



## Protein-energy wasting in maintenance hemodialysis patients – etiology and diagnosis

### Proteinsko-energetski gubitak kod bolesnika na hroničnoj hemodijalizi – etiologija i dijagnostički kriterijumi

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#### Key words:

renal insufficiency, chronic; renal dialysis; malnutrition; nutritional assessment; nutritional status; metabolism; muscular atrophy; risk assessment.

#### Ključne reči:

bubreg, hronična insuficijencija; hemodijaliza; pothranjenost; ishrana, procena; nutritivni status; metabolizam; mišići, atrofija; rizik, procena.

#### Introduction

In patients with chronic kidney disease (CKD), especially those on hemodialysis (HD), nutritional status plays an important role. It is directly connected with longevity, life quality, rate of hospitalization and mortality<sup>1-5</sup>. Despite the fact that dialysis procedure is constantly improving, common complication in HD patients is still protein-energy wasting (PEW). Although PEW is a very common problem, it often remains undiagnosed and untreated. Also, PEW is the strongest risk factor for poor clinical outcomes, including death, especially in the elderly patients<sup>4,6</sup>.

Considering that CKD has a high prevalence of 13.4%, and the number of patients with diagnosed CKD is growing worldwide, including the fact that annual mortality of dialysis patients was 20% higher compared to the mortality from cancer disease, the seriousness and the magnitude of the problem in patients with PEW seems to be much higher<sup>2,7</sup>. Several studies related to the nutritional status in the HD patients have shown that the prevalence of PEW varies from less than 20% to almost 80% depending on markers used for assessment of the nutrition status<sup>4,8,9</sup>. Many different terms, such as protein-energy malnutrition, uremic malnutrition, uremic cachexia, malnutrition-inflammation syndrome, are used for a condition associated with loss of muscle and fat,

malnutrition, and inflammation in patients with CKD, and may lead to confusion and misinterpretation of clinical data.

The existence of different criteria can produce the problems in diagnostic procedures, comparison of results and establishing recommendations for the prevention and therapy. Therefore, in order to avoid confusion in the nomenclature, the International Society of Renal Nutrition and Metabolism (ISRNM) expert panel has recommended the term “protein-energy wasting” to describe a “state of decreased body stores of protein and energy fuels” that usually results from a complex interplay of reduced nutrient intake and/or increasing catabolism<sup>10</sup>. Since protein and energy wasting sometimes occur as separate entities, terms “protein wasting” or “energy wasting” can be used to refer to the occurrence of only one of the mentioned<sup>10</sup>.

#### Etiology of PEW

Dialysis patients often develop malnutrition at a very early stage of dialysis<sup>9,11,12</sup>. PEW in patients with CKD, particularly those who are on HD, has its own specificity as compared to patients who suffer from other chronic diseases or those in which it is only the result of insufficient food intake or restrictive diets. Many factors that contribute to PEW are directly associated with chronic renal failure<sup>2,13,14</sup>.

The possible causes of PEW in CKD patients are listed in Table 1, created and presented from the ISRNM as a consensus review of current knowledge<sup>13</sup>.

A long list of causes and variety of their combination can lead to PEW in different ways in each HD patient. Although the etiology of PEW is undoubtedly multifactorial, inadequate dietary nutritional intake is likely to play an important role. Predialysis patients are mostly on low-protein diets. Sometimes these types of diets are hypocaloric and as a consequence of predialysis restrictive diets, patients start HD in poor nutritional conditions<sup>9, 11, 12, 15</sup>. Hemodialysis procedure itself can directly affect energy balance, i.e. energy intake and energy expenditure. Several studies indicated that dietary energy and protein intakes were below recommended levels or the actual needs in the HD patients<sup>9, 16-18</sup>. In addition, the progressive reduction in spontaneous food

sensing<sup>2, 13, 15, 20, 21</sup>. Malnutrition in the HD patients is also often caused by too many restrictive or monotony diets, sometimes due to unnecessary prohibition of various foods without considering the preferences, needs and possibilities of patients<sup>15</sup>. Furthermore, the imbalance between dietary intake and actual needs can be increased by additional loss of nutrients during dialysis, such as amino acids, certain peptides, glucose, vitamins, trace elements, leading to further increased risk of PEW<sup>13, 15</sup>. Although the reduced food intake or poor absorption of nutrients play a key role in most cases of PEW, other factors in addition to starvation (especially hypermetabolism, inflammation, metabolic acidosis, comorbidities and dialysis) are required for the occurrence of PEW<sup>13, 14</sup>.

