REVIEW ARTICLE

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Nutritional Management of Chronic Kidney Disease

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Chronic kidney disease, defined as evidence of structural or functional renal impairment for 3 or more months, is generally progressive and irreversible, affecting multiple metabolic pathways.[1] Altered protein and energy homeostasis, abnormal protein catabolism, acid–base derangements, and hormonal dysfunction ensue. Normal growth and development may be hindered, especially in children.[2] Chronic kidney disease is categorized in stages, with symptoms that vary across the stages (see Box S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). However, as chronic kidney disease progresses, the accumulation of nitrogen-containing products from dietary and intrinsic protein catabolism may distort taste and smell and blunt appetite.[2] Gastrointestinal nutrient absorption ultimately becomes abnormal, since uremia affects the microbiome and disrupts intestinal epithelia.[3] Muscle and fat wasting may develop as kidney failure advances, exacerbated by coexisting conditions and frailty, particularly in elderly patients, who account for a large proportion of those who are affected. Hence, nutritional status often becomes disordered, and protein–energy wasting is common, requiring dietary adjustments in this population. Beyond dietary adjustments, however, nutritional therapy may help to manage uremia, as well as other complications such as electrolyte and acid–base imbalances, water and salt retention, mineral and bone disorders, and failure to thrive. In fact, dietary interventions may also be used for the conservative management of uremia or as a means of delaying or avoiding dialysis therapy, according to the patient's preference. It is possible, though not yet unequivocally proved, that nutritional interventions slow disease progression independent of uremia management. Given that approximately 10% of the adult population worldwide has chronic kidney disease[4] and considering the exceptionally high costs and burden of maintenance dialysis therapy and kidney transplantation, dietary interventions may be increasingly chosen as a management strategy for chronic kidney disease. This review considers several aspects of the nutritional management of chronic kidney disease in adults.

Role of Dietary Constituents in Kidney Disease

Protein

Whether the quantity or quality of ingested protein is a risk factor for incident kidney disease has been debated for nearly a century. Experimental evidence suggests that long-term dietary protein intake exceeding 1.5 g per kilogram of ideal body weight per day may cause glomerular hyperfiltration[5] and proinflammatory gene expression,[6] which are known risk factors for kidney disease, as in the diabetic nephropathy model.[7] A high-protein diet, which is a popular weight-reduction strategy, has been shown to exacerbate proteinuria in persons with diabetes or

