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Precision Medicine for Nutritional Management in End-Stage Kidney Disease and Transition to Dialysis

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Summary: Chronic kidney disease (CKD) is a global public health burden. Dialysis is not only costly but may not be readily available in developing countries. Even in highly developed nations, many patients may prefer to defer or avoid dialysis. Thus, alternative options to dialysis therapy or to complement dialysis are needed urgently and are important objectives in CKD management that could have huge clinical and economic implications globally. The role of nutritional therapy as a strategy to slow CKD progression and uremia was discussed as early as the late 19th and early 20th century, but was only seriously explored in the 1970s. There is a revival of interest recently owing to encouraging data as well as the increase of precision medicine with an emphasis on a personalized approach to CKD management. Although part of the explanation for the inconclusive data may relate to variations in study design and dietary prescription, diversity in genetic make-up, variations in the non-nutritional management of CKD, intra-individual variations in responses to dietary and nondietary treatment, psychosocial factors, and dietary compliance issues, these all may contribute to the heterogeneous data and responses. This brings in the evolving concept of precision medicine, in which disease management should be tailored and individualized according not only to clinical manifestations but also to the genetic make-up and biologic responses to therapy, which may vary depending on genetic composition. Precision nutrition management also should take into account patient demographics, social, psychological, education, and compliance factors, which all may influence the therapeutic needs and responses to the nutritional therapy prescribed. In this review, we provide a novel concept of precision medicine in nutritional management in end-stage kidney disease with a transition to dialysis and propose how this may be the way forward for nutritional therapy in the CKD population.

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Keywords: Precision medicine, dietary protein, nutritional therapy, end-stage kidney disease

In recent years, the Precision Medicine initiative has emerged as a new clinical concept and approach. It involves personalization of medical treatment based on individual characteristics of each patient. The individual characteristics may include differences in genetic patterns, epigenetic changes, susceptibility to a particular disease, disease phenotype, biology or prognosis of the disease, as well as response to a specific treatment other than social and psychological considerations, which also may impact responses to treatment. Preventive or therapeutic interventions that are designed precisely according to these individual characteristics then may target individuals who will benefit from the treatment. Part of the reasons for the variability in response to nutritional therapy may relate to differences in the level of protein prescription, study design, sample size, and study duration. Other important considerations may relate to differences in genetic composition that may affect

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individual patients' responses to the protein prescription. Furthermore, clinical conditions, demographic and social factors, as well as psychological factors may affect the uptake of nutritional therapy by patients and family and influence patients' adherence and compliance to nutritional therapy.

Moreover, the controversy concerning whether diet may delay the need for renal replacement therapy also is related to whether nutritional management can slow the rate of loss of kidney function.[1] A number of meta-analyses clearly show that dietary therapy may delay the onset of renal replacement therapy.[2-6] The discrepancy in these findings probably is owing to the ability of good dietary management to reduce uremic toxicity in people with advanced chronic kidney disease (CKD), thereby allowing them to tolerate lower levels of glomerular filtration rates (GFRs) without being clinically uremic.[7] Even in the one meta-analysis that examined the effect of diet on the loss of GFR, patients assigned to low-protein diets showed a statistically significant, albeit small, reduction in the rate of loss of their GFR.[1] These findings were observed even though many patients included in this meta-analysis adhered poorly to their dietary prescription. Thus, all of these factors need to be taken into consideration when tailoring nutritional prescription in CKD patients. In this article, we review the nutritional needs and concerns in advanced CKD patients, factors or considerations that may increase nutritional needs in patients with advanced CKD who may undergo transition to dialysis, and, finally, how to tailor or individualize nutritional management in CKD patients. The rationale behind nutritional therapy and how it may benefit advanced CKD patients with transition to dialysis also is discussed.

NUTRITIONAL NEEDS IN ADVANCED CKD

CKD is a growing epidemic globally with a current estimated prevalence ranging from 9% to 14%.[8] Kidney Disease Improving Global Outcomes (KDIGO) defines CKD as abnormalities of kidney structure or function, present for 3 months or longer, with implications for health. Along with the abnormality in kidney function, there are derangements in excretory, endocrine, and metabolic function resulting in various metabolic and endocrine complications. As CKD advances, the accumulation of urea nitrogenous waste products, other uremic retention solutes, and increased levels of inflammatory cytokines may affect appetite and reduce food intake. Furthermore, there is increased net muscle protein degradation with worsening of kidney function, metabolic acidosis, and insulin resistance. Hypercatabolism also may set in with the presence of co-existing comorbidities and inflammation. Uremia may disrupt the intestinal barrier that favors pathobacterial overgrowth, disturbing the balance of gut microbiota, causing immune dysregulation and increased inflammatory responses.

Increased Risk of Protein Energy Wasting in CKD

These different factors put advanced CKD patients at increased risk for developing protein energy wasting (PEW). Advanced CKD for our purposes is defined as patients with an estimated GFR (eGFR) of 20 mL/min/1.73 m^2 or less, although evidence for PEW often begins to occur when the GFR decreases to approximately 30 to 40 mL/min.[9-11] An earlier study described a spontaneous reduction in dietary protein intake with progression of CKD. The mean dietary protein intake was 1.01 g/kg/d for patients with creatinine clearance greater than 50 mL/min, but decreased to 0.85 g/kg/d as creatinine clearance decreased to less than 50 mL/min to as low as 25 mL/min. As creatinine clearance decreased to between 25 to 10 mL/min, average protein intake decreased further to 0.7 g/kg/d and was only 0.54 g/kg/d as creatinine clearance decreased to less than 10 mL/min. The spontaneous reduction in dietary protein intake with a decrease in creatinine clearance was associated with worsening in other nutrition indices, although creatinine clearance as an estimation of kidney function may overestimate true GFR.[9] Similarly, analysis of data from the recruitment phase of the Modification of Diet in Renal Disease (MDRD) study showed a significant positive relationship between GFR, measured by iothalamate clearances, with dietary protein and energy intake and various nutrition parameters.[12]

Trajectories of Protein-Energy Status in CKD

Relatively few studies have described the time course and trajectory of protein-energy status of CKD patients as their kidney function decreased to the point of reaching end-stage kidney disease (ESKD) requiring transition to dialysis. In the recent Chronic Renal Insufficiency Cohort longitudinal analysis, significant weight loss was observed as cystatin C−based eGFR decreased to approximately 35 mL/min/1.73 m^2, and thereafter every 10 mL/min/1.73 m^2 decrease in cystatin C−based eGFR was associated with a mean reduction of 1.45 kg (95% confidence interval, 1.19-1.70 kg) body weight.[10,11] Notably, among those subjects who required dialysis initiation during follow-up evaluation and after eGFR decreased to less than approximately 35 mL/min/1.73 m^2, the adjusted risk of death after dialysis initiation was increased by 54% (95% confidence interval, 1.17-2.03) for patients with a more than 5% annual weight loss compared with patients with more stable body weight.[10,11] The African American Study of Kidney Disease and Hypertension Study showed similar findings.[10] Another analysis in children and adolescents with CKD showed that weight loss occurred mostly when eGFR decreased to less than 35 mL/min/1.73 m^2. Subjects with significant weight loss (defined as a decrease in body mass index z score >0.2 per year) after eGFR decreased

to less than 35 mL/min/1.73 m^2 had a 3.28 increased odds of ESKD compared with patients with stable z scores for body mass index (defined as z score change <0.1 per year).[11] These data showed that patients with CKD with an eGFR between 30 and 35 mL/min/1.73 m^2 or less are prone to develop PEW. Early institution of nutrition management is therefore essential to help maintain these patients in a healthy and stable protein-energy status as their CKD progresses further, requiring transition to chronic dialysis.