It was postulated that inflammation can cause PEW. Many factors, such as increased production and decreased

**Table 1**

**Causes of PEW in CKD patients<sup>13</sup>**

1. Decreased protein and energy intake
a) Anorexia
i. dysregulation in circulating appetite mediators
ii. hypothalamic amino acid sensing
iii. nitrogen-based uremic toxins
b) Dietary restrictions
c) Alterations in organs involved in nutrient intake
d) Depression
e) Inability to obtain or prepare food
2. Hypermetabolism
a) Increased energy expenditure
i. inflammation
ii. increased circulating proinflammatory cytokines
iii. insulin resistance secondary to obesity
iv. altered adiponectin and resistin metabolism
b) Hormonal disorders
i. insulin resistance of CKD
ii. increased glucocorticoid activity
3. Metabolic acidosis
4. Decreased physical activity
5. Decreased anabolism
a) decreased nutrient intake
b) resistance to GH/IGF-1
c) testosterone deficiency
d) low thyroid hormone levels
6. Comorbidities and lifestyle
a) comorbidities (diabetes mellitus, CHF, depression, coronary artery disease, peripheral vascular disease)
7. Dialysis
a) nutrient losses into dialysate
b) dialysis-related inflammation
c) dialysis-related hypermetabolism
d) loss of residual renal function

**PEW – protein-energy wasting; CKD – chronic kidney disease; GH – growth hormone; IGF-1 – insulin-like growth factor 1; CHF – chronic heart failure.**

intake occurs with a decrease in kidney function<sup>18</sup>. Factors that affect food intake including not only dietary restrictions, but also anorexia, taste changes, depression, social behavior, customs, low social status, solitude, and inability to obtain or prepare food<sup>2, 16, 19</sup>.

Anorexia in the HD patients may develop as a result of nitrogen-based uremic toxin retention as well as dysregulation in some of appetite mediators – from gastric, cytokines and adipokines to hypothalamic amino acid

elimination of proinflammatory cytokines, acidosis, oxidative stress, altered metabolism of adipose tissue, and other intracorporeal factors, contribute to persistent inflammation in CKD, especially in the HD patients. In addition to these, many extracorporeal factors mainly related to dialysis itself, such as chemical and microbiological contaminants in dialysis water, or bioincompatible in dialysis circuit, cannot be neglected<sup>13, 20, 22</sup>. Kidney has a role of a modulator of endocrine function, whilst kidney disease

causes abnormalities in the synthesis, excretion, and action of many hormones. Insulin resistance, growth hormone (GH), insulin-like growth factor (IGF)-1, and elevated glukucocorticoides levels are causative of an increase in protein and amino acid catabolism and suppression of protein synthesis. Thus, these are implicated in the loss of muscle

mass in the CKD patients<sup>2, 13, 20</sup>. Inflammation is associated with increased resting energy expenditure (REE), oxidative stress, protein catabolism, loss of muscle mass, high C-reactive protein and proinflammatory cytokine levels, hypoalbuminemia and the presence of comorbid conditions as well as with suppression of hormones such as anabolic hormones, IGF-1, and

**Table 2**

**Readily utilizable criteria proposed by International Society of Renal Nutrition and Metabolism (ISRNM) expert panel for the clinical diagnosis of PEW in CKD<sup>10</sup>**

Criteria
Serum chemistry
serum albumin < 3.8 g/dL (method: Bromcresol Green) <sup>a</sup>
serum prealbumin (transthyretin) < 30mg/dL (for maintenance dialysis patients only; levels may vary according to GFR level for patients with CKD stages 2–5) <sup>a</sup>
serum cholesterol < 100 mg/dL <sup>a</sup>
Body mass
BMI < 23 kg/m <sup>2</sup> <sup>b</sup>
unintentional weight loss over time: 5% over 3 months or 10% over 6 months
total body fat percentage < 10%
Muscle mass
muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months
reduced mid-arm muscle circumference area <sup>c</sup> (reduction > 10% in relation to 50th percentile of reference population)
creatinine appearance <sup>d</sup>
Dietary intake <sup>e</sup>
unintentional low DPI < 0.80 g/kg/day- for at least 2 months for dialysis patients or < 0.6 g /kg/day for patients with CKD stages 2–5
unintentional low DEI < 25 kcal/kg/day for at least 2 months

**At least three out of the four listed categories (and at least one test in each of the selected category) must be satisfied for the diagnosis of kidney disease-related PEW.**

**Optimally, each criterion should be documented on at least three occasions, preferably 2–4 weeks apart.**

<sup>a</sup>Not valid if low concentrations are due to abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medicines.

