Nutrición Hospitalaria

Revisión

A clinical approach to the nutritional care process in protein-energy wasting hemodialysis patients[1-3]

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Abstract

Introduction: Malnutrition/wasting/cachexia are complex-disease conditions that frequently remain undiagnosed and/or untreated in up to 75% of prevalent hemodialysis (HD) patients. The nutrition care process (NCP) based on assessment, diagnosis, intervention and monitoring of nutritional status is a systematic method that nutrition professionals use to make decisions in clinical practice.

Objective: This review examines from a clinical-nutritional practice point of view: a) nutritional status as a mortality causative factor; b) phenotypic characteristics of malnutrition/wasting/cachexia, and c) current trends of NCP with special emphasis on nutritional support and novel nutrient and pharmacologic adjunctive therapies in HD patients.

Method: A literature review was conducted using the Pubmed, Science Direct, Scielo, Scopus, and Medline electronic scientific basis. Studies which assessing nutritional status and nutritional support published from 1990 to 2013 in HD patients were included and discussed.

Results: From all the epidemiological data analyzed, NCP was the suggested method for identifying malnutrition/wasting or cachexia in clinical practice. Nutrition support as an unimodal therapy was not completely able to reverse wasting in HD patients. Novel experimental therapeutic strategies including the use of appetite stimulants, ghrelin agonist, MC4-R antagonists, anabolic steroids, anti-inflammatory drugs, cholecalciferol, and other components are still under clinical evaluation.

Conclusion: Nutritional status is a strong predictor of morbidity and mortality in HD patients. The terms called malnutrition, wasting and cachexia have different nutritional therapeutics implications. The NCP is a necessary tool for assessing and monitoring nutritional status in the current clinical practice. Novel pharmacological therapies or specific nutrient supplementation interventions studies are required.

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Key words: *Nutritional care process. Malnutrition. Protein-energy wating. Cachexia. Nutritional support. Hemodialysis.*

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ENFOQUE CLÍNICO DE ATENCIÓN NUTRICIONAL EN PACIENTES CON DESGASTE PROTÉICO-ENERGÉTICO EN HEMODIÁLISIS

Resumen

Introducción: Malnutrición/desgaste proteico-energético (DPE)/caquexia son situaciones patológicas complejas frecuentemente infradiagnosticadas o no tratadas hasta en un 75% de los pacientes prevalentes en hemodiálisis (HD). El proceso de atención nutricional (PAN) basado en la evaluación, diagnóstico, intervención y monitorización del estado nutricional es un método que los profesionales de la nutrición utilizan para tomar decisiones en la práctica clínica.

Objetivo: Esta revisión examina desde la perspectiva de la práctica clínica nutricional: a) el estado nutricional como factor causante de morbi-mortalidad; b) las características fenotípicas de malnutrición, DPE y caquexia y, c) el PAN con especial énfasis en el soporte nutricional y las nuevas terapias nutricionales y farmacológicas en pacientes en HD.

Métodos: Revisión sistemática de la literatura usando las bases científicas electrónicas Pubmed, Science Direct, Scielo, Scopus y Medline. Se incluyeron estudios publicados desde 1990 hasta 2013 que valoraban el estado nutricional y/o el soporte nutricional en pacientes en HD.

Resultados: De todos los datos epidemiológicos analizados, el PAN fue el método sugerido para identificar malnutrición/DPE/caquexia. El soporte nutricional como tratamiento aislado no era capaz de revertir totalmente la malnutrición o el DPE. Nuevas estrategias terapéuticas experimentales incluyendo el uso de estimulantes del apetito, agonistas de grelina, antagonistas MC4-R, esteroides anabólicos, antiinflamatorios y colecalciferol entre otros componentes, están siendo aún evaluados clínicamente.

Conclusiones: El estado nutricional es un predictor de morbilidad y mortalidad en pacientes en HD. Malnutrición, DPE y caquexia son términos con implicaciones terapéuticas diferentes. El PAN es una herramienta necesaria para la evaluación y la monitorización nutricional en la práctica clínica habitual. Estudios con nuevas terapias farmacológicas o intervenciones con suplementación de nutrientes específicos son requeridos.

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Palabras clave: *Proceso de atención nutricional. Malnutrición. Desgaste protéico-energético. Caquexia. Soporte nutricional. Hemodiálisis.*

ACE: Angiotensin-converting-enzyme.
BIA: Bioelectrical impedance analysis.
BMI: Body mass index.
CKD: Chronic kidney disease.
CRP: C-reactive protein.
CVD: Cardiovascular disease.
DEI: Dietary energy intake.
DOPPS: Dialysis Outcomes and Practice Patterns Study.
DPE: Desgaste proteico-energético.
DPI: Dietary protein intake.
DXA: Dual-energy x-ray absorptiometry.
EN: Enteral nutrition.
GH: Growth hormone.
IDPN: Intradialytic parenteral nutrition.
IGF-1: Insulin growth factor-1.
KDoqi: Kidney Disease Outcomes Quality Initiative.
HD: Hemodialysis.
HDF: Online hemodiafiltration.
HMB: Hydroxyl-methyl-butyrate.
IL-6: Interleukin 6.
ISRM: International Society of Renal nutrition and Metabolism.
Kt/V *urea (sp): S*ingle pool urea kinetic model.
MC4-R: Melanocortin-4 receptor antagonists.
MIS: Malnutrition-inflammation score.
NCP: Nutritional care process.
ONS: Oral nutritional supplements.
PA: Phase angle.
PAN: Proceso de atención nutricional.
PEG: Percutaneous endoscopic gastrostomy.
PEJ: Percutaneous endoscopic jejunostomy.
PEW: Protein-energy wasting.
PPAR-γ: Peroxisome proliferator-activated receptor-gamma.
s-albumin: Serum albumin.
SGA: Subjective global assessment.
s-prealbumin: Serum prealbumin.
TNF-α: Tumor necrosis factor alpha.
TPN: Total parenteral nutrition.
USRD: United States Renal Data System.

Introduction

Malnutrition, protein-energy wasting (PEW) and cachexia are prevalent complex conditions that frequently remain undiagnosed and untreated up to three quarters of hemodialysis (HD) patients[1-3]. Although an improper diet may contribute to malnutrition by itself, others factors including, increase of resting energy expenditure, systemic inflammation, endocrine disorders and metabolic acidosis, might be able to initiate wasting/cachexia syndrome in chronic kidney disease (CKD).

Annual death rates in dialysis patients with wasting/cachexia are close to 20%[4]. The Dialysis Outcomes and Practice Patterns Study (DOPPS)[5] showed that a reduction of more than 5% in serum albumin (s-albumin) six months after initiation of dialysis was associated with a relative risk of death of 1.96. The NECOSAD study[6] reported that wasting, inflammation and cardiovascular disease (CVD) remain as independent risk factors *per se,* whereas cumulatively they were also death risk factors. A recent spanish study[7], showed over 40% of wasting at 24 moths of follow-up in a sample of HD patients. A common pathophysiological link between CVD, inflammation, and wasting was reported[6,8]. The wasting/cachexia syndrome was clearly associated as an independent predictor of morbidity and mortality in incident HD patients during the subsequent two years on dialysis[9].