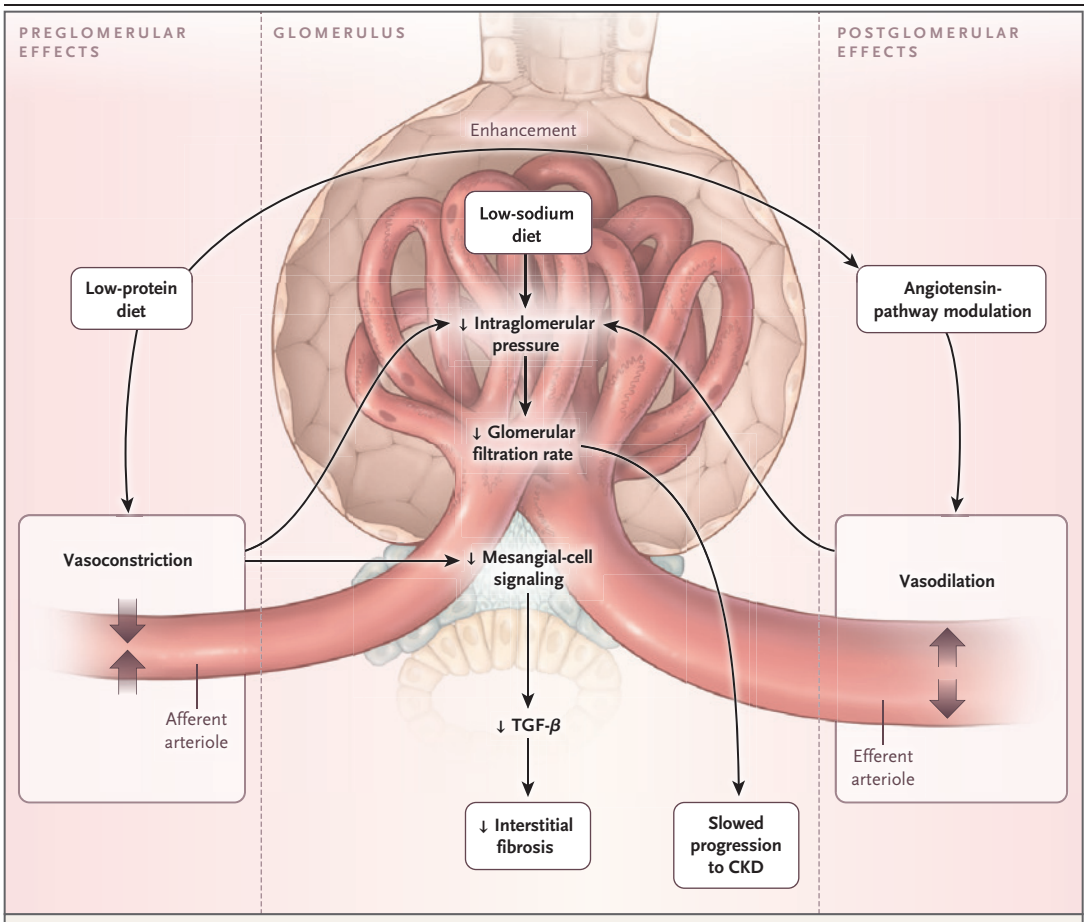

Figure 1. Effects of a Low-Protein, Low-Salt Diet on the Afferent Arteriole.

A lower intake of dietary protein leads to greater constriction of the afferent arteriole. Thus, a low-protein diet results in incremental reductions in the glomerular filtration rate, but over time, a sustained low-protein diet has been observed to diminish glomerular damage and stabilize or improve function. A potential secondary effect of lowered intraglomerular pressure is mitigation of mesangial-cell (M) signaling, leading to lower transforming growth factor β (TGF-β) expression and reduced interstitial fibrosis. It has been shown experimentally that the renoprotective effects of a low-protein diet can be synergistic with the direct effect of a low-sodium diet, as well as the effect of angiotensin-pathway modulators such as angiotensin-converting–enzyme inhibitors and angiotensin-receptor blockers, which dilate the efferent arteriole and reduce intraglomerular pressure and glomerular damage. In contrast, a high-protein diet dilates the afferent arteriole and elevates intraglomerular pressure, leading to an increased glomerular filtration rate over a short period, but the glomerular hyperfiltration ultimately stimulates mesangial-cell signaling, leading to increased TGF-β release and subsequent progressive fibrosis and renal damage. CKD denotes chronic kidney disease.

hypertension,[8] but its net effect on kidney health is unclear.

Why should the amount and type of protein intake influence the risk of chronic kidney disease? Animal models have shown that low protein intake constricts the glomerular afferent arterioles and lowers intraglomerular pressure, whereas a high-protein diet dilates the afferent arterioles, which increases glomerular filtration.[9] Over time, glomerular hyperfiltration itself may damage the remaining glomeruli.[10] Thus, a low-protein diet has a preglomerular effect that may enhance the postglomerular effect of angiotensin-pathway modulators that dilate the efferent arterioles and consequently lower intraglomerular pressure (Fig. 1).[11]

Findings from studies of dietary protein restriction in humans, however, have been less consistent. The Modification of Diet in Renal Disease (MDRD) study showed that the progression of kidney disease is only minimally decelerated by a low-protein diet,[12] though several rele-

vant limitations of the MDRD study, such as the relatively small sample and short follow-up time, should be noted (Table S1 and Fig. S1 in the Supplementary Appendix).[13] Most other controlled trials have confirmed the beneficial effects of restricted protein intake (Table S2 in the Supplementary Appendix), as did several meta-analyses that included the MDRD study.[14] Dietary protein sources may influence the outcome. A recent cohort study using a food-frequency questionnaire showed that a high intake of red and processed meat was associated with an increased risk of chronic kidney disease, whereas a lower risk was observed with a diet rich in nuts, legumes, and low-fat dairy products.[15]

Altogether, the current evidence suggests that a low-protein diet mitigates proteinuria in both experimental models[5] and human kidney disease.[16] The amelioration of proteinuria is probably related to the reduction in intraglomerular pressure (Fig. 1),[11] which is a favorable effect that is independent of angiotensin-pathway modulation.[11] Such a reduction in pressure also is relevant in any range of proteinuria[17] and when kidney disease is in a relatively early stage, before the development of renal insufficiency, particularly in a patient who was previously consuming a high-protein diet.[11,18]