<sup>b</sup>A lower BMI might be desirable for certain Asian populations; weight must be edema-free mass, for example, post-dialysis dry weight.

<sup>c</sup>Measurement must be performed by a trained anthropometrist.

<sup>d</sup>Creatinine appearance is influenced by both muscle mass and meat intake.

<sup>e</sup>Can be assessed by dietary diaries and interviews, or for protein intake by calculation of normalized protein equivalent of total nitrogen appearance (nPNA or nPCR) as determined by urea kinetic measurements.

**BMI – body mass index; CKD – chronic kidney disease; DEI – dietary energy intake; DPI – dietary protein intake; GFR – glomerular filtration rate; nPCR – normalized protein catabolic rate; nPNA – normalized protein nitrogen appearance; PEW – protein–energy wasting.**

**Table 3**

**Other potential tools (including those still in development) for assessment of PEW in individuals with CKD stages 3–5<sup>10</sup>**

Appetite, food intake, and energy expenditure
appetite assessment questionnaires
population-based dietary assessments: food frequency questionnaires
measuring energy expenditure by indirect or direct calorimetry
Body mass and composition
weight-based measures: weight-for-height
total body nitrogen
total body potassium
energy-beam-based methods: DEXA, NIR, BIA, and vector bioimpedance analysis
underwater weighing and air displacement weighing
14 kDa fragment of actomyosin
microarrays
muscle fiber size
relative proportions of muscle fiber types
muscle alkaline soluble protein
CT and/or MRI of muscle mass
Laboratory markers
serum biochemistry: transferrin, urea, triglyceride, bicarbonate
hormones: leptin, ghrelin, growth hormones
inflammatory markers: CRP, IL-6, TNF- $\alpha$ , IL-1, SAA
peripheral blood cell count: lymphocyte count or percentage
Nutritional scoring systems
SGA and its modifications.

**PEW – protein–energy wasting; CKD – chronic kidney disease.**

**BIA – bioelectrical impedance analysis; CRP – C-reactive protein; CT – computed tomography; DEXA – dualenergy X-ray absorptiometry; IL – interleukin (e.g., IL-1 and IL-6); MRI – magnetic resonance imaging; NIR – near infrared interactance; SAA – serum amyloid A; SGA – subjective global assessment of nutritional status; TNF- $\alpha$  – tumor necrosis factor- $\alpha$ .**

testosterone. Pro-inflammatory cytokines may directly decrease appetite and increase REE via influence on the central nervous system. They can also indirectly reduce the appetite in the CKD patients, through depression and consequently reduced dietary nutrients intake<sup>13, 22, 23</sup>.

Metabolic acidosis, often in the HD patients, is also a potential cause of PEW. Studies have shown that acidosis increases degradation of the whole-body protein, breakdown of the skeletal muscle protein and oxidation of branched chain amino acids decreases albumin synthesis and determines nutritional abnormalities. It also causes insulin resistance that leads to loss of muscle mass<sup>13, 20</sup>. Some of comorbidities associated with CKD such as diabetes and metabolic syndrome, cardiovascular disease, hyperparathyroidism, anemia, gastrointestinal disorders, autoimmune and rheumatologic disorders, chronic lung diseases, liver disease, psychiatric and neurologic disorders and, malignant diseases, contribute to PEW<sup>13</sup>.