Recently, a recent panel of experts suggested that utilizable criteria for clinical diagnosis and treatment of wasting so called, protein-energy wasting (PEW)[10,11], and establishes the following question, *which nutritional indicators predict clinical outcomes most specifically?"*

Current clinical guidelines recommend routine assessment of nutritional status at the early stages of CKD[12] and in dialysis patients[10,13]. However, although a number of nutritional procedures are available, no single indicator can be considered as the ideal and reliable marker of malnutrition or PEW. As nutritional status appears to be a significant mortality prognostic factor, the nutrition care process (NCP)[14] method based on assessment, diagnosis, intervention and monitoring might improve clinical outcomes in HD patients.

This review examines current clinical practice in HD patients based on the NCP as follows: a) nutritional status as a cause of morbidity and mortality; b) analysis of phenotypic characteristics of different terms: malnutrition, PEW and cachexia; and c) the current trends in nutritional intervention and monitoring with special emphasis on nutritional support and novel adjunctive strategies.

Causative factors of morbidity and mortality in hemodialysis patients

Most of the identified traditional risk factors of morbidity and mortality in the general population are greatly different in HD patients. Epidemiological data from the United States Renal Data System (USRDS)[4] showed that the relative risk of mortality increases in patients with BMI <18.5 kg/m². The DOPPS cohort study[5] reported that each 5 kg/m² decrease in BMI was associated with 20% higher death risk. Conversely, a higher BMI (>25 kg/m²), due to a phenomenon known as "obesity paradox", was considered as a survival factor in the CKD population in some studies[15-17]. Fleischmann et al.[17] reported that overweight/obese HD patients showed lower rates of hospitalization and higher survival rates than their underweight counterparts[17]. In the study of Beddhu et al.[18] the protective effect of high BMI was limited to those patients with normal or high muscle mass. In addition, abdominal fat

mass has been associated with inflammation, insulin resistance, hyperadipokynaemia, dyslipidaemia and oxidative stress in CKD patients[19-22]. Postorino et al.[23] concluded that waist circumference is an independent predictor of all-cause and CV death from underweight to obesity in HD patients. Abnormal abdominal fat depots assessed by means of a conicity index in a sample of HD patients were linked to both inflammation and wasting as well as mortality risk factor[24]. Even though these observations do not necessarily imply that principles of vascular pathophysiology differ between overweight/obesity HD patients, recent evidence[25,26] indicates that abdominal visceral adiposity intervenes in the classical relationship between CV risk factors, inflammation and wasting compared with observed outcomes in the general population.

Hypoalbuminemia is the strongest predictor of CVD and mortality in dialysis patients when compared with classical risk factors (hypertension, hypercholesterolemia, DM, obesity)[27-30] and non-traditional risk factors (anemia, oxidative stress, and dialysis modality)[9,31]. A drop of 1-g/dL in s-albumin was associated with an increased mortality risk of 47% in HD patients[32]. Low serum prealbumin (s-prealbumin) concentration is also a recognized predictor of mortality in dialysis patients. Chertow et al.[33] reported that HD patients with s-prealbumin levels < 30 mg/dL showed a relative mortality risk of 2.64. Rambod et al.[34] found that baseline s-prealbumin concentrations < 20 mg/dL were associated with increased risk of mortality even in normoalbuminemic patients. A drop of 10 mg/dL in dialysis patients with s-prealbumin levels between 20 and 40 mg/dL was also associated with a 37% increase of death risk independent of s-albumin and inflammatory markers[34].

Inflammation is an overlapping condition whose prevalence in CKD patients is 30-50%[35-38] . Serum C-reactive protein (CRP) and interleukin-6 (IL-6) are known inflammation biomarkers and independent predictors of CVD and mortality in dialysis patients[39]. Some studies[38;40] have shown high morbidity and mortality rates associated with increase in acute-phase positive reactants (CRP, fibrinogen) and proinflammatory cytokines (IL-1, IL-6, tumor necrosis factor alpha: TNF-α) in HD patients. Honda et al.[38] reported that, in dialysis patients, IL-6 levels were predictors of CVD, while CRP and IL-6 levels were predictors of wasting, and that s-albumin, IL-6, and fetuin A were predictors of mortality. A novel actin-binding prognostic protein mainly secreted by myocytes and defined as plasma gelsolin has been recently involved as a useful biomarker of chronic inflammation, muscle mass, and immunity in CKD patients[41]. Follistatin, a myostatin binder, was highly increased in wasted and inflamed patients, which suggests a role as a potential mediator of wasting and survival in CKD patients[42].

Pro-inflammatory cytokines such as plasma leptin, ghrelin and visfatin have also been involved as potential anorexigens in dialysis patients. A strong negative association exists between appetite and the level of CRP, IL-6, and TNF-α in HD patients[43]. One third of CKD patients report anorexia or appetite loss; each unit increase in log of CRP levels was associated with a 49% increase in the relative risk of hospitalization and mortality rates over 12-months of clinical observation[43]. In uremic patients a closed link between high leptin levels with impaired appetite and inflammation[44] has been reported. In addition, a higher increase of des-acyl ghrelin has been found in anorexic HD patients than in non-anorexic patients[45]. Patients with low circulating ghrelin concentrations have exhibited an increase of CRP and leptin levels as well as the highest mortality risk from all-cause and CV death risk[46]. Visfatin a proinflammatory cytokine which is related to anorexia, inflammation and decreased circulating levels of amino acids in advanced CKD patients has been recently reported[47;48].

Phenotypic characteristics of Malnutrition/Protein-energy wasting/ Cachexia in hemodialysis patients

Different terms and definitions have been used for these conditions associated with substantial loss of body stores, low protein-energy intake and inflammation in CKD patients. The term of malnutrition classified as marasmus or kwashiorkor, respectively is the consequence of a substantial decrease in energy and/or protein intake. Marasmus usually presents a starved appearance with diminished skinfold thickness, body weight loss and is not associated with significant co-morbidity or non-inflammatory response (fig. 1) (table I). The classic study in healthy volunteers in Minnesota[49] showed that an inadequate intake of food itself does not contribute to wasting or cachexia. Under semi-starvation conditions and despite of 23% body weight loss and muscle wasting, s-albumin concentrations in these subjects dropped only slightly from 4.2 to 3.8 g/dL. In uremic patients on dialysis, Bistrian et al.[50] reported that s-albumin concentrations of marasmic patients were within the normal range. In fact, Chazot et al.[51] showed that s-albumin and s-prealbumin levels were not sole markers of marasmus in over 20 year-HD patients[51]. Conversely, kwashiorkor is characterized by a marked hypoalbuminemia and fluid overload. While kwashiorkor s patients respond quickly to nutritional therapy, in marasmic patients it may be slower. It must be taken into account that uremic anorexia, catabolic HD procedure and other related factors could retard the nutritional repletion in marasmus' patients.

