

How should Nutritional Support be Provided in Chronic Kidney Disease?

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Abstract

Protein loss is common in patients with chronic kidney disease (CKD) due to malnutrition and increased catabolism. Nutritional deficiencies increase cardiovascular mortality in renal diseases. By the term “malnutrition” it is meant “wrong nutrition” which includes both little and excessive nutrition. For this reason, it is proposed to define “protein energy wasting” for loss of appetite and inflammatory processes associated with chronic kidney disease. The causes of malnutrition; anorexia, systemic inflammation, loss during dialysis, acidosis, endocrine disorders, anemia, concomitant diseases and accompanying comorbid conditions (diabetes, aging, cardiovascular diseases, respiratory system diseases).

Keywords: *Chronic Kidney Disease; Malnutrition; Protein-Energy Wasting*

Introduction

Chronic kidney disease (CKD) is an important public health problem that negatively affects patients' quality of life and lifespan. Dietary habits of patients undergoing hemodialysis and pre-dialysis patients are important for bone mineral metabolism disorders, blood pressure, and the fluid-electrolyte balance. On the other hand, preventing complications that may arise in connection with the disease and raising the quality of life of the individual are key factors. The aim of dietary practices for CKD patients should be to prevent malnutrition, improve anemia, reduce the frequency of inflammation, prevent the development of cardiovascular diseases, and to minimize symptoms such as nausea, vomiting, itching, and pain. However, CKD patients are unable to be fully nourished due to reasons such as taste disorders, acetone smell in the mouth, comorbid diseases such as diabetes, cardiovascular diseases, and gastrointestinal diseases, misperception, forgetfulness, ennui, or inadequate support from their relatives [1,2].

Nutritional therapy applied to patients with CKD requires that the most appropriate nutrition program be determined according to the clinical and laboratory findings of the patients and that it is fully applied after being correctly understood by the patient. The aim of this review is to search the answer to the question “How should nutritional support be given to patients with CKD?” in light of the information in the literature.

Pathophysiology

Patients with Chronic Kidney Disease (CKD) and renal failure consist of fairly heterogeneous groups of cases with different and sometimes conflicting objectives of the components of nutritional support, nutritional needs, and nutritional regimen [3]. Renal failure is a panmetabolic and panendocrine abnormality that affects every metabolic pathway in the body a lot or little. Despite the differences in nutritional needs in the different forms of renal failure and during the course of the disease in each patient, the metabolic changes of patients share common features [4]. The main metabolic abnormalities of patients with CKD are:

1. Peripheral insulin resistance
2. Impairment of lipolysis
3. Low-grade inflammatory condition with or without activation of protein catabolism
4. Increased catabolic response secondary to accompanying comorbidity
5. Metabolic acidosis
6. Uremic bone disease, hyperparathyroidism
7. Impairment of Vitamin D3 activation
8. Renal anemia

Nutritional Treatment of Patients with Chronic Renal Disease

Non-Catabolic Patients with Stable Chronic Kidney Disease

Patients are largely not catabolic when there is no accompanying comorbidity and metabolic acidosis compensation. Patients in this group are at high risk of malnutrition due to uremia-related factors, metabolic acidosis, decreased oral food intake due to impaired appetite, gastrointestinal side effects of uremia, and potentially misdirected dietary regimes [5]. The goals of nutritional therapy in CKD are to prevent malnutrition and/or sustain optimal nutritional support in the early stage of renal disease, to reduce or control the accumulation of waste products, to prevent cardiovascular disease by treating hyperlipidemia, to manage bone disease by treating Vitamin D deficiency and hyperparathyroidism, and to improve renal anemia to slow the progression of renal dysfunction [5]. There is a delicate balance between the occurrence of toxic effects caused by excessive nutrition and the occurrence of malnutrition due to the lack of oral intake in those with CKD. The nutritional requirements of those with CKD are summarized in table 1 [6]. Particular attention should be paid to protein, phosphorus, potassium, bicarbonate, active vitamin D3 analogs, and iron. Erythropoiesis-inducing agents should be administered when needed for the treatment of anemia [7]. The most debated subject related to diet therapy is protein intake. There is consensus on a moderate protein restriction of 0.7 - 0.8 g/kg/day. If protein intake drops to < 0.6 g/kg/day, the keto analogs of amino acids should be supplemented. The scope of electrolyte restriction varies for each patient. Bicarbonate supplementation should not be forgotten in these patients [8,9].

