Nutritional status and the risk of malnutrition in older adults with chronic kidney disease — implications for low protein intake and nutritional care: A critical review endorsed by ERN-ERA and ESPEN

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SUMMARY

Increased life expectancy is posing unprecedented challenges to healthcare systems worldwide. These include a sharp increase in the prevalence of chronic kidney disease (CKD) and of impaired nutritional status with malnutrition-protein-energy wasting (PEW) that portends worse clinical outcomes, including reduced survival. In older adults with CKD, a nutritional dilemma occurs when indications from geriatric nutritional guidelines to maintain the protein intake above 1.0 g/kg/day to prevent malnutrition need to be adapted to the indications from nephrology guidelines, to reduce protein intake in order to prevent or slow CKD progression and improve metabolic abnormalities. To address these issues, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Renal Nutrition group of the European Renal Association (ERN-ERA) have prepared this conjoint critical review paper, whose objective is to summarize key concepts related to prevention and treatment of both CKD progression and impaired nutritional status using dietary approaches, and to provide guidance on how to define optimal protein and energy intake in older adults with differing severity of CKD. Overall, the authors support careful assessment to identify the most urgent clinical challenge and the consequent treatment priority. The presence of malnutrition-protein-energy wasting (PEW) suggests the need to avoid or postpone protein restriction, particularly in the presence of stable kidney function and considering the patient's preferences and quality of life. CKD progression and advanced CKD stage support prioritization of protein restriction in the presence of a good nutritional status. Individual risk-benefit assessment and appropriate nutritional monitoring should guide the decision-making process. Higher awareness of the challenges of nutritional care in older adult patients with CKD is needed to improve care and outcomes.

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Research is advocated to support evidence-based recommendations, which we still lack for this increasingly large patient subgroup.

1. Background

Increased life expectancy is shifting healthcare priorities towards the care of older adult individuals and of patients affected by non-communicable chronic diseases (NCDs) [1]. Virtually all NCDs, including chronic kidney disease (CKD), are more common in old age; many older adults indeed have CKD or are at risk of CKD, whose prevalence may reach 30% in the elderly [2,3]. These conditions may notably lead to, or be associated with, impaired nutritional status with malnutrition-protein energy wasting (PEW) [4,5]. Aging is also independently associated with the risk of impairment in nutritional status, particularly with a progressive loss of skeletal muscle mass and function (i.e. sarcopenia) [6–8]. Importantly, overweight and obesity, also common among older adults, are additional risk factors for the development and progression of CKD and may also directly favour the onset of sarcopenia [9–12].

Malnutrition, as well as PEW and sarcopenia, are strongly associated with higher morbidity and mortality, enhancing the risk of frailty, dependency and impaired quality of life in old age in any clinical setting. The resulting burden to patients, families and healthcare systems is substantial [9,10,13]. The high prevalence of malnutrition and sarcopenia in old age has led to guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) recommending that elderly individuals have a daily protein intake at or above 1–1.2 g/kg, higher than the recommended daily allowances in the general population, presently set at 0.8 g/kg of body weight per day [14]. Conversely, strategies for managing CKD and its complications include reducing protein intake. The 2020 KDOQI guidelines on nutrition in CKD recommend a moderate to severe protein restriction in CKD patients without diabetes (0.4–0.6 g/kg/day), in order to slow disease progression, prevent or correct metabolic disorders, maintain an adequate nutritional status and postpone the start of dialysis [15]. Milder protein restriction (0.6–0.8 g/kg/day) is recommended for patients with diabetes [15]. Notably, the recommendation of low-protein diets has now been extended to CKD Stage 3 (i.e. with an estimated glomerular filtration rate - eGFR - between 59 and 30 ml/min per 1.73 m^2), in the absence of contraindications, and irrespective of age [15]. Both geriatric and renal guidelines underline the need for a concomitant adequate energy intake in order to prevent malnutrition and optimize the anabolic utilization of proteins and lean mass maintenance [14,15].

Thus, geriatric and nephrology clinical guidelines currently provide opposing recommendations with regard to daily protein intake targets to prevent malnutrition-protein energy wasting and CKD. Conflicting guidance may create confusion as to what the best course of action is. The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Renal Nutrition group of the European Renal Association (ERN-ERA) have therefore jointly prepared the present critical review paper to provide guidance on optimal choice of protein targets for older adults where CKD and malnutrition risks may intersect. We note that nutritional requirements for hospitalized patients with CKD (with or without acute kidney injury - AKI) were recently published [16], and this particular setting of inpatient conditions is not discussed in this paper.

2. Nutritional status and the risk of malnutrition in older adults with and without CKD

Malnutrition, PEW and sarcopenia have overlapping but not identical definitions [17]. The term “malnutrition” is endorsed by the clinical nutrition community to define impaired nutritional status or “undernutrition” and we will use it primarily in this paper. We will also use the term PEW, which is more commonly used in the literature on nephrology. The term sarcopenia will be employed when complications specific to muscle mass and/or function are referred to in the studies being cited [6–8].

2.1. Who are older adults?

Aging is an obvious component of the life cycle and, in its broadest sense, refers to time-related changes occurring during the life span [18]. While some changes are without major consequences for health, others lead to progressive deterioration of body functions and eventually death [18,19]. While the concept of aging is intuitive, the definition of older adults is neither obvious nor fully agreed on. Higher life expectancy in the general population has inevitably led to a progressive increase in the lower limit of “old age”, and to the use of potentially confusing sub-classifications and age categories, e.g. from “young-old” to “oldest old” [20] (Table 1). Classifications based on age have the advantage of being simple, objective and reproducible, but do not account for biological heterogeneity and clinical variability deriving from genetic background, lifestyle and comorbidities [20-22]. As an alternative, a clinical definition of older adults has been proposed, based on frailty and functional impairment [23]. The advantages of clinical, more nuanced approaches are at least partly offset by limited standardization, which makes data comparison difficult, particularly in multi-cohort studies.

Regardless of the definition, higher risk of impaired nutritional status is a common feature of aging. This is largely accounted for by the aging process, with development of metabolic alterations, sedentary lifestyle, decrease in appetite, and impairment in oral health. Non-communicable diseases and their complications are common in old age and generally increase these risk factors [19], leading to the broad definition of disease-related malnutrition (DRM), which may occur at any age and augment nutritional risk, as indicated by the ESPEN Guidelines on terminology in clinical nutrition [8].

2.2. Who are the older adults with CKD?

Reduction in kidney function increases with age; while it is well acknowledged that CKD increases morbidity and mortality, the evolution of normal kidney function during the aging process is not fully defined [24,25]. Some authors hold that an eGFR below 60 ml/min/1.73 m^2 indicates the presence of CKD independently of age, while other experts suggest that the threshold should be lower in older adults [26–29]. Practical implications are relevant, since the current KDOQI guidelines for nutritional management in CKD recommend a low-protein diet starting from Stage 3 (eGFR <60 mL/min/1.73 m^2), regardless of age, to postpone the start of dialysis and prevent CKD-related complications [15].