Advanced CKD Patients Requiring Transition to Dialysis Face Additional Metabolic Stresses

Furthermore, patients with advanced CKD requiring transition to dialysis may face additional metabolic stresses that place them at heightened risk of developing PEW. The high incidence of PEW in these patients is owing to decreased appetite, possibly in association with factors that increase protein catabolism, and nutritional needs not met by the protein and energy input. These stresses may be dialysis-related or unrelated to dialysis. The dialysis procedure itself may pose increased metabolic stress and increase the risk of catabolism. Dialysis may cause the following: (1) intradialytic hypotension and myocardial stunning; (2) bioincompatibility of membranes and tubing may increase inflammation; (3) temporary vascular accesses (eg, catheters situated in the carotid, jugular, subclavian, or femoral veins) may increase inflammation and infection risk; and (4) peritoneal dialysis may be complicated with peritonitis or exit site infections. All of these factors may increase hypercatabolism and the risk of PEW. Factors that are unrelated to the dialysis procedure may induce or intensify PEW. Thus, salt and water overload may cause inflammation, cardiomyopathy, heart failure, and hypercatabolism. The worsening uremic state with advanced CKD may suppress appetite; reduce food intake; increase insulin resistance; increase inflammatory, oxidative, and carbonyl stress; and engender metabolic acidosis, which also may promote muscle protein degradation.[13]

PEW: DIAGNOSIS, PREVALENCE, AND IMPORTANCE IN ADVANCED CKD

PEW is a term that was proposed by the International Society of Renal Nutrition and Metabolism in 2008 to describe a state of decreased body stores of protein and energy fuels, which often is associated with diminished functional capacity related to metabolic stresses. The diagnosis of PEW requires the presence of four main elements including biochemical criteria, reduced body weight, decrease in total body fat, decreased muscle mass, and low protein or energy intakes. Biochemical criteria include low serum albumin, prealbumin, or cholesterol.[14]

PEW is a frequent and important complication in ESKD and a strong predictor of mortality. Less information is available concerning the prevalence and importance of PEW in advanced CKD (defined as those with an eGFR ≤20 mL/min/1.73 m^2). By using subjective global assessment, PEW diagnostic criteria proposed by the International Society of Renal Nutrition and Metabolism, dietary records, anthropometry, or bioelectrical impedance, several small cross-sectional studies have estimated the prevalence of PEW to be approximately 10% to 30%.[15,16] A recent European multicenter observational cohort reported a prevalence of 28% for moderate to severe PEW in elderly advanced CKD patients. Muscle wasting and loss of body fat were the most frequent derangements observed in protein-energy status, especially among advanced CKD patients older than 80 years of age. The prevalence of PEW was highest among patients with a low body mass index less than 22 kg/m^2 (55%), the elderly, women, and patients with depression/dementia.[17] These data suggest that PEW is a prevalent and important complication in advanced CKD. Frailty and PEW often co-exist in advanced CKD patients, particularly in elderly patients with CKD.[7]

TREATMENT OBJECTIVES FOR NUTRITIONAL THERAPY IN PATIENTS WITH ADVANCED CKD AND IN TRANSITION TO DIALYSIS

There are several key treatment objectives for nutritional therapy in patients with advanced CKD and in transition to dialysis. First, dietary management aims to delay or postpone the onset of uremic toxicity, and reduce proteinuria and possibly kidney injury and the progression of CKD by reducing the load of sodium,[18-21] phosphorus, and protein. Much experimental data have shown that high salt and phosphorus intake and protein loading may increase kidney injury and CKD progression and some clinical data also are in keeping with this concept.[22] Second, nutritional management aims to reduce the generation and accumulation of various uremic retention solutes that potentially may have toxic effects to body organs, especially the kidneys, blood vessels, and the heart in patients with advanced CKD. Dietary protein is a rich source of nitrogen, phosphate, sodium, and acids. Its metabolism not only results in the generation of urea, but also various other uremic solutes such as phosphate, P-cresol, and indoxyl sulfate, and increases metabolic acidosis. Third, because dietary energy and protein intake spontaneously decrease as CKD progresses,[9] the other key objectives of nutritional management are to maintain a healthy and stable nutrition status and prevent the onset of PEW, especially as CKD progresses to ESKD requiring transition to dialysis.[23] Fourth, nutritional management aims to lower cardiovascular and metabolic risk in advanced CKD patients.

RECOMMENDED NUTRITIONAL INTAKE IN ADVANCED CKD

There is currently no consensus on the recommended level of protein restriction in advanced CKD as different levels of protein-restricted diets have been practiced and studied. Generally, there are two types of protein-restricted diets: the low protein diet (LPD), which provides a protein intake of 0.6 to 0.8 g/kg body weight/d; and the very low protein diet (VLPD), which generally provides a protein intake of 0.3 to 0.4 g/kg body weight/d and is supplemented with approximately 7 to 15 g/d of keto acid or hydroxyacid analogs and essential amino acids. It is essential that the recommended dietary energy intake should maintain approximately 30 to 35 kcal/kg/d in the prescription of LPD or VLPD, to avoid PEW.

KDIGO recommended lowering dietary protein intake to 0.8 g/kg/d in CKD stage 4 to 5 subjects with diabetes and without diabetes in the Management of CKD guideline in 2012. This recommendation was graded as 2C and 2B for diabetes and in nondiabetic patients, respectively. KDIGO also made the recommendation to avoid a high protein intake (>1.3 g/kg/d) in adults with CKD at risk of progression with a grading of 2C. The 0.6-g protein/kg/d diet, compared with the 0.8-g protein/kg/d diet, is also nutritionally adequate, generates less potentially toxic metabolites of protein metabolism, and usually has a lower phosphorus and potassium content. The potential disadvantages of the 0.6-g protein/kg/d diet is that it may be less appetizing to patients and it may be harder to provide an adequate dietary energy intake. For stages 4 or 5 CKD patients who are unable or unwilling to accept a 0.6-g protein/kg/d diet or cannot maintain an adequate energy intake with this diet, it is our policy to increase dietary protein intake as needed, but not to more than 0.75 g protein/kg/d. A recent article emphasized the target range of 0.6 to 0.8 g/kg/d as the recommended dietary protein intake for all patients with eGFR less than 45 mL/min/1.73 m^2 body surface area as well as any CKD stage with albuminuria greater than 0.3 g/d (KDIGO stage A3), including those who undergo transition to dialysis incrementally and with substantial residual kidney function, but not for prevalent dialysis patients with minimal residual kidney function, in whom a high dietary protein intake greater than 1.2 g/kg/d is suggested[24] (Table 1).