	Conservative Therapy	Hemodialysis	Peritoneal Dialysis
Energy (kcal/kg)	> 35	30 - 35	> 35*
Protein g/kg	0.6 - 0.8	1.1 - 1.4	1.2 - 1.5
Phosphorus mg	600 - 1000	800 - 1000	800 - 1000
mmol	19 - 31	25 - 32	25 - 32
Potassium mg	1500 - 2000**	2000 - 2500	2000 - 2500
mmol	38 - 40	40 - 63	40 - 63
Sodium gr	1.8 - 2.5 **	1.8 - 2.5	1.8 - 2.5
mmol	77 - 106	77 - 106	77 - 106
Liquid ml	Not restricted	1000 ml + DUO	1000 ml + DUO + UF

Table 1: Daily Nutritional Requirements in CKD.

*: Contains energy from the dialysate

** : Individual requirements may vary greatly

DUO: Daily Urine Output; UF: Ultrafiltration

Patients With Chronic Renal Replacement Therapy

Patients undergoing chronic renal replacement therapy, hemodialysis (HD), and chronic ambulatory peritoneal dialysis (CAPD) are often malnourished or have a very high risk of developing malnutrition. Moderate-to-severe malnutrition which may threaten the lifespan has been reported in > 20% of HD patients. Annual mortality rates among malnourished HD patients are around 25 - 30% [4].