The panel of experts from the International Society of Renal Nutrition and Metabolism (ISRNM)[10] has defined the term "protein energy wasting" (PEW) to describe the mild-moderate forms of wasting in uremic patients. According to this definition, PEW is confirmed when at least three of the four features are present:[10] a) altered laboratory markers (low s-albumin,
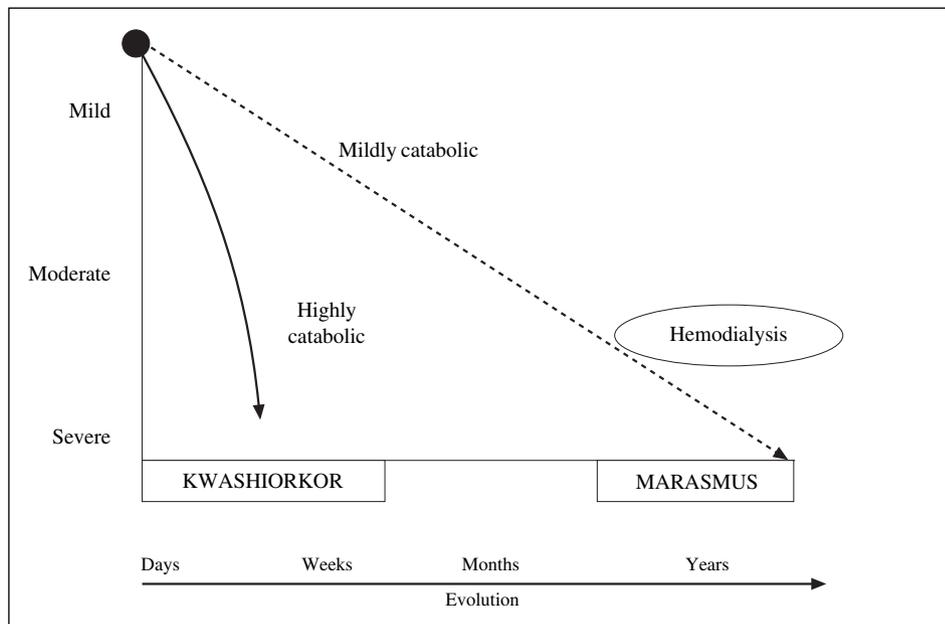
Fig. 1.—Proposed evolution of malnutrition type in hemodialysis patients. Kwashiorkor or protein malnutrition shown in the figure by a full black line is a highly catabolic process and develops in days or weeks. Marasmus or protein-energy malnutrition-represented by a dashed line- is a long-term (months or years) mild catabolic process.

Table I
Phenotypic characteristics and types of malnutrition in dialysis patients

Parameters	Malnutrition	Protein-Energy Wasting (PEW)	Cachexia
S-albumin	Normal or low	Low	Very low
Comorbidities	Uncommon	Common	Common
Inflammation	Absent	Present	Highly present
Food intake/Appetite	Insufficient/Loss of appetite	Highly insufficient/Anorexia	Very highly insufficient/Anorexia
Resting energy expenditure	Normal	Increased	Highly increased
Volume Overload	Mild	High	Very high
Oxidative stress	Increased	Highly increased	Highly increased
Protein catabolism	Normal or slighty increase	Increased	Highly increased
Reversible by dialysis and nutritional support	Yes	No	No

Source: Modified from Stenvinkel et al.[121]

prealbumin, or total cholesterol); b) reduced body mass (fat mass depletion or body weight loss); c) reduced muscle mass (muscle wasting or sarcopenia and reduced mid-arm muscle circumference) and, d) inadequate dietary intake (unintentional low dietary protein and energy intake[10] (table I) (fig. 2). In contrast to malnutrition, PEW is associated with the elevation of pro-inflammatory cytokines[52], endogenous muscle catabolism, hypoalbuminemia[53], uremic anorexia[43] and elevation of serum CRP[54] and CVD[55] in dialysis patients. Additionally, the ISRNM[10] suggested that the term cachexia be reserved for only the most severe forms of PEW. The emerging concept defined as cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss or decreased of muscle strength with or without loss of fat (corrected for overload volume)[56]. Cachexia differs in some diagnostic criteria of PEW in CKD patients. BMI < 20 kg/m^2 or weight loss of at least $5\% \leq$ in a period or equal or lower than 12 months and three of the following additional criteria are also required: anorexia, decrease muscle strength, fatigue, low fat-free mass index and altered laboratory parameters [s-albumin < 3.2 g/dL, anaemia (haemoglobin < 12 g/dL), including elevated inflammatory markers such as CRP or IL-6)] (table I). The differences in PEW compared to cachexia is that the latter encompasses only severe forms of metabolic depletion, whereas PEW is referred to mild degrees of depleted fat and muscle body mass.

Nutrition care process as systematic method in clinical practice

The Academy of Nutrition and Dietetics uses the concept Nutritional care process (NCP) as *"a systematic problem-solving method that nutrition professionals use to critically think and make decisions to*
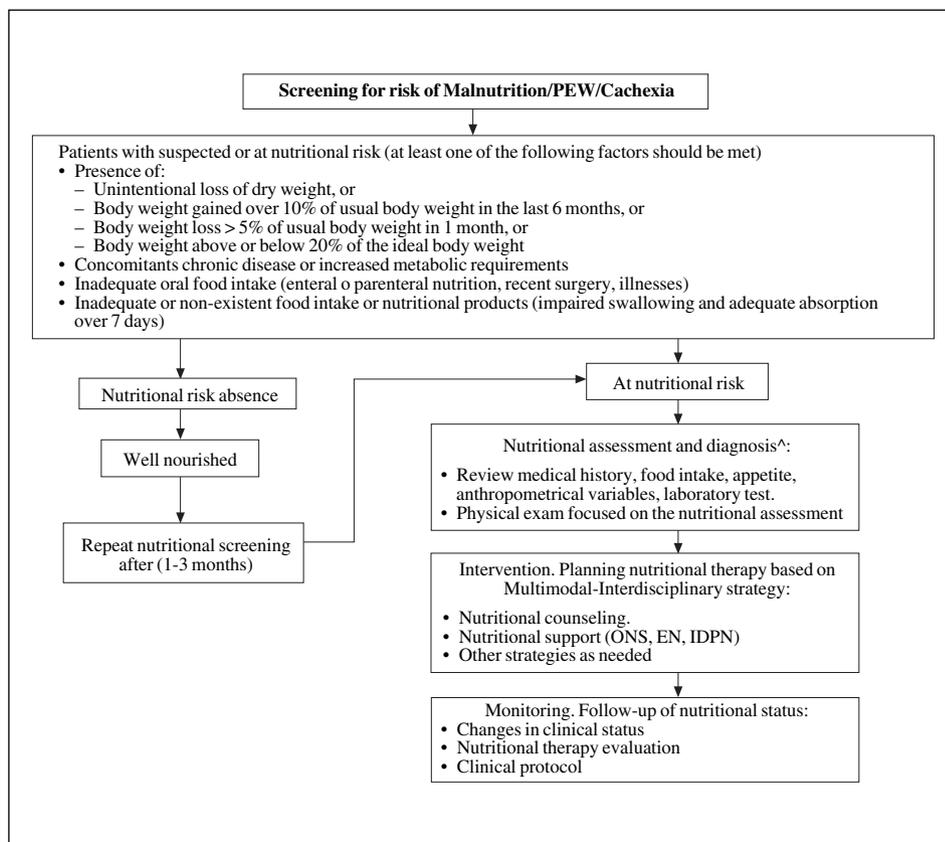
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│  Screening for risk of Malnutrition/PEW/Cachexia  │
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Patients with suspected or at nutritional risk (at least one of the following factors should be met)
• Presence of:
   – Unintentional loss of dry weight, or
   – Body weight gained over 10% of usual body weight in the last 6 months, or
   – Body weight loss > 5% of usual body weight in 1 month, or
   – Body weight above or below 20% of the ideal body weight
• Concomitants chronic disease or increased metabolic requirements
• Inadequate oral food intake (enteral o parenteral nutrition, recent surgery, illnesses)
• Inadequate or non-existent food intake or nutritional products (impaired swallowing and adequate absorption over 7 days)