PERSONALIZED NUTRITIONAL THERAPY IN ADVANCED CKD MANAGEMENT WITH TRANSITION TO END-STAGE RENAL DISEASE

Precision medicine is emerging as an important clinical management concept and model in this era.[25] Originally, this term described a new concept in which disease management is tailored and individualized based not only on clinical manifestations and diagnosis but also on the genetic predisposition to diseases and responses to therapy that vary according to the genetic and epigenetic composition.[26] The concept of personalized medicine practice has evolved and broadened now to encompass also the influence of patients' demographic, social, psychological, education, and compliance factors in guiding the therapeutic responses to the treatment given.[27–30]

Factors Affecting the Practice of Personalized Nutrition Management

Patients' Factors

The concept of precision or personalized medicine is of particular relevance when prescribing nutritional therapy in CKD patients.[31] Patients' preference and acceptance, engagement, adherence, and compliance to the prescribed dietary therapy are important factors in predicting successful implementation of LPD or keto acid (KA)-supplemented VLPD[32] other than their genetic make-up, which may influence the responses and outcomes to the nutritional therapy prescribed. Nutritional therapy may not work in every single patient because some patients may prefer to enjoy their food without restriction, despite knowing the potential importance of dietary therapy in reducing uremic manifestations, maintaining protein-energy status, and slowing CKD progression. Some patients may find it difficult to adapt their lifestyle to a LPD or KA-supplemented VLPD and maintain it on a long-term basis. The MDRD study showed that only 60% of the subjects were adherent to the prescribed dietary protein intake.[33] On the other hand, some patients may not appreciate or may not be educated about the importance of dietary therapy with LPD/VLPD for the treatment of CKD.

Health Care/Facility Factors

In addition, there are important health care or facility factors that may affect the implementation of LPD/VLPD and success of the nutritional therapy. Countries that lack dieticians or renal dietician support and countries that do not have multidisciplinary CKD care programs may face feasibility issues in not having the required resources and manpower to provide in-depth education and regular close monitoring of patients who have received a LPD/VLPD prescription.

Economic Factors

Furthermore, implementation of a LPD or KA-supplemented VLPD program may closely relate to economic factors and availability of dialysis facilities. In countries where dialysis provision is readily available, both doctors and patients may not see the need to implement stringent nutritional therapy to delay CKD progression. On the other hand, in emerging countries where

Table 1. Recommended Dietary and Nutrient Intake for Different Stages of Kidney Disease in Adults

	Normal kidney function (eGFR >60[*]) and no proteinuria, but at higher CKD risk, eg, diabetes, hypertension, or solitary kidney[†]	Mild to moderate CKD (eGFR 30 to <60[*]) without substantial proteinuria (<0.3 g/d)[‡]	Advanced CKD (eGFR <30[*]) or any CKD with substantial proteinuria (>0.3 g/d) [‡]	Transitioning to dialysis therapy with good RKF including incremental dialysis preparation[‡]	Prevalent dialysis therapy, or any CKD stage with existing or imminent PEW[§]
Dietary protein g/kg/d based on IBW[†]	<1.0 g/kg/d, increase proportion of plant-based proteins	<1.0 g/kg/d (consider 0.6-0.8 if eGFR <45 mL/min/1.73 m^2 and fast progression)	0.6-0.8 g/kg/d including 50% HBV, or <0.6 g/kg/d with addition of EAA/KA	0.6-0.8 g/kg/d on nondialysis days (eg, incremental dialysis) and >1.0 g/kg/d on dialysis days	1.2-1.4 g/kg/d, may require >1.5 g/kg/d if hypercatabolic
Dietary sodium, g/d[7]	<4 g/d (<3 g/d for HTN)[‖]	<4 g/d, avoid <1.5 g/d if hyponatremia likely	<3 g/d, avoid <1.5 g/d given high likelihood of hyponatremia	<3 g/d	<3 g/d
Dietary potassium, g/d	Same as recommended for the general population (4.7 g/d)	Same as the general population unless frequent or severe hyperkalemia excursions likely	<3 g/d if hyperkalemia occurs frequently while maintaining high fiber intake	<3 g/d if hyperkalemia occurs frequently while maintaining high fiber intake	<3 g/day,[§] target high fiber intake (see below under fibers)
Dietary phosphorus (mg/d)[¶]	<1,000, minimize added inorganic P in preservatives and processed foods	<800, minimize added inorganic P, encourage more vegetarian food (see later)	<800, minimize added inorganic P, more vegetarian food (see later)	<800, minimize added inorganic P Consider P binder therapy	<800, minimize added inorganic P Add P binders as needed
Dietary calcium, mg/d	1,000-1,300 mg/d (to be adjusted for age)	800-1,000 mg/d	800-1,000 mg/d	≤800-1,000 mg/d	<800 mg/d
Fibers, alkali, and vegetarian foods	25-30 g/d, target higher proportion (>50%) of plant-based foods such as DASH diet	25-30 g/d or more, higher proportion (>50%) of plant-based foods	25-30 g/d or higher, consider >70% vegetarian foods	25-30 g/d or higher	25-30 g/d or higher, suggest avoiding strict vegan dieting
Energy,[#] cal/kg/d	30-35 cal/kg/d,[**] adjust to target weight reduction if BMI > 25 kg/m^2	30-35 cal/kg/d, increase proportion with low-protein diet	30-35 cal/kg/d, increase proportion with low-protein diet	30-35 cal/kg/d	30-35 cal/kg/d, target higher if PEW exists or imminent
Fats	Mostly monounsaturated and polyunsaturated lipids including omega-3-fatty acids	Mostly monounsaturated and polyunsaturated lipids including omega-3-fatty acids, increase proportion with low-protein diet	Mostly monounsaturated and polyunsaturated lipid including omega-3-fatty acids, increase proportion with low-protein diet	Mostly monounsaturated and polyunsaturated lipid including omega-3-fatty acids	Mostly monounsaturated and polyunsaturated lipid including omega-3-fatty acids
Vitamin D	Nutritional D (ergo- or cholecalciferol) as needed	Nutritional D or calcifediol, consider adding 1α-OH D analogues in progressive sHPT	Nutritional D or calcifediol, add 1α-OH D analogues in progressive or symptomatic sHPT	1α-OH D analogues to control sHPT	1α-OH D analogues to control sHPT, add calcimimetics as needed
Other vitamins and trace elements	Recommend daily multivitamin intake	Avoid aluminum-based medications, monitor iron indices, and ensure iron therapy as needed	Avoid aluminum and magnesium-based agents Treat iron deficiency	Avoid aluminum and magnesium-based agents Treat iron deficiency	Avoid aluminum and magnesium-based agents Treat iron deficiency
Management of weight and cardiovascular risks	Lipid and weight reduction strategies target BMI in the 18.5-25 kg/m^2 range, recommend regular exercise training	Avoid excessive weight loss, consider careful exercise training, follow conventional lipid targets	Identify unintentional weight loss and intervene with higher energy and protein	Identify unintentional weight loss and intervene with higher energy and protein	Avoid weight loss or BMI < 23 kg/m^2 unless required for imminent kidney transplantation or other life-saving interventions
Fluid management	No fluid restriction, adequate hydration >1.5 L/d (if risk of hyponatremia is minimal)	<1.5 L/d if edematous state or hyponatremia, consider adding diuretics	<1.5 L/d,[††] consider loop diuretics and titrate the dose or sliding scale dosing[‡‡]	<1.5 L/d,[††] consider more frequent high-dose loop diuretics	<1 L/d, avoid excessive ultrafiltration on dialysis