The prevalence of CKD Stage 3 in older adults may reach 25–35%; setting the cut-point for older adults at eGFR<45 ml/min/

Table 1
Some examples of definition of "old patients".

Source	Definition	Age
National Policy for Older Persons Year 1999: Ministry of Social Justice and Empowerment [21]	Young old or "not so old"	60–69 years
	Old–old	70–79 years
	Older-old or very-old	>80 years
Garfein AJ et al. J Gerontol B Psychol Sci Soc Sci. 1995 [20]	No definition, high degree of heterogeneity of the clinical pattern of older adults	Over 60 years
Kim Y, Lee E. Health Qual Life Outcomes. 2019 [22]	Young–old	65–74 years
	Old–old	75–84 years
	Oldest-old	>84 years

1.73 m^2 would reduce prevalence to 15–20%, consequently reducing the indications for lowering protein intake. A static definition of eGFR does not make it possible to distinguish between patients with stable kidney function (estimated to be about 50% of CKD Stage 3 patients) and those with a more rapid progression [30,31]. Longitudinal data on kidney function are required to enable us to identify not only patients at risk for further kidney function impairment, but also those at risk for complications, such as cardiovascular events. While this may be intuitive, algorithms for accurate predictive evaluation are not available. Uncertainties in definitions underline the need for individual evaluations, including CKD progression, comorbidities and complications, as well as nutritional status, reinforcing the need for multidisciplinary evaluation and work-up in this fragile population, in line with the concept of personalized medicine.

2.3. Disease-related malnutrition (DRM) and protein-energy wasting (PEW): The importance of terminology

According to the ESPEN terminology guidelines, the term disease-related malnutrition (DRM) indicates a "specific type of malnutrition caused by a concomitant disease". Inflammation is commonly observed in acute and chronic diseases and is a key determinant of DRM, mainly through inflammation-induced muscle catabolism and anorexia [32–34]. Reduced physical activity or forced immobility in bedridden patients further contributes to muscle wasting in DRM [35].

The concept that malnutrition derives not only from nutritional deficits, but can also be caused by metabolic derangements and lack of physical activity is conveyed in the term protein-energy wasting (PEW), which is defined as the presence of nutritional and metabolic derangements with loss of body protein and energy stores (i.e. muscle and fat mass) [35]. DRM and PEW largely overlap in identifying age and disease-related nutritional derangements [17,35–37], and the term PEW is commonly used in the nephrology community.

Until recently, a lack of global consensus on diagnostic criteria for malnutrition, together with the need for complex and time-consuming evaluations, contributed to hampering routine implementation of nutritional care [38]. The Global Leadership Initiative on Malnutrition (GLIM) recently issued a consensus-based proposal for the diagnosis of both disease- and non-disease-related malnutrition, based on combined phenotypic and etiologic criteria, seeking to provide a simple tool that would be applicable in routine clinical practice [39]. GLIM phenotypic criteria include low body mass index (BMI), weight loss and low skeletal muscle mass, whereas etiologic criteria include involuntary low food intake and the presence of disease and/or inflammation [39]. GLIM criteria are already used in various combinations in different assessment tools [40,41]. In Table 2 the criteria for a diagnosis of malnutrition according to GLIM and for PEW are reported. At least one phenotypic and one etiologic criterion are needed for a diagnosis of malnutrition according to the GLIM criteria [39], which should be followed by full nutritional assessment; at least one criterion from three of the four domains is needed for diagnosis of PEW.

Importantly, by focusing on low muscle mass, both criteria also make possible a diagnosis of DRM or PEW in the presence of obesity, suggesting that specific attention needs to be paid to selective derangements of protein metabolism (and intake), even in the presence of preserved body fat stores, and calling for greater attention to lifestyle and exercise, as means for improving muscle metabolism [42–45].

Importantly, while diagnosis of DRM or PEW does not require assessment of skeletal muscle function, the recent KDOQI guidelines on nutritional management of CKD, in line with the GLIM consortium, underline the importance of regular assessment of muscle function as a component of subsequent full nutritional assessment, identifying the handgrip test as a practical and easily applied tool [8,14,15].

In the available studies on patients with CKD, both PEW and GLIM criteria have good predictive value for clinical outcomes and fair to very good agreement was reported between GLIM and PEW [40,41,46,47]. ESPEN and ERA acknowledge that differences in routine terminology may be confusing, and they encourage initiatives aimed at defining a common language, considering that each definition may focus on different aspects of the same condition, in keeping with disease-related nuances of nutritional impairment.

2.4. Nutritional status and the risk of malnutrition and sarcopenia in older adults without and with CKD

The definition of "normality" in relation to age is elusive: a reduction in muscle mass and function, broadly defined as sarcopenia, inevitably accompanies the aging process, although its extent and functional impact are highly heterogeneous [48–51]. As

Table 2
Comparison of criteria considered for DRM (according to GLIM) and PEW.

	Domain	Criterion	Diagnosis system
DRM: GLIM[a]	1. Phenotypic	• Involuntary weight loss • Low Body Mass Index (BMI) • Low skeletal muscle mass	At least one criterion from each domain
	2. Etiologic	• Low food intake or malabsorption • Disease and/or inflammation	
PEW[b]	1. Body mass	• Body weight loss • Body fat loss	At least one criterion from three out of the four domains
	2. Muscle mass	• Loss of muscle mass	
	3. Blood biochemical markers	• Low serum albumin, prealbumin or cholesterol	
	4. Food intake	• Reduction in energy and/or protein intake	

[a] Global Leadership Initiative on Malnutrition from the European Society for Clinical Nutrition and Metabolism (ESPEN).
[b] Protein energy malnutrition from the International Society for Renal Nutrition and Metabolism (ISRNM). A further report on an ISRNM consensus conference updating the PEW criteria in CKD is forthcoming.

a consequence, an individualized analysis of changes in body weight and body composition over time is needed to indicate which nutritional interventions would be most efficacious for a specific patient [51–53]. Longitudinal studies in older adults show an average annual decrease in muscle area of approximately 5% for each 5 years [53,54] and a higher decrease in muscle strength [53]. Multiple interrelated factors underlie a loss of muscle mass. Besides age-related impairment of energy and protein intake and less physical activity [55–57], common age-associated metabolic derangements may accelerate muscle protein catabolism and blunt muscle protein synthetic response to anabolic stimuli, a condition called anabolic resistance. Mitochondrial dysfunction and a gradual reduction in the number and size of fast-twitch type II muscle fibres have also been described as a part of the aging process [58–62]. These alterations may lead to further impairments in muscle protein anabolism in the presence of metabolic stress, for example in acute and chronic diseases [58,59]. Although changes in muscle mass are not invariably associated with altered muscle function, variable loss of muscle function is usually associated with low muscle mass [63–65].