Nutritional risk absence

Well nourished

Repeat nutritional screening after (1-3 months)

At nutritional risk

Nutritional assessment and diagnosis^:
• Review medical history, food intake, appetite, anthropometrical variables, laboratory test.
• Physical exam focused on the nutritional assessment

Intervention. Planning nutritional therapy based on Multimodal-Interdisciplinary strategy:
• Nutritional counseling.
• Nutritional support (ONS, EN, IDPN)
• Other strategies as needed

Monitoring. Follow-up of nutritional status:
• Changes in clinical status
• Nutritional therapy evaluation
• Clinical protocol

Fig. 2.—Proposed clinical nutrition screening algorithm in hemodialysis patients. ^Steps based on Nutrition Care process[14,58]. ONS, Oral nutritional supplements; EN, enteral nutrition; IDPN, intradialytic parenteral nutrition.

address nutrition-related problems and provide safe and effective quality nutrition care"[57,58]. This method consists of four consecutive steps: nutrition assessment, diagnosis, intervention, and nutrition monitoring or evaluation. It is a stepwise approach to conducting thorough nutritional assessment to provide tailored nutrition care in renal patients[14].

First and Second steps of Nutrition Care process: Nutritional assessment and diagnosis

Nutrition assessment consists of collecting biochemical data, anthropometric measurements, physical examination findings, food/nutrition history and patient history. Guidelines on Nutrition[11,13,59] recommend periodic assessment of nutritional status in the absence of malnutrition every 6-12 months in patients younger than 50. Over 5 years on HD and/or aged over 50, it is recommended every 3 months[59]. The conjoint use of subjective (nutritional screening, clinical history and physical exam) and objective (anthropometrical and laboratory tests) methods to assess and diagnose nutritional status is required.

Nutritional screening is an identification step that is outside the actual care and provides access to the NCP by referral and/or screening of individuals or groups for nutritional risk[58] (fig. 2). Subjective global assessment (SGA) has been applied to subjectively evaluate patients

at nutritional risk[59]. A refinement of SGA known as the malnutrition-inflammation score (MIS)[60] has been significantly associated with coronary heart disease[61], endothelial dysfunction[62], poor quality of life[63], anorexia[43], hyporesponsiveness to erythropoietin[64], hospitalization and mortality in dialysis patients[60,63]. Even though nutritional scoring systems are valuable tools for identifying dialysis patients at risk of malnutrition/PEW/cachexia, a global assessment of nutritional status should consider a patient's clinical history together with anthropometrical, biochemical, and inflammatory markers (fig. 3). The Kidney Disease Outcomes Quality Initiative (KDOQI)[13] asserts that a single marker by itself does not provide a comprehensive assessment of nutritional status and, thus recommends a collective evaluation of multiple nutritional parameters.

Clinical nutrition history identifies changes in appetite, food intake (likes and dislikes), body weight loss, medication use, and interactions with other pathologies that might justify the modifications in one or several nutritional parameters. Physical examination by identifying clinical signs including changes in adipose tissue and muscle mass, edema and/or ascites, paleness, bruising, and skin lesions are indicators of nutritional risk (fig. 3). Additionally, dry body weight, skinfold thickness and mid-arm muscle circumference provide valuable information longitudinally on nutritional status. Anthropometric measures should be performed immediately after the dialysis session in the non-domi-

Nutritional anamnesis	Goal-oriented physical exam to nutritional assessment
– Etiology of CKD. Time on hemodialysis and type of treatment (short daily hemodialysis, standard hemodialysis, hemodiafiltration on line). – History of recent and unintentional body weight loss. – Information on recent changes in appetite, eating habits, gastrointestinal symptoms affecting nutritional status. Food intake preferences and aversions, intolerances and food allergies. – Analysis of dietary intake compared with the usual and recommended dietary allowances. Degree of fullness. Dysgeusia. Nausea/vomiting. – Intestinal rhythm: diarrhea, constipation, steatorrhea. – Toxic habits: alcohol, smoking, other drugs. – Disorders of chewing/swallowing. Dysphagia. Odynophagia. Surgery or gastrointestinal disease. – History of prior nutritional guidance including multivitamins/minerals supplements and others. – Pharmacotherapy. – Level of physical activity. – Psychological, social or economic factors that affect nutritional status.	– **Subject characteristics and clinical signs of nutritional deficiencies.** Skin (colour, lesions, pigmentation, petechiae, ecchymosis, moisture, turgor, texture), nails (shape, colour, curvature, injuries), face (shape, symmetry, colour), eyes (conjuntive, angles), nose (nasolabial seborrhea), oral cavity mouth (angular cheilosis, no taste buds, dysgeusia, hypogeusia), neck (engorged veins, hypervolemia), abdomen (appearance, circumference, stomata, bowel sounds). – **Loss of subcutaneous fat.** Face (eyes and cheeks), skinfolds thickness (triceps, biceps) and thorax. In normo-weight patients suborbital fat accumulation resembles a mild edema. – **Loss of muscle mass.** Face (depletion of temporal fossa), shoulders, collarbone, back (scapula and ribs), hands (interosseous muscles) and legs (quadriceps, calf), – **When protein energy wasting.** Failure to clamp to shoulder muscle (acromium bulging); prominent clavicle, depression around the scapula (loss of tissue in the suprascapular depressions) and intercostal muscles; flat or depressed, interosseous muscle area (deep depression between the thumb and index finger), muscle atrophy loss tone quadriceps. – **Signs of edema and ascites** (navel inverted). Discard overhydration or inadequate dialysis. Consider hypoalbuminaemia by hemodilution in the presence of edema. Explore ankles (presence of fovea) or sacrum bedside in immobilized patients.