(*continued on next page*)

Table 1. Continued

See Kalantar-Zadeh and Fouque[24] for suggested recommendations on vitamin D, other vitamins, trace elements, management of weight and cardiovascular risks, and fluid management.
*eGFR measurements are in mL/min/1.73 m^2 body surface area.
†The ideal body weight is to be used for kilograms in the denominator of all dietary recommendations, especially in patients with a BMI > 30 kg/m^2. IBW can be estimated in kilograms in males (50 kg + 2.3 kg for each inch over 5 feet) and females (45.5 kg + 2.3 kg for each inch over 5 feet).
‡Prevalent renal transplant recipients are often in the 2 categories of eGFR 30 to <60 and >30 mL/min/1.73 m^2, or transitioning to dialysis and can be approached similarly.
§Solitary kidney can be congenital, acquired, or surgical, including status post donor or cancer nephrectomy.
||In patients with heart failure the recommendations of the American Heart Association (www.heart.org) can be considered. The American Heart Association recommends no more than 2.3 g/d (equivalent of a teaspoon of salt) and suggests an ideal limit of no more than 1.5 g/d (source: https://sodiumbreakup.heart.org)
¶Dietary phosphorus restriction is independent of hyperphosphatemia.
#Carbohydrates provide 40% to 60% of the daily energy intake, should be natural (nonrefined), and complex with high fiber content (see first column in Table 1 under "Fibers, alkali, and vegetarian foods").
**In obese patients, lower energy ranges can be targeted.
††The 0.6 g protein/kg/day diet is preferable to 0.8 g/kg/day for people with stage 4 and 5 CKD, because this former diet is also nutritionally adequate and it further reduces the generation of uremic toxins. However, with 0.6 g protein/kg/day some patients may have more difficulty with dietary adherence and also with maintaining adequate energy intake.
‡‡PEW according to the International Society of Renal Nutrition and Metabolism criteria.[14]
Certain conditions such as salt-losing nephropathies may not be subjected to sodium restriction.
In hypokalemic peritoneal dialysis patients, a higher potassium intake should be targeted.
BMI, body mass index; cal, kilocalorie; DASH,dietary approaches to stop hypertension; EAA, essential amino acids; HBV, high biologic value protein; HTN, hypertension; IBW, ideal body weight; sHPT, secondary hyperparathyroidism.
Adapted with permission from Kalantar-Zadeh and Fouque.[24]

resources are extremely limited and dialysis facility is scarce, nutritional therapy may be a useful alternative as well as an interim therapy that helps to delay the need for dialysis initiation and reduces costs tremendously.

Physician Factors

There also may be concern or worry from the physician level that LPD or VLPD may increase the risk of malnutrition in CKD and thus may reduce the enthusiasm among some physicians in prescribing protein-restricted nutritional therapy in their CKD patients. The evidence is clear that in clinically stable stage 3 to 5 nondialyzed CKD patients, the LPD and VLPD diets are nutritionally adequate unless patients have profound degrees of proteinuria.

Medical Factors

However, many CKD patients have morbid conditions that increase net protein breakdown or losses. These conditions may be particularly common in patients who are in their transition phase when progressing from advanced CKD to end-stage renal disease (ESRD) as described earlier and thus may not be suitable for LPD or VLPD prescription. Some of the factors causing increased metabolic stresses that may decrease appetite or increase catabolism during transition from advanced CKD to ESRD may include intercurrent illnesses, infections, hypercatabolism owing to inflammation, cardiovascular complications and fluid overload, metabolic acidosis causing muscle protein degradation, worsening insulin resistance, and additional metabolic stresses resulting from initiation of dialysis. Thus, a precision nutrition management approach is required to assess and select the right candidate for receiving the LPD/VLPD prescription for CKD management (Figs. 1 and 2). Of course, increasing the daily protein intake in a stage 5 CKD patient may enhance the need to begin chronic dialysis therapy.

Genetic and Epigenetics Factors

In addition, the potential role of genetics and epigenetics regulation on individual CKD/ESKD patient responses to inflammation, nutritional needs, and their potential for developing PEW should be taken into consideration when providing precision nutrition management. Differences in metabolic profiles, genetic variations in the inflammatory responses to CKD and superimposed diseases, the ability to excrete an acid load, patterns of uremic toxin accumulation, the presence of endocrine derangements such as prediabetes, diabetes mellitus, the degree of hyperparathyroidism, the presence or severity of 25- or 1,25-dihydroxycholecalciferol deficiency, the degree of resistance to growth hormone and insulin growth factor-1, as well as other co-existing comorbid conditions all potentially may affect patients' protein-energy status and response to

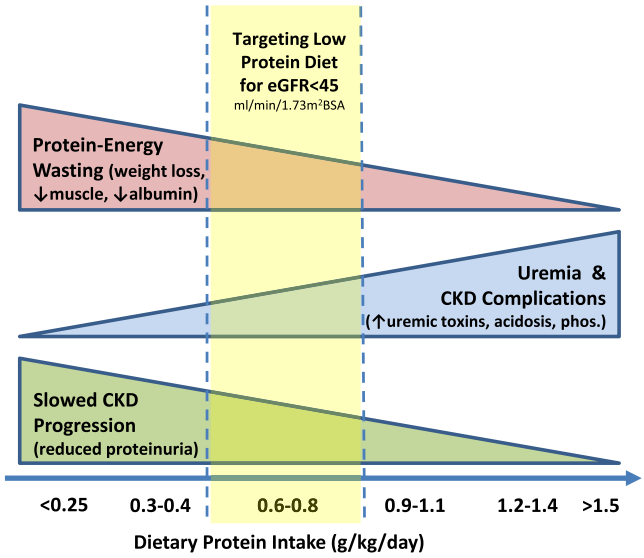

Figure 1. Schematic representation of the level of dietary protein intake and its potential risks and benefits in CKD. The 0.6 g protein/kg/day diet is preferable to 0.8 g/kg/day for people with stage 4 and 5 CKD, because this former diet is also nutritionally adequate and it further reduces the generation of uremic toxins. However, with 0.6 g protein/kg/day some patients may have more difficulty with dietary adherence and also with maintaining adequate energy intake. Adapted with permission from Kalantar-Zadeh and Fouque.[24]

dietary prescription. Thus, one needs to take into consideration all of these factors when tailoring nutritional therapy to the patients concerned. Currently, we do not have much information in this regard. More research will be needed to further our understanding and improve precision nutrition management.