Urea, uric acid, and creatinine, which are the degradation products resulting from protein metabolism, are eliminated by the kidneys. Apart from this excretory function, kidneys play a role in amino acid metabolism by enabling hydroxylation of phenylalanine to tyrosine and conversion of glycine to serine. For this reason, disorders of amino acid plasma concentrations occur in chronic kidney disease [10]. Nutrition and associated problems are closely related to morbidity and mortality in chronic kidney disease and hemodialysis patients. Inadequate intake, losses, metabolic and endocrine disorders, increased protein catabolism, and intervening medical and surgical diseases are common causes of nutritional deficiency in these patients. The most common cause is inadequate food intake. Clinical trials have shown that a significant proportion of hemodialysis patients were taking less than the recommended amount of protein and calories. The causes of inadequate intake include nausea caused by uremic toxins, vomiting and loss of appetite, diabetic or uremic gastroparesis, esophagitis, gastritis, susceptibility to infections and increased frequency of infections, depression, anemia, socioeconomic reasons, and oral and dental problems [11]. As is well known, protein restriction in the diet is often preferred in patients diagnosed with chronic kidney disease to reduce the progression of renal disease [12]. A completely protein-free diet is also not recommended, as proteins play an important role in the maintenance of muscle structure and the sustenance of immune system activity. In chronic kidney disease, the goal of nutritional therapy is to make sure that the major part of the amount of protein to be consumed within a diet in which the majority of the daily energy need is met by carbohydrates and fats consists of animal protein with high biological value [13]. Hemodialysis has a stimulating effect on protein catabolism. The reason for this is the triggering of inflammatory reactions which develop due to the weak biocompatibility of the materials that the blood runs into as it passes through extracorporeal circulation. During hemodialysis, complement and monocyte activation from an alternative pathway and interleukin-6 and tumor necrosis factor (TNF) release are increased. This leads to an increase in the accompanying lysosomal protein catabolism and amino acid oxidation. Factors such as high blood flow rate, presence of endotoxins in the dialysate, and acetate further increase catabolic stimulation [14]. In the dialyses, the loss of amino acids to the dialysate is 5 - 8 g/session for each hemodialysis on average, while it is 5 - 12 g/day in peritoneal dialysis. While there is a 6 - 12g amino acid loss in one session with low-flux membrane use, a 1 - 2g amino acid loss is expected with high-flux membrane use [15]. Taking these into account, protein intake is recommended at 1 g/kg/day for healthy adults, while it is recommended at 0.3 - 0.6 g/kg/day for chronic kidney disease (stage 1 - 5, not undergoing hemodialysis) and accompanying high biological value essential amino acid support for those undergoing hemodialysis should be at 1.2 g/kg/day and essential amino acid support, when needed, should be at 1.2 - 1.5 g/kg/day for those undergoing peritoneal dialysis [16]. A healthy person spends 1 calorie/kg/h of energy at the resting state. The calories spent per day by a 70-kg person at rest is 1680 kcal/day. If additional activities are considered, a 70-kg person who does not exercise, with an additional energy requirement of 500 - 600 calories, needs 2200 kcal/day of energy. Energy intake is 35 kcal/kg/day in hemodialysis patients under 60 years of age and 30 - 35 kcal/kg/day in patients aged over 60 years. For a balanced nutrition in an active hemodialysis patient, 2000 - 3000 kcal/day energy should be planned, and the dietary content should consist of 60 - 65% carbohydrates and 25 - 30% fats. When it is considered that protein use is related to sufficient energy intake, it has been shown that in order to prevent the protein consumed from being used as an energy source through gluconeogenesis, an adequate number of calories must be consumed and that therefore sufficient energy support has a protein conserving effect [17]. Slomowitz, *et al.* have shown that in six patients taking a fixed amount of 1.13 g/kg/day of protein, the nitrogen balance was negative when energy intake was at 25 calories/kg/day, whereas it was neutral when energy intake was at 35 calories/kg/day. When it is considered that the energy intake of most hemodialysis patients is below 35 calories/kg/day, it should not be forgotten that the energy insufficiency leads to the destruction of the dietary protein and that therefore sufficient caloric intake of hemodialysis patients is very important [10].

Nutritional Monitoring

Serum albumin levels have long been used as an indicator of the nutritional state of dialysis patients [18,19]. It is known that hypoalbuminemia may result from inadequate nutrition and inadequate dialysis treatment, and increase morbidity and mortality [18-22]. Serum transferrin, urea, creatinine, total cholesterol, potassium, inorganic phosphorus, complement, and immunoglobulin levels are also used as indicators of the nutritional state of HD patients [18,19]. Taking the dietary history, recording all food intake for at least 3 days together with the amounts with the help of the patient and their relatives, and calculating the daily protein and energy intake from these records provides very valuable information. However, it requires cooperation between the patient and their relatives and the dietitian. In stable patients, daily protein intake is equal to the protein catabolic rate (PCR). For this reason, the normalized protein catabolism rate (nPCR) calculated with the urea-kinetic method, is used as an indicator of daily protein intake in dialysis patients [23-25]. Measurements such as the body mass index (BMI), arm circumference (AC), and triceps skin thickness (TST) are used as anthropometric indicators of nutrition. In order to be able to talk about adequate dialysis in a patient, they should be in a good nutritional state first. In addition, blood pressure, anemia, acidosis, electrolyte balance, phosphorus and calcium metabolism, and uremic polyneuritis should be brought under control and several criteria such as achieving sufficient urea clearance for each hemodialysis session should be met [18]. Measurements of urea clearance achieved in each HD session are the most frequently used indicators of dialysis sufficiency. For this purpose, the urea reduction rate (URR) and Kt/V are calculated. The URR shows the rate of urea reduction in a single dialysis session. In Kt/V, K represents the clearance of the dialyzer at a given blood flow rate (ml/min), t represents the dialysis time (min), and V represents the urea distribution volume. In the Kt/V mechanistic approach, there is a consensus for recommending dialysis that the rate obtained by multiplying the clearance (K) mentioned in the dialyzer's manufacturer brochure by the dialysis time (t) and dividing that figure by the predicted body fluid (V) (about 0.58x kg of weight) should be a minimum of 1.0. It has been shown that as the Kt/V value rises, morbidity and mortality rates significantly fall [25,26]. In order to examine the effect of the efficacy of dialysis on nutrition, the first step in the treatment of malnutrition is interventions that target the cause of malnutrition. A sufficient dose of dialysis is the correction of acidosis and hyperparathyroidism and the treatment of infection. Correction of catabolic factors, pure dialysis solution, and biocompatible membrane are interventions which target the cause. The optimal dialysis dose should be adjusted as $Kt/V > 1.4$, and the urea reduction rate as > 65 . In one study, it was shown that the protein catabolism rate calculated by the urea-kinetic method reflects the daily protein intake and is dependent on the type and dose of dialysis [27]. In another study, it was reported that a protein intake of less than 0.8 g/kg/day is associated with inadequate dialysis and mortality and morbidity in dialysis patients, and that it may be considered as a daily dialysis rescue treatment for a period of 6 - 12 months in malnourished patients [28].