Nutritional status assessment and diagnosis

Anthropometry	Laboratory parameters of nutritional interest
– Body weight (actual, usual, dry, ideal, percentage of ideal body weight, percent of body weight on time). – Height. – Body mass index. – Midarm circumference, triceps, skinfolds thickness, mid arm muscle circumference. – Waist circumference. – Body composition analytis: Bioimpedance, dual-energy X ray absorptiometry.	– Glucose pre-dialysis, hemoglobin A1c (diabetic nephropathy). – Lipid profile (predialysis): serum triglycerides, total cholesterol, cHDL, cLDL, Lpa* Homocysteine*. – Visceral protein profile: Total protein, serum albumin, prealbumin and transferrin. – Adequacy in dialysis: predialysis-postdialysis serum urea, urea reduction rate (URR), Kt/V urea, weekly Kt/V urea (daily HD). – Serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone, thyroid-stimulating hormone, T4 free, L. – Serum creatinine. Uric acid. – Sodium, potassium, total CO_2. – Ferric profile: iron, serum transferrin, percent saturation of transferrin, serum ferritin. – Inflammations: C-reactive protein, IL-6*, TNF-α*. – Hemoglobin, hematocrit, RBC, MCV. Leukocytes, platelets, total lymphocyte count. – Vitamin B_{12}, folic acid. – Others: protein catabolic rate (PCR), $β_2$-microglobulin, plasma leptin, adiponectin, visfatin, gelsolin

*Fig. 3.—Comprehensive assessment and diagnosis of nutritional status in hemodialysis patients. The details of its four compounds (nutritional anamnesis, goal-oriented physical exam to nutritional assessment, anthropometry, and laboratory parameters of nutritional interest) are based on Nutrition Care process[14,58]. *Additional research is recommended for parameters with asterisks[2].*

nant or free vascular access arm[59]. More sophisticated methods such as computed tomography, magnetic resonance image scans, and dual-energy X ray absorptiometry (DXA) are used for body composition analysis[13].

Bioelectrical impedance analysis (BIA) is a validated method for evaluating hydration status and body composition in CKD and dialysis patients[65]. Phase angle (PA) emerges as an additional indicator of nutritional status in wasted patients. Thus, the relative mortality risk of patients with PA values < 3° was twice higher than patients with PA ≥ 4º (target)[66]. A study conducted in 64 HD patients[67] analyzed the suitability of the PA as a nutritional-inflammatory indicator. The prevalence of PEW was 81.2% in patients with a PA < 4º and 35% in those with a value ≥ 4º[67]. Prevalent HD patients with a PA < 4º were shown to be wasted and inflamed[67]. The conjoint use of BIA measurements, biochemical-nutritional parameters and inflammatory biomarkers may help to estimate dry body weight in hypoalbuminemic patients[67]. Current clinical practice guidelines[10,13,59] do not include inflammatory biomarkers and body composition analysis measured by BIA. The evaluation of s-albumin and s-prealbumin [≥ 3.8 g/dL and ≥ 28 mg/dL, respectively (target)][59] together with one marker of inflammation (e.g. CRP) and management of nutritional status may help to identify HD patients at high risk of mortality who might benefit from nutritional support[68].

Nutrition diagnoses list the problem, etiology, signs/symptoms (PES format)[14]. The problem (P) describes the alterations in the patient's nutritional status. The etiology (E) or related factors are those factors that contribute to the cause of a particular problem. Finally, the signs and symptoms (S) are the defining characteristics obtained from the objective and subjective nutrition assessment data.

Third step of Nutrition Care Process: Clinical approach to nutritional intervention

Nutrition intervention is needed for formulating and implementing the plan of nutrition care. There are four categories taken into account that identify the various types of nutrition interventions: a) adequacy of dialysis dose and scheme of hemodialysis (individualized treatment of dialysis: ultrapure water, biocompatible membranes, increasing the frequency-daily HD); b) nutritional counseling and oral nutrition supplementation; c) nutritional support (enteral nutrition and, intradialytic parenteral nutrition); d) coordination of nutrition care. In addition, interventions tailored to each one of type (malnutrition/PEW/cachexia) are required (fig. 4).

Adecuacy of dialysis dose and intensified dialysis strategies

Nutrition intervention remarkable factors to take into account in HD patients are the adequacy of the delivered dose (Kt/V urea single pool ≥ 1.2) and vascular

Fig. 4.—Proposed decisional algorithm in wasting patients. The clinical algorithm focuses on malnutrition/PEW/cachexia, aiming to select different types of nutritional monitoring/ evaluation based on affirmative (Yes) or negative (Not) responses in each one patient. PEW patients, as defined by their inadequate food intake (DEI ≤30 kcal/kg/day and DPI ≤1.2 g/kg/day), should receive dietary counseling and ONS. In addition, IDPN is indicated in patients unable to meet their nutritional requirements due to low ONS compliance (represented by dashed line); IDPN and ONS could be administered altogether. Patients with a functional gastrointestinal tract showing cachexia/PEW and/or those under stress conditions should receive enteral nutrition. EN: Enteral nutrition; GI: Gastrontetinal; IDPN: Intradialytic parenteral nutrition; ONS: Oral nutritional supplements; PEW: Protein energy wasting; TPN: Total parenteral nutrition.

access status. Dialysis adequacy is a prerequisite for achieving and/or maintaining nutritional status. In the HEMO study[69] no significant differences were found between high-flux and low flux dialysis membranes as well as within high and low dialysis doses as mortality causes. At present, the doses of dialysis that can improve nutritional status are still unknown.

Vascular access is a crucial factor in dialysis as a potential focus of inflammation. A low systemic inflammatory response, maximum biocompatibility of the system, and control of chronic foci of infection should be achieved[70]. Observational studies[71-73] and randomized controlled trials[74,75] improving the efficiency of HD, by increasing frequency and duration of HD treatment, demonstrated better volume control and clearance efficiency of uremic toxins, middle molecular weight compounds and improved quality of life. On-line hemodiafiltration (HDF) has attracted much attention as a promising optimum modality of HD due to

efficient improvement in dialysis adequacy and clearing small and large-size uremic toxins[76]. Studies on HDF patients showed fewer requirements of phosphate binders, better control of hypertension with fewer use of antihypertensive drugs, less doses of erythropoietin stimulating agents, and iron supplements as a result of abolishing or reducing the inflammatory response[77]. However, a recent study[78] showed that treatment with HDF did not reduce all causes of mortality compared with treatment with low-flux membranes in conventional HD therapy as non-significant differences in s-albumin, s-CRP and s-cholesterol during follow-up were found[79]. Further studies should be conducted for elucidating this issue.

Daily short or long-nocturnal HD in malnourished/PEW/cachectics patients are recommended as adjunctive therapy for 6-12 months[59]. Daily dialysis results in less fluid overload, fewer medications and dietary restrictions, better blood pressure and phosphate

control. Hemodialysis tailored to patient needs should be considered.