Timing of Dialysis Initiation and Incremental Dialysis

Last but not least, the timing of dialysis initiation is important for precision nutrition management in CKD. The appropriate timing for dialysis initiation has long been controversial in advanced CKD management. Current Kidney Disease Outcome Quality Initiative guidelines recommend dialysis initiation when GFR decreases to less than 6 mL/min/1.73 m^2 or earlier if patients have uremic symptoms.[34] Protein-restricted diets may have an important role in alleviating uremic symptoms or complications, thereby delaying the need for dialysis treatment initiation apart from slowing the rate of CKD progression in patients with advanced CKD. Furthermore, a protein-restricted diet may reduce the need for conventional frequent dialysis and may facilitate and enhance the effectiveness of incremental dialysis. Incremental dialysis may be performed by initiation of dialysis treatment at an approximate frequency of once per week, and then the dose of dialysis treatment may be titrated up gradually according to the clinical needs and residual kidney function of the patient. The rationale for combining a protein-restricted diet with less frequent dialysis is, first, to reduce the generation of uremic toxins, and, second, to reduce the need for frequent dialysis so to better preserve residual kidney function. There is some evidence that more frequent dialysis may accelerate the loss of residual kidney function (RKF).[35] A greater decrease in RKF was associated with a more adverse prognosis and greater mortality in dialysis patients.[36-38] Indeed, combined diet and dialysis therapy may be a valid alternative therapy to conventional frequent dialysis with free diet as proposed in the 1990s by different investigators.[39,40] Bolasco et al[41] recently discussed adopting incremental hemodialysis in transition of care from advanced CKD to ESRD as opposed to initiation of standard 3 times per week hemodialysis in all ESRD patients. Analysis of data from the United States has shown that incremental hemodialysis may be associated with better preservation of RKF than conventional hemodialysis.[42] Among subjects with residual urea clearance greater than 3 mL/min/1.73 m^2 or urine volume greater than 600 mL/d, all-cause mortality rates did not differ between subjects receiving incremental dialysis versus conventional hemodialysis.[42] These data suggest that incremental hemodialysis may be a viable alternative treatment option for incident dialysis patients with a minimum level of RKF. Personalizing nutritional therapy in patients receiving incremental dialysis may help to better preserve RKF and delay the need to initiate hemodialysis three times per week. This should have significant cost benefits and at the same time improve patients' quality of life by having more time off from dialysis and allowing for adjustment to more frequent dialysis treatments.

Finally, personalized nutritional management may play a role in managing patients who have advanced CKD and either have decreased chronic dialysis treatment or are not considered candidates for dialysis therapy (eg, patients with disseminated carcinomatosis by limiting uremic symptoms resulting from the generation of toxic nitrogenous metabolites and other uremic retention solutes).

WHAT ASPECTS OF DIETARY MANAGEMENT MAY BE USEFUL IN DELAYING CKD PROGRESSION AND DIALYSIS INITIATION?

Salt Restriction

Early experimental data suggested that salt restriction reduced kidney injury and fibrosis. A randomized trial in nondiabetic nephropathy patients suggested that moderate salt restriction to a guideline recommended level of 50 mmol/d sodium and as add-on to monotherapy of renin-angiotensin system blockade reduced proteinuria and blood pressure more effectively than dual blockade of the renin-angiotensin system.[43] Notably, proteinuria reduction by sodium restriction remained significant after adjusting for a reduction in blood pressure,