Nutritional Support for HD Patients

Prerequisites: treatable causes of protein-energy intake should be investigated, metabolic acidosis should be corrected, and midweek pre-dialysis bicarbonate should be ≥ 20 mmol/L [29].

The regular intervention of dietitians is necessary for nutritional counseling and monitoring of oral intake and adjusting oral supplementation in dialysis patients [29].

Oral nutritional supplements (ONS): In many studies, the positive effects of ONS on nutritional parameters have been reported. ONS should be taken 1 hour after usual meals and during HD sessions [30]. The essential amino acid administration should be kept in mind. There are various studies showing the positive effects of essential amino acids. In a study involving 52 patients with serum albumin levels less than or equal to 3.8 g/dL, patients being followed up for three months under essential amino acid support were evaluated and it was found that there was a significant increase in the albumin level and hand grip strength of patients who were receiving essential amino acids [31].

Intradialytic Parenteral Nutrition (IDPN): IDPN is the cyclic parenteral nutrition administered via the venous route during a dialysis session. Advantages of IDPN: no need for catheterization or hospitalization, removal of excess fluid and minerals by hemodialysis, correction of hyperglycemia by dialysis. The high blood flow rate in the path of vascular intervention facilitates the administration of hyperosmolar solutions.

IDPN indications:

1. If the three months pre-dialysis serum albumin is below 3.4 g/dL,
2. If the three months pre-dialysis serum urea nitrogen is below 8 mg/dL,
3. If there is a loss of more than 10% of the ideal body weight,
4. If there is moderate-severe malnutrition (clinical-anthropometric),
5. If there is a history of reduced dietary intake (< 0.8 g/kg protein and < 25 kcal/kg), then IDPN should be given [30].

Studies have shown that the addition of IDPN to oral supplements does not provide an advantage in terms of mortality, morbidity and nutritional state [7]. IDPN should only be prescribed for patients who are intolerant to or cannot conform to oral supplements [7].

Enteral therapy: If oral support is inadequate, solutions of nutrition with a nasogastric or percutaneous entero-gastrostomy tube should be applied. Indications: for those who do not recover from malnutrition despite diet and oral support, intensive care patients with the poor general condition, and patients who have had a cerebrovascular event [32].

Other malnutrition treatments: In addition to oral or parenteral support, growth hormone and insulin-like growth factor I may be given [33]. The androgenic anabolic steroids used in the treatment of malnutrition are nandrolone decanoate and oxandrolone. Nandrolone decanoate should be administered for 3 - 6 months if there is resistance to optimal nutritional measures in cases of severe malnutrition. Androgens should be administered weekly or bi-monthly. Patients should be monitored at regular intervals for side effects and for hirsutism, voice change, priapism, changes in lipid profile, liver enzyme elevation, and prostate-specific antigens. It should not be given to those with known prostate cancer [34]. Megestrol is a progesterone derivative and is not recommended for use as an appetite enhancer in hemodialysis patients due to side effects such as hypercoagulability, adrenal insufficiency, and hypertension [35].

