# 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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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