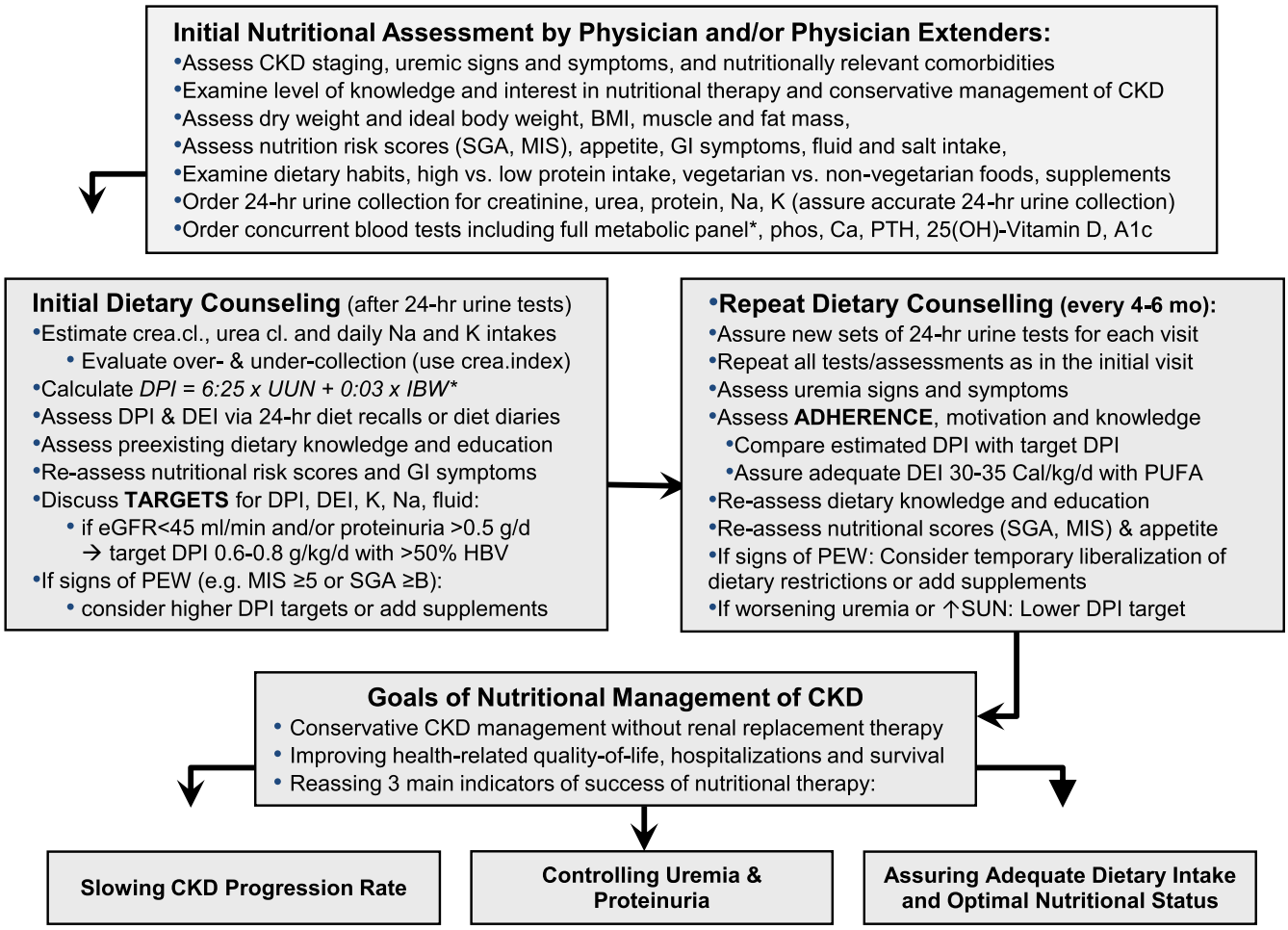

Figure 2. Suggested algorithm and steps for the approach to the nutritional management of patients with CKD. Note that in addition to direct dietary assessments, periodic 24-hour urine collections should be used to estimate dietary protein, sodium, and potassium intake to assess adherence to dietary recommendations. Comprehensive metabolic and glycemic panels include electrolytes, SUN, creatinine, glucose, hemoglobin A1c, liver function tests, and the lipid panel. The full equation is as follows: dietary protein intake = 6.25 × urine urea nitrogen + 0.03 × ideal body weight. Add the amount of daily proteinuria in grams if proteinuria is greater than 5 g/d. Calculate the creatinine index (24-hour urine creatinine divided by actual weight or ideal body weight if obese) and compare it with the expected value of 1 to 1.5 g/kg/d for women and 1.5 to 2 g/kg/d for men. Dietary supplements can be added to provide additional sources of energy and/or protein including, but not limited to, CKD-specific supplements, essential amino acids, or ketoanalogues (keto acids) of amino acids. To ensure adequate dietary energy intake of at least 30 to 35 kcal/kg/d, higher fat intake can be considered (eg, nonsaturated fats, omega 3–rich flaxseed, canola, and olive oil). If worsening uremic signs and symptoms occur, a dietary protein intake less than 0.6 g/kg/d with or without supplements can be considered. BMI, body mass index; DEI, dietary energy intake; DPI, dietary protein intake; GI, gastrointestinal; HBV, high biologic value; IBW, ideal body weight; MIS, malnutrition–inflammation score; Phos., phosphorus; PTH, parathyroid hormone; PUFA, polyunsaturated fatty acids; SGA, subjective global assessment; SUN, serum urea nitrogen; UUN, urine urea nitrogen. Adapted with permission from Kalantar-Zadeh and Fouque.[24]

suggesting an independent effect of sodium restriction on renoprotection both on its own or when used in combination with blockade of the renin-angiotensin system.[44]

In type 2 diabetic nephropathy patients, salt restriction is useful in enhancing antiproteinuric effects of angiotensin-receptor blockers.[45] Several post hoc analyses from large randomized trials including the Ramipril Efficacy in Nephropathy Trial, and the Reduction of Endpoints in noninsulin-dependent diabetes mellitus with the Angiotensin II Receptor Antagonist Losartan Study/Irbesartan Diabetic Nephropathy Trial, examined 24-hour urine sodium excretion.[46] Results showed that in the angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker (ARB) treatment arm, the risk of reaching renal or cardiovascular end point was at least two-fold higher among subjects in the highest tertile of 24-hour urine sodium excretion than those in the lowest tertile. Furthermore, treatment benefit from ARB over conventional antihypertensive treatment was seen in subjects with 24-hour urine sodium excretion in the lowest tertile.[47] These data suggest that in CKD patients, dietary sodium intake amount affects the efficacy of renin-angiotensin aldosterone system (RAAS) blockade treatment. In subjects with moderate dietary sodium restriction, treatment with RAAS blockade is associated with significant renal and cardiovascular benefits. However, in patients ingesting excessive sodium, RAAS blocker treatment failed to exert significant antiproteinuric

effect.[47] Thus, sodium intake is an important target in dietary management of CKD patients.

The KDIGO guideline recommended the daily sodium intake should be restricted to less than 2 g/d (or 90 mmol sodium/d) for CKD patients.[48] Restricting sodium intake to no more than 2 g/d is also one of the current top priorities for the World Health Organization to combat the huge global burden of noncommunicable diseases.[49]

Protein Restriction

Low-protein diets have been recommended for CKD management for more than a century. Its efficacy was first observed in animal studies showing how high protein intake relative to functioning renal mass may contribute to progressive kidney function decline by dilatation of afferent arterioles, causing glomerular hyperfiltration and up-regulation of proinflammatory gene expression, resulting in glomerular injury.[50,51] Because a reduction in the number of functioning nephrons occurs as kidney disease progresses, there are compensatory or adaptive hemodynamic changes that occur in the remnant nephrons. Brenner et al[52,53] proposed that these hemodynamic changes result in glomerular hypertension and hyperfiltration that contribute to progressive deterioration in kidney function. Restricting dietary protein intake early in the course of renal disease minimizes the compensatory hemodynamic changes and glomerular hyperfiltration and thereby may reduce progression of kidney disease. Other mechanisms that damage the remaining functional nephrons also may come into play as kidney disease progresses.

However, data examining the efficacy of LPD in CKD patients has not been conclusive in the past 30 years. In the MDRD study, renal clearance of iothalamate was used to assess glomerular filtration rate. The study consisted of two parts. Study A included nondiabetic patients with a GFR of 25 to 55 mL/min who were randomized to receiving usual phosphorus and protein (1.3 g/kg/d) versus low phosphorus and low protein intake (0.58 g/kg/d). Study B included nondiabetic patients with a GFR of 13 to 24 mL/min who were randomized to a low protein diet (0.58 g/kg/d) or ketoanalogue-supplemented VLPD (0.28 g/kg/d). The primary conclusion was that there was no difference in the rate of decrease in GFR between the two diets in study A, and there was a slight but not clearly significant slowing in decrease in GFR with the VLPD in study B ($P = .067$).[33] Secondary analyses of study A showed that the low protein diet was beneficial to CKD patients. By separating the time course of the MDRD study into two phases, GFR showed a significantly slower GFR decrease in the low protein diet group compared with the usual protein diet group (mean difference, 1.1 mL/min/y) after the initial 4 months on LPD. However, within the first 4 months, the mean GFR decrease was significantly faster in the LPD group (mean difference, 1.6 mL/min/y) compared with the usual protein diet group.[54] The initial greater decrease in GFR with low protein diet was interpreted to be owing to reversible hemodynamic changes and not reflect greater renal injury. The subsequent slower decrease in GFR with the low protein diet was considered to be a renoprotective effect of this diet that reduced continued renal injury. Several other early and small studies also suggested that a protein-restricted diet may slow the decrease in GFR and delay the onset of ESKD in both nondiabetic[55] and diabetic CKD patients[56] and is nutritionally safe.[55] However, other studies failed to confirm these findings or showed only very modest effects on slowing of kidney function decline.