Parallel with muscle derangements, aging also commonly induces an absolute or relative increase in body fat; fat accumulation is often associated with fat dysfunction and with adipocyte hypertrophy and pro-inflammatory adipokine and cytokine secretion patterns, contributing to visceral adiposity and ectopic lipid accumulation, which also involve muscle tissue [9,66–70]. Since elderly individuals are frequently overweight, the definition of ideal body weight for this population may need to be revised. Chronic low-grade inflammation, associated with dysfunctional fat tissue and related insulin resistance, may further accelerate muscle catabolism and its functional and clinical complications [71–73]. Acknowledging age-related changes in body composition, the GLIM criteria indicate a higher BMI threshold for diagnosis of malnutrition in individuals who are over 70 (22 kg/m^2 compared to 20 kg/m^2). As mentioned above, fulfilment of the low skeletal muscle mass criterion in GLIM and in PEW makes diagnosing malnutrition possible also in the presence of a normal or high BMI [39]. The increasingly recognized problem of sarcopenia in overweight or obese individuals has led to the term “sarcopenic obesity”, underscoring the high prevalence of muscle loss in obese persons; the prevalence of this condition increases in aging and in chronic diseases, and is extensively reported in all stages of CKD [10,74–79].

2.5. Protein requirements and recommendations for older persons without CKD

Aging per se is characterized by a lower adaptive and regenerative capacity, resulting in slower and less efficient rehabilitation and hindering recovery following acute disease or decompensation of chronic diseases. The ESPEN guidelines on clinical nutrition and hydration in geriatrics therefore recommend that “all older persons independent of specific diagnosis and including also overweight and obese persons shall routinely be screened for malnutrition with a validated tool” [14].

The recommended daily protein allowance in adults of 0.8 g/kg body weight per day has been challenged for older adults, as prospective studies showed that a daily protein intake of at least 1 g/kg body weight leads to better preservation of skeletal muscle mass in otherwise healthy older persons, without harmful effects [80–84]. Also considering that older adults often spontaneously reduce protein intake [85,86], a daily protein allowance of 1.0–1.2 g/kg body weight is increasingly being suggested [14]. Similar recommendations have been proposed for older adults after kidney transplantation [14,80,85,87–91] and in various studies a protein intake of 1.2–1.5 g/kg or higher is recommended in the presence of acute diseases, frailty or malnutrition [80,92]. No evidence-based recommendations are available on whether plant- or animal-based proteins are preferable, and the susceptibility of older adults to the toxic effects of additives, preservatives and processed or ultra-processed food is not known.

2.6. The risk of malnutrition in older persons with CKD

CKD is a major cause of DRM and PEW, and in older adults nutritional risk factors associated with aging may act synergistically. In addition, CKD in older adults is commonly caused by, or associated with comorbid conditions (diabetes, cardiovascular diseases), with further potential nutritional risk [93,94]. For CKD patients, as for the overall population, malnutrition and PEW, particularly in regard to a low skeletal muscle mass component, are well-known independent negative prognostic factors for major clinical outcomes, including survival [95–99]. The association between nutrition-inflammation markers and outcomes in CKD or dialysis patients is so deep and intricate that the comprehensive scores derived from subjective global assessment for nutritional status and the malnutrition-inflammation score (MIS) are presently considered highly reliable prognostic markers of mortality, morbidity and CKD progression [100–104]. Although the individual use of nutritional and inflammatory markers, such as cholesterol and albumin, is not recommended, their combined use in prognostic scores has an important predictive value [15]. Regarding the role of actual nutrient intake, while dietary protein intake may decrease with increasing age, as well as in advanced CKD [105–107], it should be noted that spontaneous low protein intake is not an invariable finding and could be less frequent than previously thought, even in “very old” patients. For example, less than 12% of patients aged over 90 followed up in a pre-dialysis unit in France had a spontaneous protein intake below 0.8 g/kg/day, thus emphasizing the need for contextualizing results [108,109].

In general, while unintentional reduction in energy intake and hyper-catabolism were considered to play a major role in the onset of malnutrition-PEW in CKD, comorbidities and cardiovascular disease also clearly play a relevant role in older patients with CKD [36,110]. While this represents an element of caution in restricting protein intake in fragile patients with CKD, a high comorbidity burden increases the risk that dialysis will be poorly tolerated, with low survival and a drastically reduced quality of life, thus making the prevention of progression of kidney impairment a clinical priority [111–114].

3. Low-protein plans for patients with CKD

3.1. Low protein intake in CKD: potential benefits and drawbacks

Low-protein diets (with adequate energy intake) are the mainstay of nutritional CKD management at all ages, together with control of nutrient quality, and avoidance of excessive intakes of sodium, potassium and phosphate [15,115]. Strong clinical evidence and pathophysiological considerations justify reducing protein intake in the presence of reduced kidney function, the main rationale being avoidance of glomerular hyper-filtration with an increased nephron workload [115–118]. Oral protein loads contribute to hyper-filtration with increased haemodynamic stress, augmented production of cytokines and growth factors, lower glomerular membrane perm-selectivity and tone of afferent arteriole via increased glucagon levels [118–121]. Single-nephron hyper-filtration increases intra-glomerular pressure and protein leak, leading to glomerulosclerosis and tubulointerstitial fibrosis, a major contributor to CKD progression. Tubulointerstitial fibrosis is further augmented by metabolic acidosis, also associated with high

protein intake, mainly from animal sources [115,122,123]. Serum urea levels accordingly closely reflect protein intake in patients with CKD, and high urea levels increase protein carbamylation and reactive oxygen species generation. Acidosis, high urea and high phosphate levels also increase uremic toxins produced by the gut microbiota (such as indoxyl sulfate, p-cresyl sulfate and trimethylamine N-oxide), which in turn may reduce appetite, leading to the vicious cycle of anorexia, metabolic derangements and hypercatabolism that characterizes advanced CKD [122–125]. Prescribing a low-protein diet in CKD therefore aims to slow the decline in kidney function, mitigating the metabolic derangements coming from the loss of renal function, thus delaying the need for renal replacement therapy and thereby improving well-being [15,115,126].

It should be noted that in the absence of CKD it is not possible to associate spontaneous low protein intake with better renal function and outcomes, since lower protein intake may be associated either with overall healthy dietary habits or reflect disease-related malnutrition. Conversely, high protein intake is overall selectively associated with negative long-term renal outcomes in individuals with "less than optimal" kidney function [127–130]. Most importantly, compliance with low-protein diets is essential to their efficacy. The pivotal MDRD trial (Modification of the Diet in Renal Disease), the first large randomized trial testing the effect of low-protein diets in kidney disease, failed to demonstrate a significant clinical advantage in on-diet patients in the intention to treat analysis [131,132], and it is likely that this was a result of limited dietary compliance, since in diet-adherent patients kidney benefits became statistically significant [133]. This finding generally highlighted the importance of dietary adherence [133–136]. Indeed, results from later studies on the positive effects of low-protein diets in advanced CKD were associated with strict selection and careful follow-up of enrolled patients [137–140].