Restricting dietary protein also results in a proportional reduction in urea generation.[19] After protein breakdown, individual amino acids are deaminated by removal of an α-amino group, leaving a carbon skeleton of ketoacids, which can be recycled to form other amino acids and proteins or can be used for energy generation through the tricarboxylic acid cycle,[20] while urea is generated through the urea cycle (Fig. 2). A persistently high blood urea level, termed azotemia, which is a commonly used marker for uremia, may enhance protein carbamylation and generate reactive oxygen species, leading to oxidative stress, inflammation, endothelial dysfunction, and ultimately, cardiovascular disease.[21] Ameliorating azotemia by reducing protein intake results in parallel reductions of other nitrogenous compounds that are thought to act as uremic toxins.[22] Although uremic symptoms diminish by the consumption of less protein, only limited studies have examined the effectiveness and safety of a low-protein diet as a means of deferring or avoiding the transition to dialysis therapy.[23,24]

Of the various ranges of low protein intake (Table S3 and Fig. S2 in the Supplementary Appendix), 0.6 to 0.8 g per kilogram of body weight per day is the most frequently recommended target for adults with moderate-to-advanced kidney disease (estimated glomerular filtration rate [eGFR], <45 ml per minute per 1.73 m^2 of body-surface area) and for the management of substantial proteinuria (urinary protein excretion, >0.3 g per day). However, the so-called very-low-protein diet (<0.6 g of protein per kilogram per day), supplemented with essential amino acids or their ketoacids, is also used.[25] People at increased risk for kidney disease, such as those who have undergone nephrectomy for kidney donation or for cancer treatment or who have diabetes mellitus or hypertension or polycystic kidneys, may benefit from modest protein intake (<1 g per kilogram per day) in order to maintain a moderately low intraglomerular pressure.[26]

The safety and feasibility of low protein intake are among the main concerns associated with a low-protein diet, along with the risk of protein–energy wasting and adherence to dietary restrictions (Table 1).[27] For healthy persons, the recommended dietary allowance for protein is 0.8 g per kilogram per day, whereas 0.66 g per kilogram per day is the estimated average requirement for adults who have chronic kidney disease but are otherwise healthy. Hence, a diet consisting of 0.6 to 0.8 g of protein per kilogram per day fulfills dietary needs, especially if half the protein is of "high biologic value" (e.g., dairy products); the other half may be plant proteins. In clinical trials of low-protein diets administered at the lower threshold (0.6 g of protein per kilogram per day), deterioration of nutritional status has rarely, if ever, been reported.[12,27] However, for most children, as well as adults who are at increased risk for malnutrition, protein intake closer to 0.8 g per kilogram per day may be necessary to ensure appropriate growth and development and to prevent or correct protein–energy wasting. The safety of and adherence to a low-protein diet can be improved by providing adequate energy (30 to 35 kcal per kilogram per day) and ongoing nutritional education and surveillance.[28,29]

SODIUM AND FLUIDS

The association between dietary sodium intake and blood pressure is most pronounced in persons who consume a high-sodium diet (>4 g of