Nutritional counseling and oral nutrition supplementation

The recommended dietary energy and protein intakes for HD patients are 30-35 kcal/kg/day and 1.2 g protein/kg/day, respectively[13,59,80]. Low dietary energy intake (on dialysis and non-dialysis treatment days) has been reported in these patients[81]. Preventive nutritional strategies include nutritional counseling adapted to each stage of CKD and dialysis modality, might help to reduce and/or prevent malnutrition and some of the PEW conditions. It is important to note, that prolonged and often unnecessary periods of fasting, multiple laboratory tests, missed meals due to dialysis, and restrictive diets during periods of intercurrent diseases are potential precursors of malnutrition and wasting. Periodic re-evaluation and nutritional counseling are essential practices even in well-nourished patients. To ensure their nutritional intake HD patients must receive nutritional counseling and routine management of nutritional status[82;83]. Oral nutrition supplementation (ONS) is the first choice of nutritional support in malnourished/PEW patients whose spontaneous intakes are ≤ 20 kcal/kg/day[84]. ONS can provide additional 7-10 kcal energy/kg/day and 0.3-0.4 g protein/kg/day to meet dietary recommendations[85]. Beutler et al.[86] compared the results of nutritional counseling alone with supplemented HD patients. S-albumin improved significantly in patients given ONS, but decreased in those who only received nutritional counseling. Seven of the twelve studies listed in table II, are randomized controlled trials reporting significant improvements in nutritional status. Recently, a retrospective matched-large cohort study[87] of in-center HD patients with low s-albumin was performed. A total of 5,227 HD patients receiving intradialytic ONS with matched-pairs controls were compared. In the intention-to-treat analysis, survival was 9% and up to 34% in the as-treated group when compared with controls. Results of the study support that providing ONS coincident with three-weekly HD sessions in hypoalbuminemic patients may increase protein and energy intakes and improve survival rate[87]. To achieve protein and energy intakes, ONS should be received two-to-three times a day, preferably one hour after each main meal[85] as well as ONS given during dialysis session which increases adherence to the treatment and improves nutritional status[88].

Nutritionally complete formulas can be used, either as ONS or even as modular products (carbohydrates, lipids, proteins). Protein modular products may be ineffective in malnourished/PEW patients unless administered together with adequate energy intake. Hence, an ONS with 100% whey protein has a high biological value, and an absence of free phosphorous content may be preferred. Disease-specific formulae for CKD and dialy-sis patients (high energy density, low potassium, sodium and phosphorus) are tailored for the requirements of these patients. Cockram et al.[89] studied the effect of three medical nutritional products (one standard formula and two disease-specific formulas) in well-nourished HD patients. Disease–specific formulas improve serum phosphorus levels and the calcium/phosphorus ratio in comparison to the standard formulae. Fouque et al.[90] reported that renal-specific ONS might prevent malnutrition in HD patients without increasing the need for phosphate binders.

A recent randomized controlled trial[91], assessed the effect of combined disease-specific formulas with anti-inflammatory and antioxidative properties in HD patients during the hemodialysis session. Daily intakes of disease-specific formulas for 3-month observational period were well tolerated and associated with 0.2 g/dL improvement of serum albumin concentration in HD patients.

However, the principal limitations of ONS involve low patient compliance, gastrointestinal intolerance, unpleasant flavor and long-time use of the same formulas. High-energy formula (1.5-2 kcal/mL) to avoid volume overload is recommended[92,93]. The combination of ONS and nutritional counseling is safe and may be useful in terms of improving nutritional status. To date, ideal ONS (100% whey protein, free from phosphorous, potassium and vitamin A), has not been formulated in HD patients. Current disease-specific formulas with antioxidative and anti-inflammatory components require further considerations.

Nutritional support

The second step of nutrition intervention for malnourished/PEW/cachectics patients who do not respond successfully to nutritional counseling and ONS involves: a) intradialytic parenteral nutrition (IDPN), alone or in combination with ONS, and b) enteral nutrition by nasoenteral tube feeding or ostomy (EN) (fig. 4).

IDPN involves the administration of a macro and micronutrient solution through the venous chamber and does not require additional vascular access in HD treatment. The volume administered can be ultrafiltrated during the HD session. As shown in figure 4, PEW/cachectic patients should receive daily nutritional support to achieve the nutritional requirements. Nonetheless, to date, IDPN studies on survival are controversial[94]. Dezfuli et al.[94] demonstrated that s-albumin levels increased 3.5-fold in hypoalbuminemic HD patients receiving IDPN. Joannidis et al.[95] found that IDPN increased body weight but did not modify the inflammatory status of 6 patients. Foulks et al.[96] reported a body weight gain of at least 10% and a significant reduction of hospitalization and mortality rates in 45 hypoalbuminemic HD patients who received IDPN for 6 months. In a retrospective study, Chertow et al.[97] compared 1,679 HD patients who received one or more infusions of IDPN with 22,517

Table II

Randomized and non-randomized controlled trials of oral nutritional supplementation in hemodialysis patients[1]

Study	Patients (n) and nutritional status. Intervention modality, study design and duration	Results and clinical nutrition significance
Milano et al. (1998)[122]	22 HD patients. Moderate to severe PEW. Glucose polymer (100 g per day, 380 kcal). Non RCTs for 6 months	Increased body weight, BMI and triceps skinfold thickness at 3 and 6 months. Few gastrointestinal adverse effects. Increased triglyceride levels (136 ± 40 to 235 ± 120 mg/dL). Fat mass was maintained for 6 months after ONS was discontinued.
Kuhlmann et al. (1999)[123]	18 HD patients. Malnourished (based on SGA and biochemical parameters). Renal-specific ONS (Renamil®, Kora Healthcare, Dublin, Ireland) and Renapro® (Kora Healthcare) vs. usual diet. Non RCTs for 3 months	Renal-specific ONS showed increased weight and s-albumin levels (1.0 ± 0.5 g/dL); weight gained correlated with dietary energy intake. Unchanged s-prealbumin and cholesterol levels. Good compliance and tolerance.
Patel et al. (2000)[124]	17 HD patients. Low nPCR and DPI <1.2 g/kg/day. Standard ONS (Ensure®, Abbott Nutrition and Protein-Forte®, Fresenius Kabi, Bad Homburg, Germany). Non RCTs for 8 months	Baseline s-albumin 4.2 g/dL. At baseline nPCR of 0.95 increased up to 1.21 g protein/kg/day. DPI increased from 0.75 g/kg/day to 1.10 g at 2 months and 0.78 g/kg/day at 8 months.
Sharma et al. (2002)[125]	40 HD patients: Cases (10 and 16); Control (14). Baseline s-albumin 3.4 g/dL. Renal-specific ONS (Reno care® II, Criticare, Mumbai, India) 500 kcal and 15 g protein vs. standard home-prepared ONS (500 kcal and 15 g protein) vs. routine care. RCTs for 1 month	Improved dry body weight and BMI in both groups. Significant increase in s-albumin in the groups receiving renal-specific ONS and home-prepared ONS vs. routine care (3.9 g/dL and 4.0 g/dL). Mild-hypophosphatemia in supplemented group. Good tolerance
Caglar et al. (2002)[88]	85 HD patients. S-albumin ≤3.7 g/dL. In-center Renal-specific ONS (Nepro®, Abbott Nutrition) thrice-weekly on hemodialysis (415 kcal and 16.6 g protein per session). Non RCTs for 6 months	No changes from baseline levels over a 3-month period. During intervention period, s-albumin levels increased from 3.33 g/dL to 3.6 g/dL. S-prealbumin increased from 26.1 mg/dL to 30.7 mg/dL. SGA increased by 14%. Non-significant increase in BMI and dry body weight.
Kalantar-Zadeh et al. (2005)[126]	40 HD patients: Case (20); Control (20). In dialysis center. Patients with s-albumin ≤3.8 g/dL: Nepro®/Oxepa® (Abbott Nutrition) thrice-weekly on HD. RCTs for 1 month	S-albumin levels increased between 18th and 26th days of intervention. No adverse effects observed. Well-tolerated including oral Oxepa®.
Leon et al. (2006)[127]	180 HD patients. S-albumin <3.7 g/dL. Targeting several nutritional barriers (ONS was a small component of intervention). RCTs for 12 months	Significant increase in albumin levels, DEI, and DPI in intervention group vs. control group. No relationship between change in albumin levels and inflammatory markers.
Cano et al. (2007)[98]	186 HD patients: ONS (93); ONS + IDPN (93). ONS vs. ONS + IDPN. ONS: 5.9 kcal and 0.39 g protein/kg/day. IDPN: 6.6 kcal and 0.26 g protein/kg/day. RCTs for 12 moths	After 3 months: increased BMI, s-albumin and s-prealbumin levels in both groups, regardless of CRP. No inter-group differences. An increase in s-prealbumin levels of >30 mg/dL within 3 months predicted improved 2-yr survival, hospitalization rate and Karnofsky score in all patients.