Some barriers to a general implementation of protein restriction for patients with CKD are also associated with limitations in studies demonstrating their efficacy. While not excluding older patients, the large clinical trials, whose data is included in meta-analyses and guidelines, tend to limit recruitment of very fragile individuals, and may therefore provide sub-optimal information on potential side effects, including impact on nutritional status and quality of life [141–143]. Whether low-protein diets sometimes increase the risk of malnutrition and PEW in non-selected fragile elderly patients with CKD therefore cannot be inferred from RCTs, since selection criteria usually include patients at lower risk of malnutrition. An exception comes from the study by Brunori and coworkers, which specifically included older patients in "pre-dialysis" phase, where no detrimental effect of being on a very low-protein diet versus starting dialysis was recorded [137]. Large observational studies also reassure us of the nutritional safety of low and very low-protein diets, at least in the short term, provided that experienced staff is involved to monitor, advise and encourage patient adherence [142–146]. These findings suggest that dietary approaches in renal disease should be considered an example of precision medicine and tailored individually to each patient [147,148].

The impact of low-protein diets on the quality of life of older adults with CKD, which may already be challenged by CKD per se, is also poorly studied. While there is limited evidence in favour of improved quality of life, there is no evidence of any possible harm caused by limiting protein intake [149,150]. It should be noted, however, that these studies were performed in settings where multiple dietary choices were offered and in the context of a highly personalized nutritional approach [149–153]. Of note, interest in testing new dietary approaches in a cohort of older adults with low educational levels was recently reported [154]. Even if available evidence is reassuring, changes in dietary habits are intrusive in patients' lives and having to follow complex nutritional advice may be a constant reminder of the presence of CKD, with a potentially negative psychological impact, whose weight may be higher in a population in which old age, comorbidities and malnutrition are significantly associated with depression [155,156].

3.2. *Practical strategies: multiple choice and unrestricted meals in older patients with CKD on low-protein diets*

One potential issue that may limit long-term adherence to low-protein diets is their monotony, potentially causing two opposite problems: progressive reduction of food intake (energy and calories) leading to or exacerbating malnutrition, and failure to follow the diet prescribed [157]. Dieticians can help people adhere to their diets by proposing personalized, tailored solutions; useful suggestions can also be found in cookbooks and in leaflets made available by many scientific societies and patient associations, but long-term success appears to require intensive support and monitoring, whose organization (including remote monitoring and e-learning programs) depends upon resources and cultural habits [158,159]. Different options are available for low-protein diets, tailored to individual needs and preferences, with examples reported in Table 3 [149–153,160,161].

Allowing occasional or planned (once or twice weekly) unrestricted meals (often referred to as a "joker day") may also counteract or prevent diet-tiredness, favouring long-term compliance, and reducing the risk of nutritional deficits [151,152,160,162]. Along these lines, some authors suggest allowing for shifts in the low-protein dietary schemes, for example from plant-based to omnivorous diets with protein-free food, or by providing multiple-choice diet systems [152,163]. The option of unrestricted meals also allows the patient to participate in social occasions, with a potentially positive impact on their quality of life [162].

Overall, explaining clearly why changes in protein intake are being proposed, and involving the patient in planning their diet is the key to its success. Nutrition education about which foods are good sources of protein and energy favours self-empowerment and self-management [164–170].

3.3. *Energy first: a shared rule*

Energy intake influences utilization and requirements of dietary proteins, since insufficient energy leads to the degradation of amino acids for energy production, via ketogenesis and gluconeogenesis pathways [45,171–173]. While the main focus of this paper is on protein intake, the recommendation that adequate energy intake be provided and maintained as a way to increase protein utilization is found both in high-protein geriatric and low-protein nephrology approaches for maintaining optimal clinical and nutritional status [14,15]. In particular, it is essential that energy intake should not be allowed to fall below the safety threshold of 20–25 kcal per kg per day, and individual monitoring should support decision making and dietary adjustments. Differences in studies on energy intake in CKD are relevant, and recent reports find a wide variability of energy intakes at all ages [109,174].

The ESPEN guidelines on nutrition in geriatrics recommend an energy intake of 30 kcal/kg/day, to ideally be further optimized according to resting energy expenditure (REE). REE may decrease with age, mainly due to decreased fat-free and muscle mass, and varies widely from one individual to another, based on biological heterogeneity, physical activity and comorbidities with overall basal values of approximately 20 kcal/kg/day [14,175–180]. Adjustments in energy intake should also be based on disease stage, gender and nutritional status (including obesity), as well as on

Table 3
The diet menu: some options for protein-restricted diets.

Type of protein restricted diet	Protein restriction (g/kg/BW)	Main features	Notes
"Traditional"	0.6–0.8 g/kg/day; mixed protein sources (animal- and plant-derived)	Modulated quantity of usual food; can be based on traditional regional cuisines.	Often corresponds to what older adults already eat, in particular if they cook their own food using unprocessed ingredients.
Plant-based	0.6–0.8 g/kg/day; mainly or exclusively plant proteins	Average protein intake in unrestricted vegan diets is 0.7–0.9 g/kg/day; due to variations in bioavailability, a 0.7 g vegan diet roughly corresponds to a 0.6 g mixed protein diet.	This diet is based on consuming cereals and legumes at each meal, thus ensuring complementarity of amino acids.
Vegan supplemented (moderate restriction)	0.6 g/kg/day; plant proteins, supplemented with keto and amino acids	Based on forbidden (animal- origin) and allowed (all other) food. Animal-derived food is allowed at unrestricted meals. Supplementation with keto and amino acids is tailored to nutritional status and clinical situation (1:8 −1:10 kg/BW).	Amino acid - and keto acid supplements help to reach the minimum requirements for essential amino acids intake if different types of plant-derived food fail to do this.
Diet with protein-free food	0.6 g/kg/day; mixed proteins	Protein-free pasta, bread and other carbohydrates replace standard bread, pasta and rice. Widely used in Italy, where protein-free food is available to patients free of charge, and in some Asian countries.	Since carbohydrates are the basis of Mediterranean cuisine, substituting them allows patients to achieve the recommended energy intake while easily reaching a protein intake of 0.6 g/kg/BW in the "traditional" LPD and helping them achieve the targets in the supplemented very low-protein diet.
Very low-protein supplemented vegan diet	0.3–0.4 g/kg/day; only plant proteins, supplemented with keto and amino acids, with protein-free food (where available)	This diet is usually vegan and supplementation with keto and amino acids (1:5 kg/BW) is required. May be integrated with protein-free food.	This diet is demanding and requires taking the large number of pills employed in supplementation. It is not prescribed as a "first line" diet.
Tailored solutions	Usually 0.6 g/kg/day, plant or mixed protein	These solutions employ different combinations of protein-free food, vegan diets and supplementation.	The main reason for prescribing these diets is to take the patient's needs into account. An example is one vegan-supplemented meal and one meal with protein-free food.

goals, compliance and tolerance of nutrition intervention. In this context, the KDOQI guidelines have lowered the previous indication of a minimum of 30–35 kcal/kg of ideal body weight/day to 25–30 in patients with CKD. This decision takes into account studies by Kopple and Avesani that suggested that REE could be lower than previously estimated, and likewise acknowledges common difficulties in maintaining a high calorie intake in older patients with CKD in clinical practice, with risk of fat accumulation which could further impair their clinical and functional status [15,181,182].