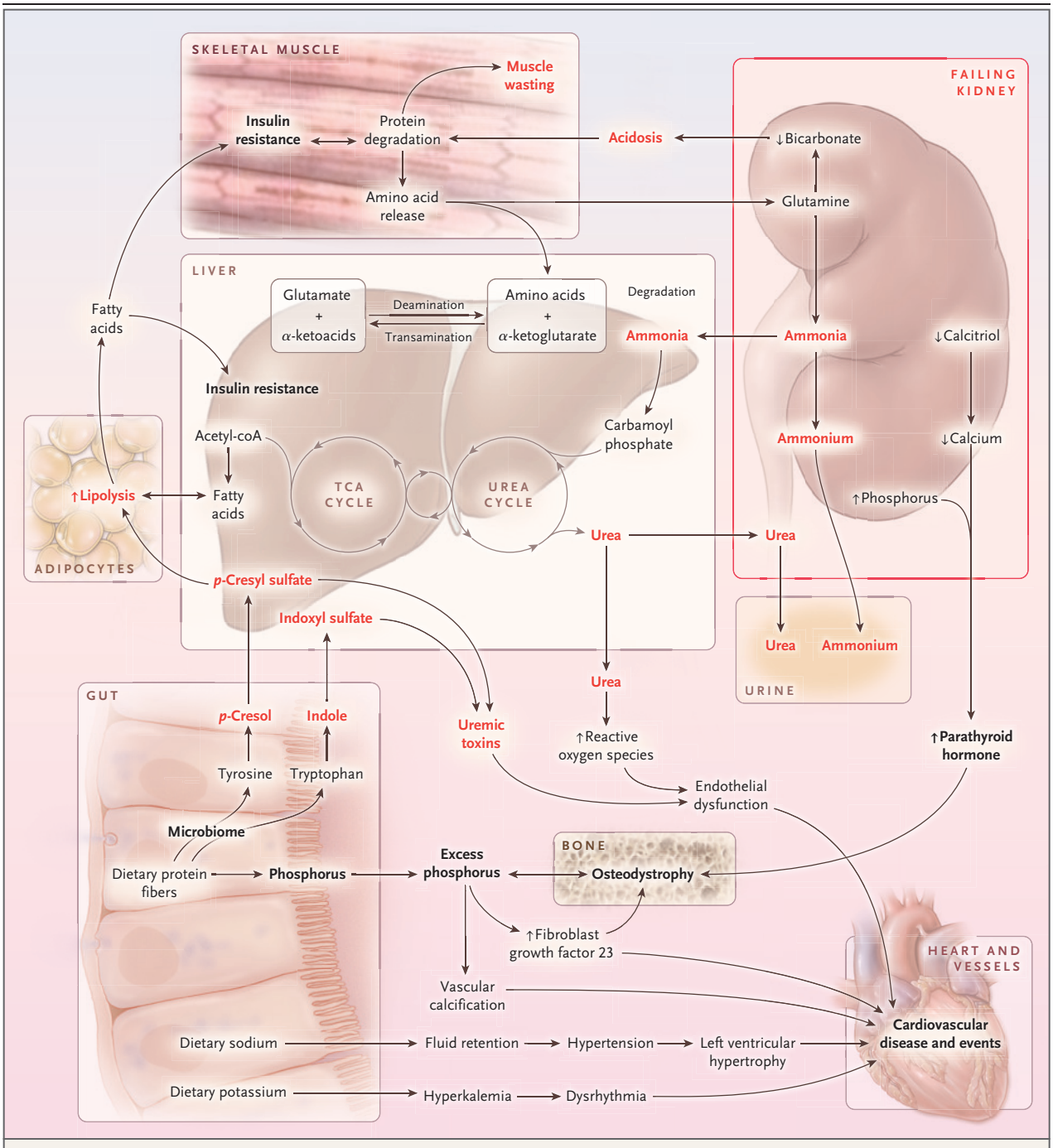

Figure 2. Pathways Involved in Protein and Amino Acid Metabolism in Chronic Kidney Disease.

The tricarboxylic acid (TCA) cycle comprises a series of chemical reactions that can metabolize amino acids. Amino groups are the products of amino acid deamination. Urea is synthesized through the urea cycle in the liver from the oxidation of amino acids or from ammonia. These mechanisms serve to trap and neutralize the highly volatile and toxic ammonia that is released from α-amino groups on transamination of amino acids in the liver. (Fig. S2 in the Supplementary Appendix provides more details on the intestinal tract.) Acetyl-CoA denotes acetyl–coenzyme A.

Table 1. Potential Benefits and Challenges of a Low-Protein Diet (LPD) in the Nutritional Management of Chronic Kidney Disease (CKD).*

Measure	Potential Benefits of LPD	Challenges and Risks of LPD	Comments
CKD progression	Synergistic effect with angiotensin-pathway modulators to lower intraglomerular pressure†	In first several months, slight drop in GFR may be observed, as shown in MDRD study‡	Inconclusive results in MDRD study, but small effect size in meta-analyses§
Proteinuria	Consistent antiproteinuric effect, which may mitigate hypoalbuminemia	LPD is contrary to notion that DPI must be increased to replace urinary protein loss	Some data suggest that even larger effect may be achieved with DPI of <0.6 g/kg/day
Uremia management and deferral of dialysis	Supported by consistent and biologically plausible data for almost a century	Unlikely to worsen uremia but potential risk of resurfacing or exacerbating PEW	Patients at increased risk for PEW may benefit from supplements (e.g., EAA or KA)
Metabolic acidosis	H^+ generation decreased in proportion to reduction in DPI, especially with larger proportion of plant-based food	The need for >50% HBV protein may prompt higher intake of non–plant-based foods that are more acidogenic	Although >50% HBV protein is recommended, the remainder can be from plant-based foods
Mineral and bone disease	The lower phosphorus content of LPD improves measures of mineral bone disease, including sHPT and high FGF-23	Higher calcium content in some KA preparations may increase calcium load	Additional improvements in bone health are possible by alleviating acidosis
PEW	Ameliorating hypoalbuminemia in patients with proteinuria may help neutralize circulating inflammatory compounds	Weight loss may occur; the habit of LPD intake may continue after starting thrice-weekly hemodialysis, when higher protein intake is recommended	Half of dietary protein source should be HBV protein; liberalize diet during correction of PEW
Cardiovascular and metabolic health	Lower protein intake is associated with lower dietary salt and saturated fat intake and may be less atherogenic, given higher proportion of plant-based food	Higher dietary fat intake (to achieve DEI of 30–35 kcal/kg/day) may confound the goal of achieving a heart-healthy diet	Higher proportions of unsaturated fat and complex carbohydrates recommended
Glycemic control and insulin response	Improvement in insulin resistance is likely	With LPD or VLPD, higher carbohydrate and fat intake (to achieve DEI 30–35 kcal/kg/day) may worsen glycemic control	Given increased insulin half-life and "burnt-out diabetes" with CKD progression, preventing hypoglycemic episodes is prudent
Quality of life and adherence to LPD	Enhanced patient-centeredness, given that many patients seek nutritional therapies and dietary advice	Challenges with adherence; diet fatigue, poor palatability, and cravings reported	Recommend creative recipes and strategies to engage patients
Mortality	There are no convincing data to suggest reduced mortality, although dialysis deferral is a potential mechanism, given high mortality during early dialysis	Increased mortality highly unlikely with DPI of 0.6–0.8 g/kg/day unless severe PEW emerges and is uncorrected	Consider supplements or other corrective strategies whenever PEW is suspected or diagnosed
Hypertension management	MDRD and other data suggest improved BP control	Reduction in BP is more likely a result of concomitant lower salt intake than of LPD itself	Higher potassium intake from more plant-based foods may be a potential mechanism
Microbiome modulation	Improved microbiome profile may be achieved through reduced uremic toxin generation	Possibility of promoting unfavorable microbiome milieu cannot be excluded	Uremia itself can lead to unfavorable microbiome