Anti-inflammatory therapy: Steroids, pentoxifylline, statins, acetylsalicylic acid, anti-cytokine therapy (Thalidomide, thiazolidinediones), vitamin E, and anti-adhesion therapy (anti-ICAM) have been tried in the treatment of malnutrition [36].

Antidepressant treatment: The psychological state of the patients is important. It has been shown that the nutrition is impaired with depression and that malnutrition is improved with antidepressant treatment [37].

Nutritional Treatment of Renal Transplantation

Renal transplantation is the most common solid organ transplant procedure. The nutritional therapy of renal transplantation is divided into four periods as the pre-transplant period, transplant surgery, early post-transplant period, and late-post transplant period [38].

Pre-transplant Period

The goal of pre-transplant nutritional therapy is to optimize early and late post-transplant period results. In a pre-transplant nutritional intervention, adequate protein and energy intake should be provided in order to reduce the risk of infection, improve wound healing, and maintain muscle mass. It is also a goal to achieve calcium and phosphorus balance to maintain bone structure. It may be appropriate for obese transplant candidates to lose body fat [38].

Transplant Period

Because, during transplantation, surgery is often associated with fluid retention and subsequent mobilization, the primary goal should be to prevent volume overloading. It is also necessary to regulate the electrolyte (especially potassium) and the acid-base balance. This

patient group receives high-dose steroids that accelerate protein catabolism in addition to the usual postoperative stress. Surgery and the post-op recovery process increases the need for energy and protein [39].

Post-Transplant Period

Early Post-Transplant Period

In renal transplant recipients, nutritional therapy is needed in the early postoperative period in order to maintain the persistence of visceral protein deposits despite increased protein catabolism, to enable wound healing, to prevent infections related to surgery and immunosuppression, and to regulate the electrolyte imbalance that accompanies rapid changes in renal function. For this purpose, 1.3 - 1.5 gr/kg of protein content and 30 - 35 kcal/kg of calorie support should be provided in the first month following the transplantation. From the 2nd post-transplant month onward, calorie support which will provide and maintain optimal weight with 1.0 g/kg of protein content should be provided [39].

Late Post-Transplant Period

The efficacy and safety of protein restriction in the diet to slow the progression of renal insufficiency in transplant kidneys are questionable. The nutritional state and body muscle mass should be carefully and regularly monitored when restricting dietary protein. About 800 mg/day may be wise for dietary phosphorus restriction and phosphate-binding treatment may be necessary [40].

Conclusion

In conclusion, CKD is a panmetabolic and panendocrine abnormality which affects each metabolic pathway in the body more or less. In no other patient group is there such a narrow gap between the occurrence of toxic effects and the development of malnutrition. Patients with CKD are at greatest risk of malnutrition due to uremia-related factors, metabolic acidosis, decreased appetite, decreased oral intake, and the gastrointestinal side effects of uremia. In CKD, nutrition is directly linked to mortality and quality of life and the diet should be specific to each patient. Malnutrition should be suspected in patients with a continuous decrease in weight from ideal body weight, with albumin levels below 4 g/dL, with low pre-dialysis blood urea nitrogen and creatinine levels, and with a dietary protein intake below 1 g/kg/day. Anthropometric assessments, in addition to biochemical evaluations, may provide practical, accurate, and fast results. Malnutrition in CKD may be prevented by effective and biocompatible dialysis, reaching an adequate dose of dialysis, fighting against psychosocial problems, and adequate protein and energy intake in addition to cooperation between physicians, nurses, dieticians and family relatives.

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