protein catabolism; hypoalbuminemia; amino acids metabolism
Inhibition of glomerular hypertrophy and intraglomerular hypertension, decrease in tubular transport overload, suppression of cytokines and uremic toxins synthesis: TGF-β, AII and RO, TIMP, indoxyl sulfate, guanidine, phosphate, oxalic acid, NO	Decrease in proteinuria, correction of hypertension, slowing down of glomerulosclerosis and tubulointerstitial fibrosis, and GRF stabilization
Partial correction of dyslipidemia: • of hypercholesteremia; • of hypertriglyceridemia; • decrease in insulin resistance	Slowing down of atherosclerosis progression, decrease in risk of cardiovascular complications and mortality
Decrease in serum phosphate and PTH levels, increase in calcitriol	Suppression of hyperparathyroidism, vascular calcification, improvement of anemia, and decrease in erythropoietin doses

TGF-β: transforming growth factor β; AII: angiotensin II; RO: reactive oxygen; TIMP: tissue inhibitor matrix metalloproteinases; NO: nitrogen oxygen; PTH: parathyroid hormone; and GFR: glomerular filtration rate is calculated by CKD EPI creatinine equation.

Table 5. Mechanisms of action and clinical effects of low-protein diet (LPD).

The effect of LPD directly depends on the correct compliance by patients with the prescribed restriction of the amount of protein in the diet (0.8–0, 6–0.3 g/kg body weight/day), depending on the stage of CKD, the ratio of animal and vegetable proteins in it, and also on high caloric intake (30–35 kcal/kg body weight/day) [1, 14, 21].

According to the re-analysis of the MDRD multicentre study (Modification of diet in renal disease), in the background of LPD in patients with GFR more than 25 ml/min, the rate of CKD progression decreased by approximately 10%, and with GFR less than 25 ml/min, it was an average of 30% for every 0.2 g/kg of protein excluded from the diet [1].

The results of the research indicate that "strict" LPD (0.3 g/kg/day of vegetable protein) and the use of a complex of EAA and KA (ketosteril 1 table/5 kg of body weight per day) in patients with stage 4 CKD provide a more effective reduction of uremia symptoms and provide an extension of the predialysis period than conventional LPD (0.6 g protein/kg/day) [6, 11]. Strengthening of the nephroprotective role of LPD by combining it with α-ketoanalogs of amino acids is associated with a lesser effect it has on intra-glomerular hypertension, as well as with their ability as an additional source of calcium to inhibit hyperphosphatemia and slow the formation of uremic hyperparathyroidism [1, 11]. LPD in combination with EAA and KA enhances the antihypertensive and antiproteinuric effects of RAAS blockers, the corrective effect of erythropoietin preparations on the anemia, the effects of synthetic analogs of vitamin D and calcimimetics on manifestations of hyperparathyroidism, and the hypolipidemic effect of statins [10].

The replacing of a portion of the animal protein (0.1–0.2 g/kg/day) in the LPD (0.6 g protein/kg body weight/day) with a highly purified soy protein (an equivalent amount) contributed to retardation of CKD progression [4]. Soy protein is less able than animal protein (meat, fish, milk, etc.) to increase hyperperfusion and hyperfiltration in remnant nephrons [30]. The results of studies on the model of unilateral ureteral obstruction in rats receiving LPD demonstrated a decrease in the expression of the nuclear factor of Kappa B transcription (NFkB), the most important mediator of activation of many proinflammatory and profibrotic cytokines and TGF-β-key as a profibrotic factor in the renal tissue [28, 30]. LPD with an addition of soy protein to the diet reduces tubulointerstitial fibrosis also due to suppression of tyrosine protein kinase as a powerful sclerosis stimulant [30]. Currently, the possibility of LPD influence to maintain the serum level of klotho protein, as an established strong early cardio and nephroprotective factor, is being actively studied [29].

4. Conclusion

Thus, the restriction of daily food protein intake to 0.3–0.6 g/kg/day prevents accumulation of toxic products, retards, and delays terminal renal failure. Replacing a portion of the animal protein in a LPD by an equivalent amount of highly purified soy protein enhances the nephroprotective effect of a LPD and favors more pronounced slowdown of CKD progression. The use of keto-analogues of essential amino acids with LPD at predialysis stage of CKD allows preserving CKD patients from nutrition status disorders and contributes to slow down of CKD complications. Control of nutrition status in CKD should be carried out regularly. A comprehensive assessment of NS in CKD patients can be quickly performed using bioimpedance analysis.

Acknowledgements

This work was supported by Russian Science Foundation (grant No. 14-15-00947 2014).

Abbreviations

ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blockers
BCM	Body Composition Monitor
BMI	Body mass index
CKD	Chronic Kidney Disease
CRP	C-reactive protein
CRF	Chronic Renal Failure
CV	cardiovascular

CVC	Cardiovascular complications
CVE	cardiovascular events
DN	diabetic nephropathy
EAA	essential amino acids
EPO	erythropoietins
FGF-23	fibroblast growth factor
GFR	Glomerular Filtration Rate
GS	glucocorticosteroids
HD	Regular Hemodialysis
KA	Keto-analogues
LVH	left ventricular hypertrophy
LPD	low protein diet
NS	nutritional status
NSD	nutritional status disorders
PTH	parathyroid hormone
PCR	protein catabolism rate
RAAS	renin angiotensin aldosterone system
PEW	protein-energy wasting
RRT	renal replacement therapy
SFFT	thickness of the skin-fal fold
SMV	Shoulder muscles volume
TBW	total body water

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