A number of systematic reviews has examined the efficacy of LPD or VLPD in patients with CKD (Table 1). Pedrini et al[4] showed that LPD reduced renal failure or renal death in nondiabetic CKD and decreased the GFR decrease in diabetic CKD versus the usual protein diet. In the pooled analysis by Fouque and Laville,[2] LPD (0.6 g/kg/d) reduced renal death by 24% whereas VLPD (0.3-0.6 g/kg/d) reduced renal death by 37% compared with the usual protein diet in nondiabetic CKD patients. On the other hand, Kasiske et al[1] showed in a systematic review of 1,919 patients that LPD modestly slowed down the rate of decrease in eGFR by 0.53 mL/min/y (95% confidence interval, 0.08-0.98 mL/min/y). In another recent systematic review, LPD (<0.8 g/kg/d) was associated with a lower risk of progression to ESKD and a trend toward lower all-cause death risk. VLDL (protein intake, <0.4 g/kg/d) was associated with a lower risk of progression to ESKD and a greater preservation of kidney function and a trend toward less azotemia in CKD stage 3 to 5 subjects.[3] Together, these data suggest potential benefits of LPD or VLPD in slowing CKD progression to ESKD and delaying the need for dialysis initiation. On the other hand, another pooled analysis showed no benefit of LPD on CKD progression in diabetic kidney disease.[57] The differences in the results between the meta-analysis may relate to the fact that the article by Fouque and Laville[2] used renal death or onset of renal replacement therapy as the study outcome versus Kasiske et al,[1] who used a decrease in GFR as the outcome.

A LPD of 0.6 g/kg/d is considered nutritionally safe for most stable CKD patients without hypercatabolic conditions and will result in generation and retention of less uremic solutes than higher protein intakes, including the 0.8 g protein/kg/d diet. However, a protein intake of 0.6 g/kg/d often is less well tolerated compared with higher protein intakes, and some patients may have difficulty in maintaining adequate energy intake. It is also more challenging to achieve long-term adherence with lower protein intake. The VLPD generally provides 0.3 to 0.4 g/kg/d protein intake and will require supplementation with 7 to 15 g ketoanalogues, which provide 5 keto acid or hydroxyacid analogue of essential amino acids, also the essential amino acids histidine,

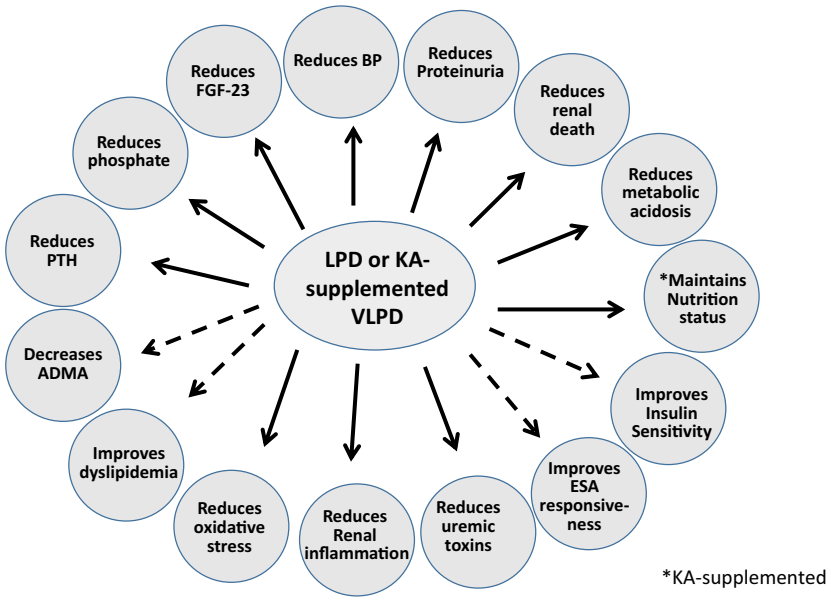

Figure 3. Benefits of low protein diet and keto acid–supplemented very low protein diet. ADMA, asymmetric dimethyl arginine; BP, blood pressure; ESA, erythropoietin stimulating agent; FGF, fibrogenic growth factor; PTH, parathyroid hormone.

tryptophan, lysine, and threonine, and often one or two nonessential amino acids.

In a more contemporary prospective randomized controlled trial, ketoanalogue-supplemented vegetarian VLPD (0.3 g/kg vegetable proteins with 1 capsule per 5 kg/d ketoanalogues) was compared with the conventional low protein diet (0.6 g/kg/d) in 207 nondiabetic CKD stages 4 to 5 patients over a treatment period of 15 months. The primary composite end point was initiation of renal replacement therapy or more than a 50% reduction in initial eGFR. In both the intention-to-treat and per-protocol analyses, the number of patients with an eGFR less than 30 mL/min/1.73 m^2 needed to be treated to avoid one primary composite end point of dialysis initiation or greater than 50% reduction in eGFR without causing detrimental effects on the nutrition status were 4.4 (95% confidence interval, 4.2-5.1) and 4.0 (95% confidence interval, 3.9-4.4), respectively. However, when a lower eGFR threshold of less than 20 mL/min/1.73 m^2 was considered, only two patients needed to be treated to avoid one composite end point and three patients needed to be treated to avoid one dialysis initiation. The results were similar in both the intention-to-treat and per-protocol analyses. Interestingly, the KA-supplemented VLPD appeared to have more favorable effects via improved mineral metabolism and phosphate control and reduced metabolic acidosis and inflammation, than by a reduction in eGFR decline.[22]

A very recent observational longitudinal analysis of data from the Taiwan National Health Insurance Database also showed that among advanced CKD patients receiving LPD, patients receiving ketoanalogue supplementation had a lower risk for long-term dialysis and composite outcome of long-term dialysis or all-cause mortality when the daily keto acid dose was more than 5.5 tablets. The beneficial effect was consistent in subgroup analyses and was independent of age, sex, and comorbidities.[58] Similarly, Piccoli et al[59] reported that a LPD of 0.6 g/kg/d may help delay the need to initiate dialysis and thus be more cost saving.

MECHANISMS OF THE BENEFICIAL EFFECTS OF LPD OR KETOACID-SUPPLEMENTED VLPD

The potential benefits of LPD or keto acid–supplemented VLPD are shown in Figure 3.