Although inadequate dialysis can lead to PEW itself, some factors associated with dialysis may contribute to PEW through nutrient losses into dialysate, infectious, inflammation, hypermetabolism and loss of residual renal function. Amino acid and protein losses during the dialysis session, together with low nutrients intake, promote low availability of nutrients for muscle synthesis. Dialysate loss of proteins, including amino acids, peptides and whole proteins, are estimated to be approximately 10–12 g per session. Dialyses procedure is a catabolic event, that accelerates the rate of whole-body and muscle proteolysis and stimulates active muscles on the release of amino acids, raising net whole-body and muscle protein loss. These undesirable effects of net skeletal muscle protein breakdown persisted for at least 2 hours after the completion of the HD procedure. Simultaneous amino acid supplementation can prevent or reverse these adverse effects in the HD patients which can be an opportunity for the treatment of PEW<sup>2, 13, 20, 24, 25</sup>.

### Diagnostic criteria for PEW

Clinical guidelines recommend routine assessment of nutritional status in the CKD and HD patients. There is not a single specific measurement that provides complete assessment of the nutritional status of the HD patients, although many different parameters for assessing the PEW are used in clinical practice and research<sup>5, 15, 26, 27</sup>. Therefore, the ISRNM established a set of criteria for identifying PEW in the CKD patients. According to the ISRNM expert panel diagnostic criteria, PEW has 4 categories in assessment: biochemical indicators, body mass, muscle mass and dietary intake. The ISRNM recommended that the diagnosis of PEW at least 3 out of 4 criteria categories, and that at least one test from each of the selected categories must be abnormal, on at least 3 examinations 2–4 weeks apart. Then, as a potential indicator of the PEW additional measures of nutrition and inflammation are recommended (Table 2)<sup>10</sup>.

#### *Biochemical indicators*

Among biochemical indices, serum albumin concentration has been used in detection of malnutrition in the HD patients for a long time. Low serum albumin level is a relatively late manifestation of malnutrition, since albumin has a long half-life and hepatic synthetic reserve is very large<sup>10, 15, 26</sup>. The association between serum albumin levels and mortality is highly gradual and linear. A decrease of 0.3 g/dL in serum albumin levels is associated with an increased risk of mortality by 20% in the HD patients<sup>3</sup>. However, serum albumin is also influenced by several non-nutritional factors which are often present in the HD patients, including infection, inflammation, comorbidity and hydration status. Serum albumin should always be taken into account when assessing malnutrition in the HD patients. Thus, low albumin level in the HD patients may not always result from PEW, and albumin alone is not a clinically useful marker for PEW. The serum albumin concentration should be measured monthly<sup>5, 10, 26, 28</sup>. Prealbumin, or transthyretin has a shorter half-life than albumin, a close relationship with nutritional status, and acts as a good predictor of clinical outcome in the HD patients<sup>5, 10, 26, 28</sup>. The serum total cholesterol concentration is reduced in PEW. It is a less sensitive nutritional marker, cheap, and more accessible<sup>5, 10, 26</sup>.

Although, the expert panel did not recommend numerous laboratory markers as part of criteria for the diagnosis of PEW, such as serum transferrin, bicarbonate, urea, triglyceride, hormones (leptin, ghrelin, growth hormones) concentration, inflammatory markers (CRP, IL-6, TNF- $\alpha$ , IL-1, SAA) levels and lymphocyte count or percentage, they could be useful indicators of protein-energy nutritional status in maintenance dialysis patients and potential tools for assessing PEW (Table 3)<sup>10</sup>.

#### *Body mass index (BMI)*

Even though BMI is one of the most used indicators of body mass, it has some limitations<sup>29</sup>. In general population normal range of BMI is between 18.5 and 24.9 kg/m<sup>2</sup>, while according to the ISRNM criteria, BMI less than 23 kg/m<sup>2</sup> is a marker of PEW in the HD patients<sup>10, 26, 30</sup>. A higher BMI is associated with increased cardiovascular mortality in the general population. It is quite the opposite situation in the HD patients where higher BMI is associated with lower death risk (“obesity paradox”)<sup>31</sup>. While obesity is a long-term risk for cardiovascular diseases in general population, in the HD patients, the risk mentioned above is not crucial. In the CKD patients risk of short-term consequences related to PEW is much greater than the risk of obesity, thus mortality depends on short-term risk meaning malnutrition. Therefore, in the CKD patients, especially in the HD patients, it is crucial to improve their nutritional status and prevent malnutrition and PEW<sup>1</sup>. All anthropometric measurements should be performed after a routine HD session and must be performed by trained personnel<sup>5, 10, 26</sup>. Since BMI is influenced by hydration status, it is recommended to use an edema-free mass to calculate BMI. Unintentional edema-free weight loss of 5% over 3 months or 10% during 6 months indicate risk of PEW<sup>10</sup>.