3.3.1. *Oral nutritional supplements*

When dietary energy intake is deemed insufficient and nutritional goals are not being reached, oral nutritional supplements may be needed. Three main types of oral supplements are available: those rich in proteins and energy (the most widely used); those rich in energy and comparatively low in proteins (new products tailored to patients with CKD); amino acid and keto acid supplements, usually added to specific types of low-protein diets [183–187]. Chronic use of oral protein-rich nutritional supplements has little place in the clinical management of CKD, unless CKD is in the very early stages or is stable. An increase in protein intake of short duration (as in the case of hospitalization for medical or surgical reasons and during recovery from acute illness) is unlikely to cause detrimental effects to kidney function, but an increase in protein intake may worsen metabolic acidosis and hyperphosphatemia and increase the level of urea (and other toxins), thereby potentially interfering with appetite and well-being (15). Careful monitoring of serum urea, creatinine, electrolytes and bicarbonate is strongly advised.

Energy-rich supplements with low protein content have recently become available [184,186]. Their use to optimize utilization of dietary proteins for anabolic purposes in patients with CKD is an option when energy intake is too low. Most energy-rich supplements are sweet in taste, but new unsweetened products marketed for cancer patients are becoming available and represent an interesting alternative. Homemade solutions, such as savoury herb muffins with controlled amounts of sodium, potassium and phosphate may represent inexpensive alternatives to supplements [188]. Alpha-ketoacids and amino acid mixtures are commonly employed in very-low protein diets and in some moderately protein-restricted plant-based diets. Their effectiveness has not been validated in other settings, but they could be considered for patients at risk of protein malnutrition, balancing a lower effect on appetite with an increased pill burden [152,187,189].

Finally, enteral and parenteral nutrition should be considered to maintain adequate nutritional status in selected patients when oral nutrition has failed to reach nutritional targets, but a discussion of these options falls beyond the aims of the present paper.

3.4. *Setting priorities and defining goals for the nutritional care of older patients with CKD*

While acknowledging the complexity of prescribing nutritional care for older patients with CKD (Fig. 1), we propose parameters that should be considered when making decisions about nutritional approaches, from both the nephrology and geriatric-nutritional perspectives. Although a one-size-fits-all approach is generally not feasible, a stepwise approach with initial evaluation and individualized assessment can provide a framework for clinical decisions in routine clinical practice. In all cases, initial assessment of renal and nutritional status and careful monitoring of their modifications should be the basis of decision making and modulation of nutritional care. Various combinations of renal and nutritional parameters, and risk-benefit assessment should guide individual decisions placing priority on renal (CKD patient who is elderly) or nutritional-functional problems (elderly patient with CKD) (Fig. 2):

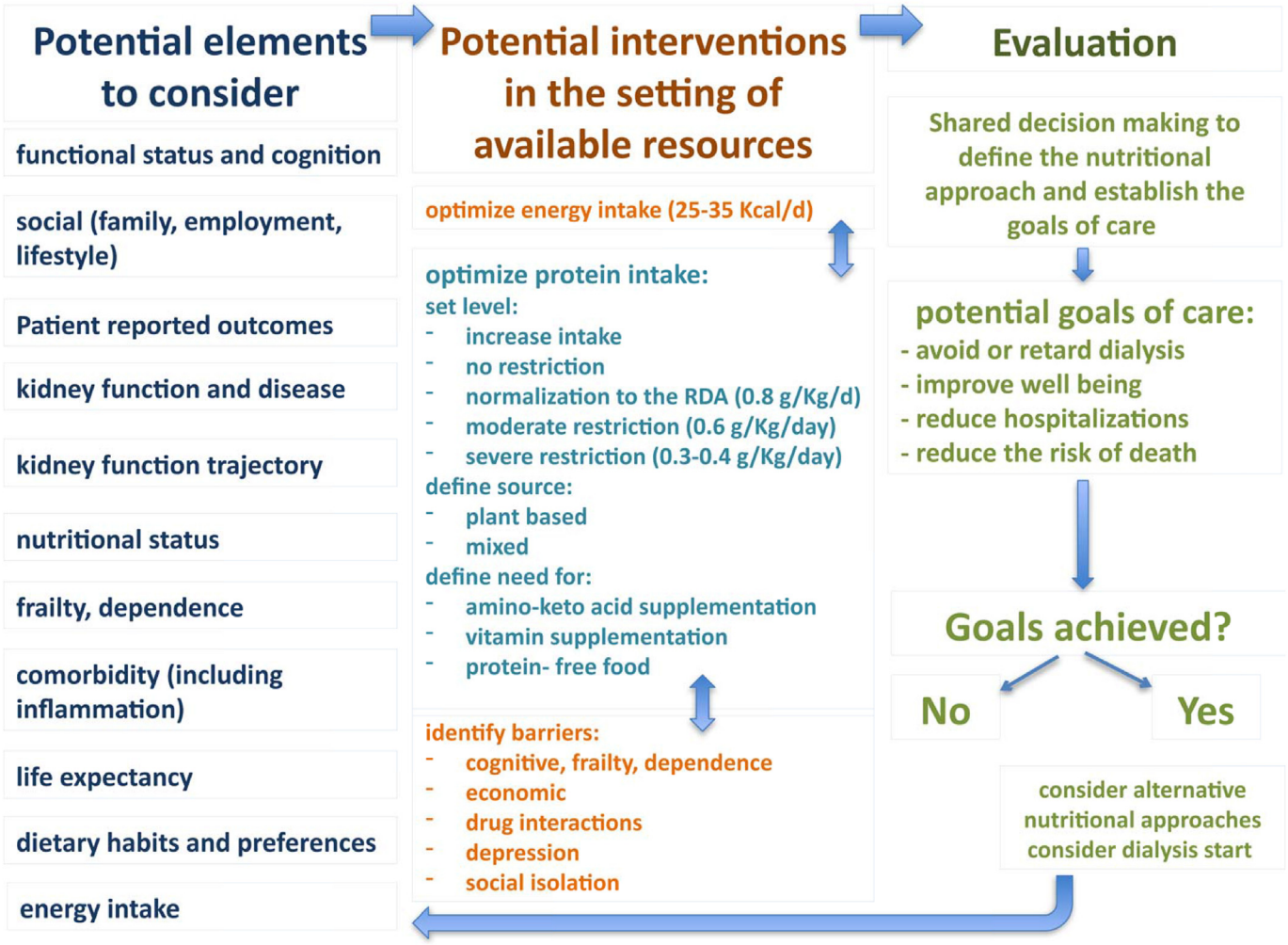

Fig. 1. The complexity of a high-quality dietary prescription in elderly CKD patients (freely inspired by reference [189]).