Beneficial Effects on the Kidney

LPD or KA-supplemented VLPD may ameliorate kidney injury via a number of different mechanisms other than reducing glomerular filtration and direct cellular injury. Experimental studies have shown that LPD ameliorated renal inflammation and protected the kidneys against oxidative stress, thus reducing mesangial proliferation, glomerulosclerosis, and kidney fibrosis.[51] There is some suggestion that KA-supplemented LPD may play a more protective role against oxidative stress than LPD alone.[60] Furthermore, KA-supplemented LPD may ameliorate kidney injury by repressing inflammation and oxidative stress, which up-regulates expression of Kruppel-like factor-15 in mesangial cells. Kruppel-like factor-15 is a transcription factor that plays a negative regulatory role in cardiac fibrosis and increased Kruppel-like factor-15 significantly decreased type IV collagen and fibronectin expression from mesangial cells, thus reducing glomerulosclerosis and kidney fibrosis in an experimental model of CKD.[61] Notably, in an experimental glomerulonephritis

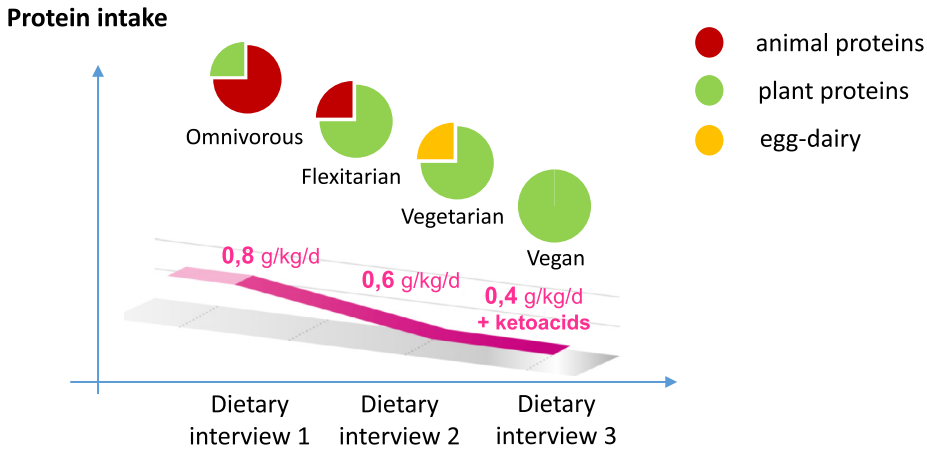

Figure 4. A stepwise approach to implement and reach the prescribed target for a low protein diet or keto acid–supplemented very low protein diet.

model, combined treatment of LPD with angiotensin-receptor blockade was more effective in reducing proteinuria, transforming growth factor-β overexpression, and glomerular matrix accumulation compared with ARB or angiotensin-converting enzyme inhibitor treatment alone, suggesting that a protein-restricted diet may reduce kidney injury via mechanisms different from renin-angiotensin system blockade.[62] Similarly, there are human data supporting an additional antiproteinuric effect by combining LPD with angiotensin-converting enzyme inhibition in human renal disease.[63]

Metabolic Benefits

Protein-restricted diets have other important metabolic benefits including decreasing sodium intake and improving blood pressure control in patients with advanced CKD.[64] LPD and VLPD reduces phosphorus load and serum phosphate, which reduces fibrogenic growth factor-23 (FGF-23) secretion. In a prospective randomized cross-over study in advanced CKD patients, a greater reduction in fibrogenic growth factor-23, serum and urine phosphate were observed after a 1-week treatment with VLPD compared with LPD.[65] High fibrogenic growth factor-23 levels induce left ventricular hypertrophy[66] and are associated with an increased risk of death, cardiovascular events, and initiation of dialysis in advanced CKD.[67] High phosphorus loads also attenuate the antiproteinuric effect of VLPD[68] as well as angiotensin-converting enzyme inhibition in CKD.[69]

Beneficial Effects on Uremic Retention Solutes Generation

A protein-restricted diet also reduced the generation of urea nitrogen as well as various uremic retention solutes including p-cresol sulfate and indoxyl sulfate. Experimental data have suggested that these latter two uremic retention solutes may increase oxidative stress and induce toxic effects on vascular endothelial cells, cardiac myocytes, mesangial cells, and tubular cells, causing both cardiovascular disease and further kidney injury.[70] The experimental evidence is consistent with observational data showing that P-cresol sulfate and indoxyl sulfate concentrations are associated with the progression of CKD and all-cause mortality.[71–74] Notably, the free p-cresol sulfate fraction of the protein-bound uremic retention solutes may be one factor causing the increased risk of mortality and cardiovascular events in CKD.[75,76]

Effects on Acids Generation Beneficial

VLPD with KA supplementation also reduces acid generation and metabolic acidosis in CKD.[77,78] In CKD, higher acid loads may be associated with higher serum phosphate and phosphaturia.[79] Treatment of metabolic acidosis with fruits and vegetables reduces acid generation and is associated with less kidney injury in CKD.[80–82] There is some evidence that VLPD may improve insulin sensitivity in advanced CKD patients.[83] However, it currently remains unclear whether the multiple potential benefits of LPD or keto acid–supplemented VLPD may be mediated partly via the use of ketoanalogues.

PRACTICAL CONSIDERATIONS IN IMPLEMENTATION OF LPD

Although LPD and VLPD may have potential benefits in slowing CKD progression, an important practical problem frequently encountered in clinical practice with LPD/VLPD prescription is patients' adherence to LPD/VLPD prescription. Adherence to dietary protein

prescription has been defined as the actual protein intake being within a 20% difference from prescribed protein intake. Various studies have reported adherence rates to LPD of 42% to 70%.[84–86] In the study by Garneata et al,[22] fewer than half of the patients who fulfilled study inclusion criteria agreed to follow a vegetarian diet and only 14% were compliant during the run-in phase and randomized further into the study. This is consistent with our experience that approximately 15% of CKD patients will adhere well to prescribed low-protein diets. Some data suggest that adherence to LPD may be related inversely to the severity of protein restriction. In one trial, compliance to a protein intake of 0.55 g/kg/d was only 27%.[87] Thus, a personalized approach is essential in identifying and selecting the appropriate CKD candidates for LPD/KA-supplemented VLPD therapy. Intensive dietary counselling and ongoing close frequent monitoring are required to improve dietary adherence. Another strategy that may improve adherence to nutrition therapy is to allow dietary "liberalization" for perhaps one meal per week, as suggested by Piccoli et al.[88] In one study, no specific medical or social factor was identified to predict adherence to KA-supplemented VLPD.[88] In the study by Garneata et al,[22] patients who were older than age 65 years or younger than age 45 years showed greater adherence to VLPD intervention. Having strong family and social support and being a vegan also favored adherence to dietary intervention. These data suggest that making the appropriate candidate selection appears a crucial first step for successful implementation of a KA-supplemented VLPD. One practical strategy to improve adherence to LPD or KA-supplemented VLPD is to adopt a graduated approach in which the prescribed protein intake amount is reduced by 0.2 g/kg/d through each dietary counseling and consultation visit. Over three or more dietary consultations, the prescribed dietary protein intake will reach the target level of 0.6 g/kg/d for LPD or 0.3 to 0.4 g/kg/d for keto acid−supplemented VLPD (Fig. 4).

CONCLUSIONS

Precision medicine is an evolving clinical concept and effort that is applicable to the nutritional management of patients with advanced CKD and ESKD with transition to dialysis. Numerous genetic, epigenetic, phenotypic, social, demographic, and psychological factors of patients and health care manpower and facilities, as well as economic factors, may interplay to determine individual patient responses and outcomes to the tailored nutritional therapy and prescription. This approach is especially relevant for the prescription of a protein-restricted diet in advanced CKD patients. An important understanding of these various factors will be essential in identifying and selecting the right candidate for successful implementation of protein-restricted diets in advanced CKD patients.

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