### *Muscle mass*

Reduced muscle mass is one of the most important criteria for the presence of PEW<sup>10</sup>. Mid-arm muscle circumference (MAMC) is useful in assessment of muscle mass. MAMC depends upon lean body mass and body water. It is thus expected that MAMC could increase when body water increases, although the lean body mass and somatic protein can be kept stable. It is necessary to bear this in mind when using MAMC in the HD patients as an index of somatic proteins status<sup>5,26</sup>.

### *Dietary intake*

To evaluate the nutrition status, it is important to provide an adequate assessment of the food intake by some of the available methods like dietary diaries or interviews<sup>5,10,26</sup>. In metabolic stable patients, it may be useful to indirectly assess dietary intake of protein by counting normalized protein equivalent of total nitrogen appearance (nPNA)<sup>5,10,26</sup>. As food data collection, the following tools can be used: 24-hour recall, food diaries, and food frequency questionnaire (FFQ), but each of these tools has some limitations. 24-hour dietary recall covers a short period of time and it does not represent a typical food intake. Food diary covers a longer time period (3–7 days) and it is recommended to patients to include dialysis and non-dialysis days. It is a more useful tool, if the patient weighs the portions of food<sup>32</sup>. FFQ can estimate the long term dietary intake. A diet that contains a daily energy intake of 35 kcal/kg body weight (bw) (30–35 kcal/kg bw for those aged 60 years and older) and 1.2 g protein/kg bw (at least 50% is of high biological value), is usually prescribed for the HD patients<sup>1,5</sup>. According to the ISRNM expert panel, unintentional low dietary protein intake less than 0.80 g/kg bw/day and unintentional low dietary energy intake less than 25 kcal/kg bw/day for at least 2 months can be associated with PEW<sup>10</sup>.

According to the ISRNM, nutritional scoring systems were not included in diagnostic criteria of PEW (only in potential tools), but others advised subjective global assessment (SGA) and its modifications for dialysis malnutrition score (DMS), and malnutrition inflammation score (MIS) for the diagnosis of malnutrition in the HD patients<sup>5,8,10,26,33</sup>. SGA is based on history and physical examination, and gives a global score of protein-energy

nutritional status. SGA is a practical, inexpensive, easily doable clinical tool, with one potential problem – its subjective nature which may reduce its reproducibility. SGA should be used in combination with other measures in diagnosis of PEW<sup>10,33</sup>. Body composition, except by anthropometry, can be assessed by more sophisticated methods such as bioelectrical impedance analysis (BIA) or dual energy X-ray absorptiometry (DEXA). There is a good correlation between anthropometry and BIA and DEXA but they are expensive and not widely available<sup>5,10</sup>.

### **Monitoring**

Nutritional status is considered an important prognostic factor for the risk of mortality, so early diagnosis and nutritional interventions could improve clinical outcome in the HD patients. Therefore, regular screening of the HD patients on PEW is extremely important. Nutritional status of the HD patients should be assessed at the start of HD and reassessed every 3–6 months. Malnourished and unstable patients may require monitoring at shorter intervals. Individual parameters such as serum albumin, BMI, nPNA, midweek predialysis creatinine should be evaluated monthly, but body weight should be measured on each dialysis<sup>2,5,26</sup>.

### **Conclusion**

The available evidence suggests that nutritional status in the HD patients is an extremely important predictive and causative factor for the good clinical outcome. Nutritional deficits and PEW are frequent problems in the dialysis population and implies an increased risk of negative health outcomes such as mortality risk and quality of life deterioration. There is no single specific measurement that provides complete assessment of the nutritional status in the HD patients, and the results should be analysed in the clinical context of each individual patients. As malnutrition is potentially reversible with appropriate nutritional support, early identification of patients at high nutritional risk may facilitate effective treatment and improve prognosis in the HD patients.

### **Acknowledgements**

This work was supported by the Ministry of Defence of the Republic of Serbia, Project No MFVMA/8/15-17.

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Received on September 2, 2016.

Accepted on October 3, 2016.

Online November, 2016.