* A diet that provides 0.6 to 0.8 g of protein per kilogram of body weight per day is recommended most frequently. BP denotes blood pressure, DEI dietary energy intake, DPI dietary protein intake, EAA essential amino acids, FGF-23 fibroblast growth factor 23, GFR glomerular filtration rate, HBV high biologic value, KA ketoacids, MDRD Modification of Diet in Renal Disease, PEW protein–energy wasting, sHPT secondary hyperparathyroidism, and VLPD very-low-protein diet.

† Angiotensin-pathway modulators include angiotensin-converting–enzyme inhibitors and angiotensin-receptor blockers. See Tables S4 and S5 and Box S2 in the Supplementary Appendix for additional data and examples of meals.

‡ The MDRD study data were originally presented by Klahr et al.,[12] with an additional analysis by Levey et al.[13]

§ A meta-analysis by Kasiske et al. showed a significant but rather small effect size of an LPD in slowing the CKD progression rate.[14]

sodium per day), have underlying hypertension, or are over the age of 55 years.[30] In patients with established chronic kidney disease, dietary sodium restriction is invariably recommended to control fluid retention and hypertension and to improve the cardiovascular risk profile.[31] However, it is not clear that dietary sodium chloride restriction can slow the progression of established kidney disease. Since cardiovascular trials involving dietary sodium restriction often exclude patients with renal disease, there are limited relevant interventional data for such patients.[32] A reduced sodium intake enhances the effects of a low-protein diet and angiotensin-modulation therapy in decreasing intraglomerular pressure (Fig. 1)[33] and may also decrease proteinuria and slow the progression of kidney disease.[34]

Observational studies using urinary sodium excretion as a surrogate for sodium chloride intake have yielded inconsistent data, with some studies showing no association between dietary sodium intake and renal disease progression[35] and others showing a positive association.[36] A longitudinal study published in 2016, which involved serial 24-hour urine collections from 3939 patients with chronic kidney disease, suggested that the highest quartile of urinary sodium excretion (≥4.5 g per day), as compared with the lowest quartile (<2.7 g per day), was associated with 45% higher mortality and a 54% higher risk of disease progression.[36] Incrementally worse cardiovascular outcomes were observed when dietary sodium intake exceeded 4 g per day.[37] Observations in the general population suggest a J-shaped association; dietary sodium intake that is higher than 5 g per day and intake that is lower than 3 g per day are each associated with an increased risk of cardiovascular disease and death.[38] Although a daily dietary allowance of less than 2.3 g of sodium (<100 mmol) is often recommended for patients with cardiovascular disease, there is no evidence that patients with kidney disease will benefit from this very low level of sodium restriction. Therefore, a daily dietary sodium intake of less than 4 g (<174 mmol) is recommended for the overall management of chronic kidney disease and its associated risks, with a sodium intake of less than 3 g (<131 mmol) for the specific management of symptomatic fluid retention or proteinuria. Evidence supporting a sodium intake of less than 1.5 g per day (<87 mmol per day) for patients with renal insufficiency is lacking, given the risk of hyponatremia and adverse outcomes,[39] and patients with certain conditions, such as salt-losing nephropathies, should not be subjected to such stringent sodium restriction (Table 2).