Table II (cont.)

Randomized and non-randomized controlled trials of oral nutritional supplementation in hemodialysis patients[1]

Study	Patients (n) and nutritional status	Intervention modality, study design and duration	Results and clinical nutrition significance
Fouque *et al.* (2008)[90]	86 HD patients: Case (46). Control (40). Baseline s-albumin of 3.5 g/dL in both groups	Renal-specific ONS (Renilon®, Nutricia, Schiphol, The Netherlands) vs. standard care. RCTs for 3 months	Increased DPI and DEI, and improved SGA and quality of life in the group receiving ONS. No differences in s-albumin or s-prealbumin levels between groups. Change in s-albumin and s-prealbumin correlated with protein intake. Phosphatemia was unaffected and use of phosphate binders remained stable or decreased.
Scott *et al.* (2009)[28]	88 HD patients	One can of renal specific ONS (Nepro®) thrice-weekly during hemodialysis vs. standard care. Non RCTs for 3 months.	No differences in s-albumin concentration between baseline and 3 months in the nutrition group but, decreased in controls. Quality of Life-Short Form score improved significantly in the treated group. Good tolerance of ONS. Compliance 80%
Malgorzewicz *et al.* (2011)[29]	55 HD patients: PEW (30) Control (25)	Renal-specific ONS (Renilon®, Nutricia, Schiphol, The Netherlands) 125 mL twice a day vs. standard care. RCTs for 3 months	S-albumin, s-prealbumin and plasma leptin had increased in 30 PEW patients after 3 months of intervention, regardless of CRP levels in both groups (NS).
Rattanasompattikul *et al.* (2013)[91]	74 hypoalbuminemic HD patients: Group A (19) Group B (22) Group C (22) Group D (21)	Group A: Nepro®+Oxepa® (2 cans) + PTX (400 mg). Group B: Nepro®+Oxepa® (2 cans) + placebo PTX. Group C: Placebo (2 cans) + PTX (400 mg). Group D: Placebo (2 cans) + Placebo PTX RCTs. Intervention: Thrice weekly while on HD session for 16 weeks.	Significant increments in s-albumin after all three interventions were found, but not in placebo group. In the assigned treatments only ONS was a significant predictor of post-trial albumin. Unchanged inflammatory biomarkers (CRP, IL-1b and IL-6). No significant decline in serum leptin with PTX treatment. Four patients from 93 randomized patients discontinued the study due to gastrointestinal side effect.

[1]Randomized controlled trials and crossover studies were included. Abbreviations: CRP, C- reactive protein; DEI, dietary energy intake; DPI, dietary protein intake; IDPN, Intradialytic parenteral nutrition; HD, hemodialysis;IL-1b, interleukin 1b; IL-6, interleukin 6; nPCr, normalized protein catabolic rate; NS, no significant; ONS, oral nutritional supplements; PTX, pentoxifylline; RCTs, Randomized controlled trials; SGA, subjective global assessment.

non-IDPN controls. The relative odds ratio for mortality depends highly on the decrease in s-albumin levels of the IDPN patients with ≤ 3.0 g/dL and on their increase in patients with > 4.0 g/dL[97]. Furthermore, a prospective randomized controlled study[98] evaluated the effects of combining IDPN and ONS therapy with respect to the ONS treatment alone in 182 malnourished HD patients over one-year period. These investigators reported that the patients administered with IDPN together with ONS did not improve hospitalization rates, Karnofsky scores, BMI, biochemical parameters on 2-year mortality rates in comparison to patients receiving ONS alone. Multivariate analysis indicated that only the ONS group showed sustained s-albumin and prealbumin improvements after 1-year. Interestingly, s-prealbumin levels of ≥ 30 mg/dL during the first 3 months of ONS were associated with a decrease in the 2-year mortality rate[98]. IDPN should be considered more of a therapeutic strategy for intravenous nutritional supplementation than a total nutrition support. Clinical guidelines on parenteral nutrition proposed in order to ensure optimal tolerance[84]: a) IDPN should be infused at a constant rate during 4 h dialysis session; b) IDPN delivery should be progressively increased during the first week to a maximum of 16 mL/kg/day without ever exceeding 1000 mL/per HD session; and, c) ultrafiltration should be controlled and 75 mmol Na+ added per liter of IDPN solution to compensate for sodium losses[84]. IDPN is recommended whether s-albumin < 3g/dL[11].

In addition, IDPN appears to reverse body protein catabolism during the HD session and to normalize the amino acid profile[99,100]. Losses of 6-8 g of amino acids into the dialysate per dialysis session were reported[101]. Pupim et al.[99,100] investigated the effect of IDPN on protein metabolism in two randomized studies. In the first study[99], seven HD patients were randomized with or without IDPN two hours before, during, and two hours after the HD session by using a primed-constant infusion of L-(1-^{13}C) leucine and L (ring-^{2}H$_5$) phenylalanine. IDPN induced a large increase in whole-body protein synthesis and a significant decrease in whole-body protein proteolysis associated with an increase in forearm muscle protein synthesis getting a positive protein balance in whole body and forearm muscle compartments[99]. In their second study, Pupim et al.[100] demonstrated that exercise combined with IDPN doubled forearm muscle essential amino acid uptake and net muscle protein accretion during the HD session. While the anabolic benefits of of IDPN provides only a transient improvement during HD session, ONS resulted in persistent anabolic benefits for muscle protein metabolism in postdialysis when anabolic benefits of IDPN had disappeared[102].These results show that IDPN contributes to synthesis rather than catabolism and could counterbalance the catabolic effect of hemodialysis procedure.