Renal priority (focus on CKD): CKD is identified as the leading clinical problem; priority shifts towards maintenance of residual kidney function and control of uremic symptoms. The priority is therefore the implementation of guideline-recommended low-protein diets for patients with advanced CKD, particularly in the presence of rapid CKD progression and uremic symptoms, ideally with personalized protocols and follow-up by experienced multi-disciplinary teams.

Factors supporting RENAL PRIORITY include:

-Advanced CKD (e.g. Stage 4–5)
-Rapid CKD progression in the absence of an identified trigger
-Uremic symptoms associated with the decision to postpone dialysis
-Good nutritional status

Nutritional priority (focus on age): age-related impairment of nutritional and functional status is identified as the leading clinical problem; priority shifts towards maintenance or recovery of nutritional and functional status. Protein restriction is not recommended, but nutritional interventions aimed at implementing a well-balanced diet are warranted. This may hold for patients with stable CKD, particularly Stage 3, and/or overt malnutrition-PEW, sarcopenia or frailty.

Factors supporting NUTRITIONAL PRIORITY include:

- Diagnosis of malnutrition-PEW
- Early CKD stage (e.g. Stage 3a-3b)
- No or slow CKD progression
- Comorbidities and short life expectancy (for example because of advanced neoplasia)

The issue of comorbidity and of all situations at risk for PEW and DRM remains open. Comorbidity is almost the rule in older patients with CKD, for example, in a large cohort of CKD patents followed up in Central France, the median Charlson Comorbidity index was 7, and cardiovascular diseases and type 2 diabetes were 35% and 44% respectively; both conditions notably increase the risk of DRM [109]. A general limitation of the use of low-protein diets in patients with high comorbidity level (and as a consequence higher risk of malnutrition-PEW) would selectively exclude those patients that might benefit most from postponing or avoiding dialysis.

A patient–centred, personalized approach, which should be crucial in deciding protein intake, should be based on the following examinations:

(1) Nutritional screening using validated tools (e.g. MUST, NRS2002), and malnutrition diagnostic procedures (e.g.

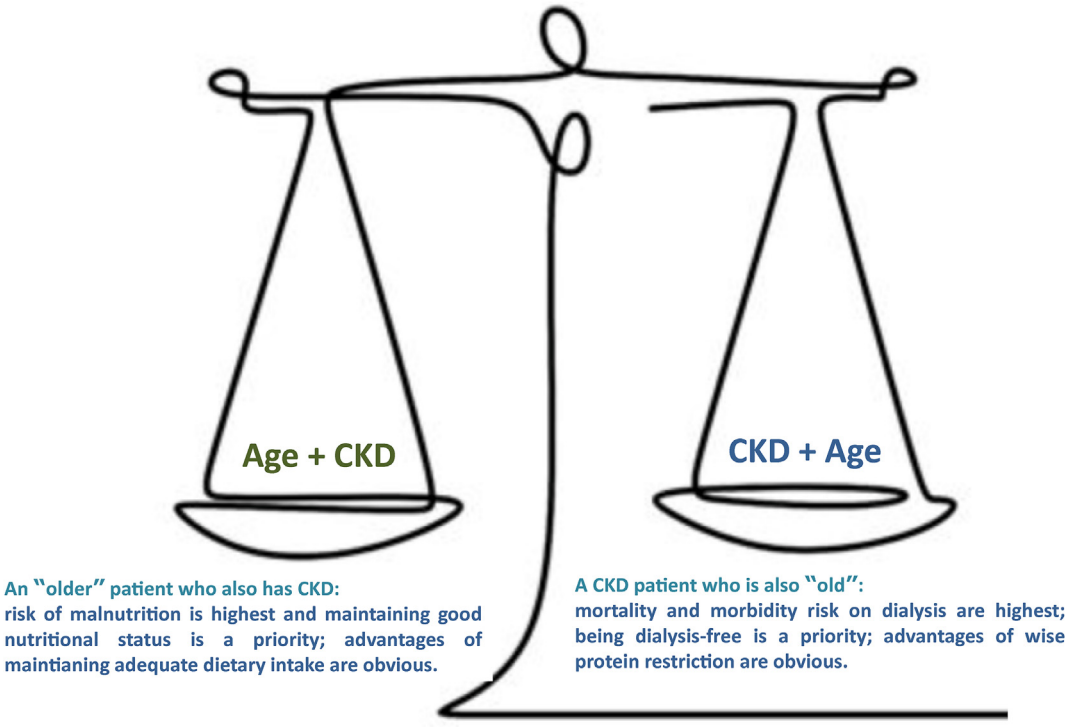

Fig. 2. Balancing age and CKD.

GLIM criteria, PEW criteria, MIS) followed by detailed nutritional assessment (e.g. SGA). The approach can be adapted to available resources and expertise. Initial screening should be followed by referral to a nutrition specialist, whenever necessary and possible.

(2) Careful monitoring of nutritional status before and during implementation of dietary restrictions, with individual cost-benefit assessment, particularly in case of worsening nutritional parameters.

(3) Careful monitoring of muscle mass and function before and during implementation of low-protein diets, with individual cost-benefit assessment as stated above.

(4) Dietary counseling and treatment to ensure adequate energy intake and optimal protein intake and adherence, particularly in the presence of risk of malnutrition, sarcopenia, frailty or full-blown malnutrition-PEW.

Although the current paper does not seek to discuss the methods used for assessing body composition, muscle mass and muscle function, introducing muscle assessment in routine clinical practice is of vital importance. As indicated in recent papers from the GLIM core group for implementation of routine nutritional diagnosis, several methods for assessing muscle mass or its surrogates (e.g. lean body mass) have been validated and should be implemented, based on availability, expertise and available cut-offs for normality [190]. Similar considerations are expressed in the KDOQI guidelines, with a comprehensive discussion of nutritional assessment methods, scores and tests, highlighting the strong connection between nutritional and functional status [15]. Despite its known limitations, particularly in the presence of oedema, obesity or underweight, the use of anthropometry is encouraged in the absence of more sophisticated approaches [190]. Preferred methods for assessment of muscle function include strength measurement, with particular regard to handgrip strength. The latter may provide the best compromise between easy availability and precision, and prognostic validity for patients with CKD has been shown to be good [191].

3.5. *Personalized nutrition and individual risk-benefit assessment*

Guidelines are undoubtedly useful in advising general approaches to common diseases and in establishing standards of care. However, clinical complexity justifies and indeed mandates patient-centred approaches and more nuanced attitudes in all fields of medicine. Guideline-driven and personalized nutritional care are in no way mutually exclusive. Personalized nutrition (PN) was recently described as "a field that leverages human individuality to drive nutrition strategies that prevent, manage, and treat disease and optimize health, delineated by three synergistic elements: PN science and data, PN professional education and training, and PN guidance and therapeutics" [192].