Whereas adequate fluid intake may mitigate the risk of kidney disease,[41] patients with renal insufficiency generally have isosthenuria. This is the basis for the recommendation that patients with stage 3 chronic kidney disease limit fluid intake to less than 1.5 liters per day in order to avoid hyponatremia[39]; adjustment of that limit for a hot climate and other conditions associated with high insensible fluid losses is imperative. Adjunctive therapy with loop diuretics is often prescribed, particularly for patients who tend to have symptomatic fluid retention or hyponatremia, given the association of such conditions in chronic kidney disease with poor outcomes.[39]

POTASSIUM

Many potassium-rich foods, such as fresh fruits and vegetables, are considered healthy choices for most people, given the high fiber and vitamin content and low acidogenicity of such foods.[42] In some large population cohorts at high risk for cardiovascular disease[35] or diabetes,[43] higher urinary potassium excretion is associated with a lower likelihood of all renal complications except for hyperkalemia. Given the well-established association of higher dietary potassium with lower sodium intake and lower incidences of hypertension, stroke, nephrolithiasis, and kidney disease, a relatively high daily potassium intake, 4.7 g (120 mmol), is recommended for healthy adults, including those at high risk for kidney disease.[44] A higher dietary potassium intake, however, may be associated with a higher risk of kidney disease progression.[36] Among patients with very advanced chronic kidney disease, the highest quartile of dietary potassium intake, as compared with the lowest quartile, is associated with an increase in the risk of death by a factor of 2.4; the association is independent of the plasma potassium level and other nutritional measures.[45] In epidemiologic studies, both moderately low plasma potassium levels (<4.0 mmol per liter) and high levels (>5.5 mmol per liter) are associated with more rapid kidney disease progression.[46] Dietary potassium restriction is often recommended in patients with hyperkalemia, especially those with more advanced stages of

Table 2. Recommended Dietary and Nutrient Intake in Adults, According to the CKD Stage.*

Dietary Constituent	Normal Kidney Function with Increased CKD Risk	Mild-to-Moderate CKD†	Advanced CKD†	Transition to Dialysis†	Ongoing Dialysis or Any Stage with Existing or Imminent PEW
Protein (g/kg/day)	<1.0; increase proportion of plant-based proteins	<1.0 (consider 0.6–0.8 if eGFR <45 ml/min/1.73 m^2 or rapid progression)	0.6–0.8, including 50% HBV protein, or <0.6 with addition of EAA or KA	0.6–0.8 on nondialysis days and >1.0 on dialysis days	1.2–1.4; may require >1.5 if hypercatabolic state develops
Sodium (g/day)‡	<4 (<3 in patients with hypertension)§	<4; avoid intake of <1.5 if hyponatremia likely	<3; avoid intake of <1.5 if hyponatremia likely	<3	<3
Potassium (g/day)¶	4.7 (same as recommended for general population)	4.7 unless frequent or severe hyperkalemia excursions likely	<3 if hyperkalemia occurs frequently during high-fiber intake	<3 if hyperkalemia occurs frequently during high-fiber intake	<3; target high-fiber intake
Phosphorus (mg/day)‖	<1000; minimize added inorganic phosphorus in preservatives and processed foods	<800; minimize added inorganic phosphorus and encourage consumption of more plant-based foods	<800; minimize added inorganic phosphorus and encourage consumption of more plant-based foods	<800; minimize added inorganic phosphorus; consider phosphorus binder	<800; minimize added inorganic phosphorus; add phosphorus binder as needed
Calcium (mg/day)	1000–1300 (adjusted for age)	800–1000	800–1000	800–1000 or less	<800
Fibers, alkali, and plant-based foods (g/day)	25–30; target higher proportion (>50%) of plant-based foods (e.g., DASH diet)	25–30 or more; higher proportion (>50%) of plant-based foods	25–30 or more; consider >70% plant-based foods	25–30 or more	25–30 or more; suggest avoiding strict vegan diet
Energy (kcal/kg/day)**	30–35; adjust to target weight reduction if BMI >30††	30–35; increase proportion with LPD	30–35; increase proportion with LPD	30–35	30–35; target higher intake if PEW present or imminent
Fats	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids; increase proportion with low-protein intake	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids; increase proportion with low-protein intake	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids

* Normal kidney function is defined as an estimated GFR (eGFR) of at least 60 ml per minute per 1.73 m^2 of body-surface area. Patients in this category do not have substantial proteinuria but are at increased risk for CKD because of another condition (e.g., diabetes, hypertension, or polycystic kidney) or a solitary kidney. (A solitary kidney can be a congenital or acquired state, with the latter due to nephrectomy for donation or cancer treatment.) Mild-to-moderate CKD is defined as an eGFR of 30 to less than 60 ml per minute per 1.73 m^2 without substantial proteinuria (<0.3 g of protein per day). Patients with advanced CKD have an eGFR of less than 30 ml per minute per 1.73 m^2 or substantial proteinuria (>0.3 g per day). Patients transitioning to dialysis therapy usually have good residual kidney function. Protein–energy wasting (PEW) is defined according to the criteria of the International Society of Renal Nutrition and Metabolism.[40] In the denominator of the dietary recommendations for protein and energy, kg denotes the ideal body weight (IBW), especially for persons with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) above 30. The IBW can be estimated in males as 50.0 kg+2.3 kg for each inch over 5 ft (each 2.5 cm over 152.4 cm) and in females as 45.5 kg+2.3 kg for each inch over 5 ft. To convert phosphorus to millimoles per day, multiply by .03229. To convert calcium to millimoles per day, multiply by 0.02495. DASH denotes Dietary Approaches to Stop Hypertension.

† Kidney-transplant recipients may have an eGFR of 30 to less than 60 ml per minute per 1.73 m^2 or less than 30 ml per minute per 1.73 m^2 or may be transitioning to dialysis; the transition-to-dialysis stage includes incremental dialysis preparation. These three subgroups of patients can be approached similarly with respect to dietary management.

‡ Patients with certain conditions such as salt-losing nephropathies should not be subjected to sodium restriction.

§ For patients with heart failure, the American Heart Association recommends no more than 2.3 g of sodium per day (equivalent to 1 teaspoon of salt) and suggests an ideal limit of 1.5 g of sodium per day (https://sodiumbreakup.heart.org/how_much_sodium_should_i_eat).

¶ Patients who are undergoing peritoneal dialysis and have hypokalemia should have a goal of increasing their potassium intake.

‖ Dietary phosphorus should be restricted regardless of the patient's status with respect to hyperphosphatemia.

** Carbohydrates, which provide 40 to 60% of the daily energy intake, should be natural (nonrefined) and complex with a high-fiber content.

†† In obese patients, lower energy ranges can be targeted. Table S5 in the Supplementary Appendix provides recommendations for vitamin D, other vitamins, trace elements, management of weight and cardiovascular risks, and fluid management.

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kidney disease. However, excessive dietary restrictions can expose patients to less heart-healthy and more atherogenic diets[47] and worsen constipation, which may actually result in higher gut potassium absorption.[48] Despite a higher risk of hyperkalemia with the progression of kidney disease, few studies have examined the effects of dietary potassium restriction or methods of extracting potassium during food preparation and cooking. It is not clear whether potassium-binding agents can allow liberalization of dietary potassium intake with the inclusion of healthier potassium-rich foods.[42] In patients with a tendency toward hyperkalemia (>5.5 mmol of potassium per liter), a dietary potassium intake of less than 3 g per day (<77 mmol per day) is recommended, with the stipulation that a balanced intake of fresh fruits and vegetables with high fiber should not be compromised (Table 2).

PHOSPHORUS

In the general population, higher plasma phosphorus levels have been associated with an increased risk of incident kidney disease.[49] Overt hyperphosphatemia is infrequent in stages 1, 2, and 3 of chronic kidney disease, given the high circulating and tissue levels of parathyroid hormone and fibroblast growth factor 23 (FGF-23) in renal insufficiency, which promote urinary phosphorus excretion.[50] Elevated parathyroid hormone and FGF-23 levels can cause renal bone disease, left ventricular hypertrophy, vascular calcification, and accelerated progression of kidney disease from vascular and tubulointerstitial injury (Fig. 2), highlighting the importance of dietary phosphorus management, even in patients without apparent hyperphosphatemia.[51] Although a low-protein diet also decreases phosphorus intake, the quantity and bioavailability of phosphorus differ according to the type of protein. For instance, the phosphorus-to-protein ratio of egg whites and egg yolks (which have 3.6 and 2.7 g of protein per egg, respectively) is 1 to 2 mg and 20 to 30 mg per gram, respectively.[52] The gastrointestinal absorption of phosphorus, mostly in the form of phytates, is lower from plants (along with fibers) than from meat (30 to 50% vs. 50 to 70%).[53] Since food additives include readily absorbable inorganic phosphorus, ingestion of processed foods results in an even higher phosphorus burden (Table S4 in the Supplementary Appendix).[54] Restricting dietary phosphorus intake to less than 800 mg per day (26 mmol per day) is recommended for patients with moderate-to-advanced kidney disease, and processed foods with a high phosphorus-to-protein ratio should be minimized. However, in patients with stage 5 chronic kidney disease who receive dialysis therapy or who are at increased risk for protein–energy wasting, excessively stringent restriction of protein intake to control hyperphosphatemia may be associated with poor outcomes.[55] Thus, an individualized dietary approach that incorporates ample use of phosphorus binders is optimal.[56]