PEW/cachectic patients who have spontaneous food intakes < 20 kcal/kg/day or are under stress conditions should receive daily nutritional support by enteral nutrition (EN). Nutritional support by tube feeding is less expensive, produces fewer metabolic and septic complications, and contributes much more to the digestive tract morphology maintenance than intravenous feeding[84]. EN should be used when nutritional counseling, ONS therapy and IDPN are unable to achieve nutritional requirements[92], or when stress conditions are presented[84]. Enteral nutrition guidelines[92] recommend nutritional support in CKD patients with a BMI < 20 kg/m², body weight loss >10% over the previous 6 months, s-albumin < 3.5 g/dL, and s-prealbumin < 30 mg/dL. EN by tube feeding (nasogastric or nasojejunal tube), or for long-term ostomy [percutaneous endoscopic gastrostomy (PEG) or percutaneous endoscopic jejunostomy (PEJ)], are preferred to intravenous nutritional support. Nasojejunal tube feeding is recommended in patients with gastroparesis or in those who are non-responsive to prokinetic drugs[92]. PEG or PEJ is indicated in PEW or cachectics patients who do not respond to conventional therapy for a period of more than 4 weeks[92]. Even though the use of specific renal-disease formulas is preferred, standard formulas whose compositions are adapted to the nutritional requirement of the patient, can also be used[92]. Oligomeric formulas containing partially digested proteins are indicated when dyspepsia and/or malabsorption are involved.

However, when EN cannot meet individual nutritional requirements, or it is contraindicated –due to GI dysfunction or other pathological conditions (peritonitis, intestinal obstruction, ileus, GI ischemia, or enterocutaneous fistulas)–, total parenteral nutrition (TPN) by a central or peripheral vascular access is recommended to allow the digestive tract to recover from the effects of the concomitant condition.

Fourth step of Nutrition Care Process: Nutrition Monitoring and Evaluation

The purpose of monitoring and evaluation is to determine the degree to which progress is being achieved[57]. It requires and active commitment to measuring and registering the appropriate outcome indicators relevant to the nutritional diagnosis' signs and symtoms. The re-evaluation of outcomes may also involve additional data collection in order to explore why the nutritional changes have not occurred as expected. Systematic use of these process provides consistency in the practice, adds value and demonstrates effectiveness of nutritional care.

Future adjuctive therapies

Combinations of new and promising therapeutic strategies including the use of appetite stimulants, growth hormone (GH), ghrelin agonist, melacortin-4

receptors (MC4-R) antagonists, anabolic steroids and anti-inflammatory drugs (steroids, pentoxifylline, statins, ACE inhibitors and anticytokine antibodies) are under clinical evaluation. These therapies are based on several studies[91;103-117] which are briefly commented on.

Physical exercise activates peroxisome proliferator-activated receptor-gamma (PPAR-γ) and increases insulin-like growth factor type 1 (IGF-1), insulin sensitivity, and protein synthesis[103,104]. Omega-3 fatty acids can stimulate PPAR-γ by decreasing muscle tissue inflammation[103]. Fish oil supplementation potentiates the effect of exercise[103] and decreases the inflammatory response to the HD procedure[105,106]. Appetite stimulants (hydralazine sulfate, metoclopramide, prednisolone, megestrol acetate) may also improve nutritional status. Pentoxifylline with or without ONS combination showed a significant improvement in s-albumin concentrations[91]. Emerging therapeutic strategies with some effective results as thalidomide, COX-2 inhibitors, proteosome inhibitors and anti-myostatin peptibody are still under clinical evaluation. Recombinant human growth hormone (rhGH) and IGF-1 improved protein synthesis in dialysis patients participating in pilot studies with pentoxifylline[107,108]. Garibotto et al.[109] showed significant improvement in net muscle protein balance over a 6-week administration of 50 μg rhGH in cachectic HD patients. Uremia produces peripheral resistance to anabolic hormones (GH, insulin, IGF-I) and their administration has been shown to improve whole-body protein homeostasis. Ghrelin or its analogs may constitute an orexigen therapeutic strategy in CKD patients. In two subsequent studies[110,111] subcutaneous ghrelin injection achieved in short-intermediate term induced a sustained positive change in anorexic dialysis patients. Nonetheless, ghrelin infusion induces lipolysis and insulin resistance independently of GH and cortisol[112]. Further studies are needed to evaluate the adverse side effects and the long-term efficacy of ghrelin in improving appetite and nutritional status. Recently, oral administration of active MC4-R antagonists has been proposed as a promising candidate for the treatment of anorexia and involuntary weight loss in PEW/cachectic patients. In a mouse model of uremic cachexia, Cheung et al.[113] demonstrated that intraperitoneal administration of NBI-12i (a MC4-R antagonists) stimulated food intake and increased lean body mass and fat mass in treated uremic mice. However, to date, reports of the effects of MCR4-R antagonists have not been presented in human studies. Antioxidant and anti-inflammatory nutrients as omega-3 fatty acids, gamma-tocopherol and phytoestrogens and physical exercise have been proposed. Cholecalciferol[114], gamma-tocopherol and docohexanoic acid[115] induced inflammation decrease in HD patients. In addition, nandrolone decanoate in association with exercise increases lean body mass, quadriceps muscle, and knee extensor muscle strength[116,117]. The combination of aminoacids supplement has been tested. The mixture of hydroxyl-methyl-butyrate, arginine and glutamine was shown to be effective in increasing fat-free mass of middle-aged and elderly patients with advanced-stage cancer[118] and in younger subjects with AIDS-associated wasting[119,120]. The potential benefit of these therapies merits further research. Randomized controlled and large cohort studies are needed to determine the multimodal beneficial effects and clinical outcome of these promising therapeutic strategies.

Conclusions and future remarks

This article has reviewed some issues with regard to NCP (assessment, diagnosis, intervention and monitoring) as well as novel adjunctive therapies to be applied in HD patients. Lastly, clinical research for the prevention and treatment of malnutrition/PEW/cachexia has been conducted. There is controversy on the development of malnutrition or other conditions such as inflammation or comorbidity related to PEW or cachexia. However, there seems to be less disagreement concerning the consistent association of nutritional status with poor outcomes in dialysis patients. PEW/cachexia is a predictable event in many HD patients, readily diagnosed by assessment of body weight, change in appetite, low albumin and a concomitant increase in bioinflammatory markers. At the onset and throughout the course of illness, HD patients should have access to a nutrition team, to take part in a rehabilitation program tailor-made to their needs and consider the use of specific nutritional support and pharmacologic interventions. As a compromised nutritional status is still a common feature of HD patients, the above simple assessments should form a consistent part of the clinical procedure to diagnoses and treatment as early as possible in order to improve survival and positively affect patients' quality. Furthermore, studies on nutritional status should also incorporate the beneficial role of tailored exercise programs. Novel and complementary therapies such as oral active MC4-R antagonist and proteosome inhibitors may be promising candidates for attenuating disease-associated anorexia and muscle wasting of PEW/cachectics patients. Further studies with nutrients and compounds as hydroxyl-methyl-butyrate and branched chain amino acids with a particular role in protein synthesis should be conducted. From all the epidemiological data analyzed, nutrition support as a unimodal therapy was not completely able to reverse mild PEW and cachexia. Thus, further holistic nutrition-dialysis approaches are required.

Statement of authorship

All authors have significantly contributed to the paper, had access to all the data in the study and approved the final version of the manuscript to be submitted for publication. MR is the corresponding

author and guarantor and the paper and has contributed to the design, writing and discussion of the paper. GB and FJS-M have contributed to the critical reading and discussion of the paper.

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