In nephrology, the recent guidelines of the International Society for Peritoneal Dialysis (ISPD) exemplify how this combined approach can be implemented [189]. The guideline title (Prescribing high-quality goal-directed peritoneal dialysis) underscores how goals should result from discussions with patients in a decision pathway adapted to specific conditions, expectations and adherence to treatment. This approach can also be implemented when prescribing protein intake, resulting in shared decisions, which can be expected to be more effective than rigid adherence to ideal figures (Fig. 1).

In Table 4, we summarize approaches and suggestions for personalization of nutritional care, considering patients' priorities and informed preferences, and ultimately their decisions.

The following four cases exemplify the application of the proposed pathways in clinical practice (Boxes 1-4).

Case 1. Nutritional-geriatric priority - when old age is the dominant factor

A 90-year-old physician, still active, with a tendency to gain weight because of limited ability to exercise due to knee arthrosis, on 5 mg of steroids for polymyalgia. Serum creatinine increased from 1.1 mg/dL at 70 years of age, to 1.45 mg/dl at 89 and 1.5 at 90, with an eGFR of 40 ml/min/1.73m^2; at the last control urea was 45 mg/dl. No proteinuria was present. Further data: normotension under low-dose Beta-blockers, previous stenting and aortic valve replacement; IgA monoclonal gammopathy, stable over time; haemoglobin 12 g/dl; total proteins 6.8 g/dL, albumin 4 g/dL, PTH in the normal range. Protein intake estimated at 0.9–1.1 g/kg of actual body weight/day (82 kg, height 174 cm, BMI 27 kg/m2), and 1.1–1.3/kg of ideal body weight/day.

Comment: this is an older patient with Stage 3 b CKD, with very slow progression over time. A significant progression of CKD is unlikely, as is the need for renal replacement therapy. The good results obtained with long-term steroid treatment indicates that maintaining a relatively high protein intake might be helpful. However, since clinical balance in this patient is fragile, strict controls of the kidney function are needed and a decrease in protein intake may be needed in case of rapid CKD progression.

Suggestions: no restriction of protein intake, nutritional evaluation and monitoring of kidney function, electrolytes, blood cell counts, serum albumin and pre-albumin at least three times per year, to be increased in case of changes in clinical status or comorbidity. Increase physical activity (home-based exercises).

Suggested references and considerations: older patients often benefit from a high protein intake [109]; an unrestricted diet is an option that can be considered for high comorbidity patients [187]; many older patients have a slow CKD progression [112,193–195].

Case 2. Renal priority – low-protein diet (e.g., when patient refuses dialysis)

An 84-year-old retired math teacher living with her husband in a big city is advised to start preparation for dialysis when her eGFR falls below 15 mL/min/1.73m^2. Diagnosed with IgA nephropathy by kidney biopsy 40 years earlier, she leads an active, independent life. Her BMI is normal-low for age (21 kg/m2); she is hypertensive, in good control. She requests a second opinion about dialysis and states: "My life will not be long; I don't care about what I can do, except that I don't want to start dialysis".

At referral she is otherwise in good clinical condition; her urea level is 180 mg/dL, with acceptable albumin levels for age (3.5 g/dl). A nutritional interview reveals a high protein intake, considered appropriate for age (1.2 g/kg/day).

Comment: the clinical picture is dominated by CKD Stage 5, with slow, but gradual, and presumably irreversible deterioration over time. The patient was followed up without dietary management, also based on the common belief that dietary intake is spontaneously low in older patients. Refusal to start dialysis means the treatment plan must be reconsidered, and dietary management to minimize progression of CKD must be included.

Suggestions: Since the patient is on a "high-protein" diet, a stepwise approach is an option, starting from normalization, then a further reduction in protein intake to as low as 0.3–0.4 g/kg of protein per day, supplemented with alpha keto-analogues and essential amino acids (considering apparent motivation and compliance so that dialysis can be postponed or avoided). While a dietary prescription of this kind may be difficult to follow, age should not be considered a limitation for prescription. Given the patient's age and life-expectancy, it is hoped that by stabilizing kidney function she will be able to avoid dialysis. Strict monitoring of energy and protein intake and muscle mass and muscle function is suggested (once monthly), and maintaining the highest possible level of physical activity to preserve muscle mass and function is advised.

Suggested references: "Diet or dialysis in the elderly" is a pivotal trial showing the feasibility of severely protein-restricted diets in older patients with CKD [137]; protein intake is not always reduced in older adults, and nutritional assessment should be proposed regardless of age [109]; in avoiding sarcopenia, physical activity is probably as important as protein intake [65,196,197].

Case 3: Renal priority - acute illness and newly diagnosed CKD: different priorities over time (focus on nutrition first and on CKD afterwards, with gradual adaptation of protein intake)

A 79-year-old housewife living in a remote rural area, obese (BMI pre-acute illness 32 kg/m^2), hypertensive, under lipid lowering agents, was referred after surgery for cholelithiasis with an eGFR of 20 ml/min/1.73m^2; surgery was complicated by sepsis, leading to acute kidney injury (AKI); she lost 10 kg during hospitalisation, with clinical signs of sarcopenia. At referral urea was 220 mg/dL, albumin 2.8 g/dL; there was no proteinuria. She presented: well-controlled hypertension under calcium channel blockers, diuretics and low dose ARBs; moderate anaemia (Hb 9.8 g/dl); total proteins 6.0 g/dl; high phosphate and normal calcium; PTH 150 pg/ml; low levels of vitamin D, B9 and B12; and metabolic acidosis (bicarbonate 16 mEq/l). Upon inquiry, it was learned that eGFR had already decreased to 27 ml/min/1.73m^2 before the acute episode. At renal ultrasound kidney longitudinal size was 9.0 and 8.9 cm, with regular margins, and a high resistance index (0.95 right, 0.96 left) suggesting a diagnosis of nephroangiosclerosis.

At referral in nephrology she was on two oral nutritional supplements (20 g proteins, 400 K calories). Nutrition journal: the patient eats little "regular food", feels compelled and under pressure to use oral supplements; complains of nausea.

Comment: This is a patient with previously unrecognized CKD Stage 4 and advanced age. Late referral is frequent and is reported in 30% or more cases, especially for patients living in rural or remote areas. The patient had never had a nephrology or dietetic consultation and her high BMI probably contributed to masking malnutrition and sarcopenia. Short-term goal (preservation of nutritional status) and medium- to long-term goals (adapting the diet to CKD) are foreseen.

Suggestions: Offsetting catabolic status is the priority; increasing energy intake is the first goal; discontinuation of protein-rich oral nutritional supplements is advised, together with equilibration of nutritional deficits. When optimal energy intake is reached, protein intake can be limited to 0.8 g/kg per day, on account of uremic symptoms with high urea level and severe acidosis associated with anorexia and nausea. Adding high-energy, low-protein supplements should be considered, but resuming or increasing regular dietary intake should be the priority. The addition of a mixture of keto-acids and amino acids could help to increase substrate availability without affecting urea levels. While in very low-protein diets the recommended dose is 1 tablet/5 kg, and in moderately restricted diets it is 1/10 kg, in case of the need for additional nutritional support the dose can be personalized according to patient tolerance, preference and existing pharmacological burden. Once the energy goal is reached, vitamin stores are replenished and regular food intake is resumed, a low-protein diet with 0.6 g/kg/day should be discussed; based on patient's wishes, a multiple-choice diet menu may facilitate adherence.

Suggested references: unrecognized CKD is common [196,198–200]; energy requirements first, in acute and chronic kidney disease [14–16]; multiple diet choices may improve compliance [152].

Case 4. Renal priority – a patient starting incremental dialysis. Dietary adaptation with increasing protein intake

A 90-year-old man with established CKD, still living alone; has help with housekeeping but is otherwise independent. Nutritional status is good. He is evaluated at the start of incremental dialysis. The decision to start incremental haemodialysis is motivated by frequent hospitalizations linked either to water overload or dehydration in the context of high diuretic needs and a very low eGFR (6 ml/min/1.73m^2). In an attempt to avoid dialysis, the patient followed a low-protein diet (0.6 g/kg/day of proteins from mixed sources) for two years, with acceptable compliance (usual intake up to 0.8 g/kg/day of proteins) and adequate energy intake; hypertension is well controlled on calcium channel blockers. After the start of dialysis the patient spontaneously increased his protein intake to about 1 g/kg/day.

Comment. This is a patient with CKD Stage 5 who is starting incremental haemodialysis (one session per week). While in patients who start full dialysis, the guidelines suggest a high protein intake, partly to compensate for potential catabolic derangements and albumin losses, no guidelines specifically address nutritional management on incremental haemodialysis. While some authors hold that a low-protein diet should be continued to maximize the time on an incremental schedule and avoid additional dialysis sessions, others do not suggest specific dietary management. Frequent monitoring seems needed to tailor incremental dialysis doses.

Suggestions: Since the patient has adapted to a moderately protein-restricted diet which he follows without difficulty, liberalizing the diet on the day before the dialysis session could be a reasonable choice, with protein restriction on other days, keeping the patient under strict nutritional surveillance. In this case the patient spontaneously increased his protein intake and considering his age, the fact that the main goal (stabilization of clinical status) was reached with a dialysis dose that did not affect his daily activities, no correction was proposed.

Suggested references: the story of the person whose case is reported here can be found in Reference [201]; incremental haemodialysis may make long-term stabilization possible in some patients, with or without nutritional management [202–204]; incremental and decremental schedules constitute implementation of precision medicine in dialysis treatment [204,205].

4. What this review does not address

We have not attempted to address the detailed pathophysiology of aging, nutritional homeostasis and kidney disease. We do not discuss the important role played by physical activity in modulating both protein and energy requirements and metabolism. Furthermore, we do not describe in depth the available tools for assessment of nutritional status in older adults, considering that these have been extensively discussed in the guidelines on nutritional management of patients with CKD and older adults [15,206]. Adaptation and specific requirements in acute conditions during hospitalization are likewise discussed in the recent ESPEN guidelines on hospitalized patients with AKI or CKD [16].

5. Future research agenda and unmet objectives

Throughout this review we have discussed the difficulty of making a one-size-fits-all recommendation for the protein needs of older patients with CKD. We advocate that a research agenda for optimization of nutritional management in older patients with CKD be implemented, as summarized in Table 5. We recommend prospective studies that address this issue, and systematic reviews incorporating the complementary evidence of both observational and interventional studies. In future studies, patient stratification based on age, nutritional and functional status is advised in order to identify high-risk groups and optimize risk-benefit ratios, moving towards precision nutrition and patient-centered, personalized

Table 4
Patient-centred indications for protein intake in older adults with CKD (Adapted from [189]).

Nutritional treatment should be prescribed after shared decision making between the person with CKD and the healthcare team. The nutrition prescription should take into account local resources, as well as the wishes and lifestyle of the person needing treatment, and those of their family and caregivers, especially if they are providing extensive assistance.
The first step in the decision-making process is the identification of the dominant problem: CKD in an older adult versus an older patient with CKD. This makes it possible to establish realistic care goals that (1) maintain or improve quality of life by enabling patients to achieve their life goals (2) minimize symptoms and treatment burden (3) ensure that high-quality care is provided.
Different clinical goals should be hierarchized; main goals include: (1) delaying or avoiding dialysis (2) maintaining or improving nutritional status (3) maintaining or improving quality of life.
The second step in the decision-making process is establishing parameters to be used to help ensure the delivery of high-quality nutrition care:
Patient reported outcome measures: this should be the first measure of how a person with CKD is experiencing life and his/her feeling of well-being. It should take into account symptoms, impact of the diet on quality of life, mental health and social life.
Nutrition status: in the context of recommendations summarized in the main text, monitoring of nutrition status should regularly include comprehensive evaluation of appetite, clinical examination with body weight measurements, and blood tests. Body composition and functional tests should also be included and the choice of tests (such as bioimpedance, anthropometry, handgrip strength) should be based on availability, team experience and patient preferences.
For some people who have advanced CKD and who are old, frail or have a poor prognosis, there may be a quality of life benefit from a flexible dietary prescription that minimizes the burden of dietary management.

Table 5
Research agenda.

What is missing	
Implementation studies	Well-designed studies in older adults with CKD with nutritional and renal outcome measures
Studies in specific (sub) populations	Patients with diabetes Patients with obesity Incremental dialysis patients
Studies on protein quality	Animal- vs. plant-based
Studies on patient preferences	Tools to be developed

approaches [207–210]. Surveys addressing the specific needs and preferences of older patients are also needed, as are studies focused on the relationship between diet and drugs for slowing the progression of CKD.

Promotion and increased awareness of the importance of tailored and personalized approaches in the nutritional care of older patients with CKD should be a priority target for clinical research, while approaches in clinical practice should seek to optimize individual treatment through identification of nutritional needs stemming from the combined presence of old age and CKD, with individualized risk-benefit assessment. Medical societies should further promote such awareness by disseminating the findings presented in the current paper, including future potential joint activities in this field.

6. Conclusion

In older adults with CKD, nutritional management should consider potential challenges stemming from simultaneous and potentially conflicting risks of renal disease progression and malnutrition-PEW. Identification of primary underlying causes and needs should be routinely implemented, seeking personalized approaches with individual risk-benefit assessment. Maintenance of a high protein intake can be allowed and may indeed be desirable in some patients with stable or slowly progressing CKD, whose clinical picture is dominated by old age and related challenges to their nutritional and functional status. On the other hand, protein restriction should be implemented in older adults whose primary clinical challenge is CKD with significant progression, especially if their nutritional status is stable. In prescribing a diet the patient's preferences and quality of life should be considered and when necessary, family members and caregivers should be involved. Nutritional screening, malnutrition-PEW diagnosis and subsequent extensive nutritional assessment and monitoring should be an integral part of this pathway, starting from referral and continuing through followup. Goal-oriented interventions should be flexible and make use of all the available tools for reaching the best targets attainable.

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