CALCIUM AND VITAMIN D

The renal insufficiency–associated decline in 1,25-dihydroxyvitamin D diminishes gastrointestinal absorption of calcium; however, passive diffusion of ionized calcium continues and may lead to a positive calcium balance, aggravated by diminished urinary calcium excretion due to secondary hyperparathyroidism.[57] Increased calcium release from bone in hyperactive renal bone disease (increased bone resorption because of secondary hyperparathyroidism) enhances the positive calcium balance and may worsen vascular calcification.[58] Gut calcium absorption varies because of differences in dissociation and bioavailability from one type of elemental calcium to another; for instance, calcium citrate is more readily absorbable than calcium acetate.[57] Two studies suggested that an intake of 800 to 1000 mg of elemental calcium per day (20 to 25 mmol per day) can result in a stable calcium balance in people with stage 3 or 4 chronic kidney disease.[57,59] Hence, whereas the suggested calcium intake for persons without kidney disease is 1000 to 1300 mg per day (25 to 32 mmol per day),[57] in patients with moderate-to-advanced chronic kidney disease, 800 to 1000 mg of elemental calcium per day from all sources should suffice (Table 2).[57,59]

Native vitamin D supplementation (cholecalciferol or ergocalciferol) may be offered to patients with chronic kidney disease in whom circulating vitamin D levels have been documented as low. In some studies, vitamin D analogues have been associated with decreased proteinuria in addition to healing of renal osteodystrophy.[60] Notwithstanding inconsistent data on the requirement for and effect of vitamin D in certain subpopulations of patients with chronic kidney disease,

including black Americans, who have lower total vitamin D levels and higher parathyroid hormone levels than white Americans,[61] hydroxylated vitamin D agents may be needed in addition to native vitamin D to control progressive secondary hyperparathyroidism.[62]

VEGETARIAN DIET, FIBER, AND THE MICROBIOME

Comparisons of data from populations with largely vegetarian diets and data from populations with meat-based diets do not clearly distinguish a difference in the risk of kidney disease between plant-based and animal-based protein.[63] Plant-based foods are recommended as part of many strategies for the prevention and management of kidney disease, since these foods contain smaller amounts of saturated fatty acids, protein, and absorbable phosphorus than meat, generate less acid, and are rich in fibers, polyunsaturated and monounsaturated fatty acids, magnesium, potassium, and iron. In patients with chronic kidney disease, a diet with a higher proportion of plant sources (>50%) has been associated with better outcomes.[64] Constipation can lead to higher retention of uremic toxins and hyperkalemia, whereas loosening stools may enhance fluid loss and removal of nitrogenous products.[65] The protein in a vegetarian diet is less fermentable and has high fiber content, increasing peristalsis and the number of bowel movements, and is associated with less uremic toxin production, exposure, and absorption.[66]

Uremia itself, as well as dietary restrictions and pharmacotherapy, including antibiotics, may alter the gut microbiome, and this change may have a bearing on the symptoms and progression of kidney disease (Fig. S3 in the Supplementary Appendix).[67] Microbiome modulation through dietary interventions such as probiotics may offer an opportunity to control the production, degradation, and absorption of certain uremic toxins that are fermentation by-products of gut microbial activities, including indoxyl sulfate, *p*-cresol, and trimethylamine.[67] As an example, in a study involving 40 patients with moderate-to-advanced chronic kidney disease, a lower ratio of dietary fiber to protein was associated with higher blood levels of indoxyl sulfate and *p*-cresol.[68] Nutritional and pharmacologic interventions, including the use of absorbent ingestible agents and high-fiber or vegetarian diets, are being tested as a means of reducing gut absorption of uremic toxins in order to control uremic symptoms and slow disease progression.[69]

CARBOHYDRATES, FATS, AND DIETARY ENERGY

Unrefined carbohydrates account for half the usual daily energy intake, and the proportion may be even higher with a low-protein diet. In patients with kidney disease, carbohydrates should be complexed with high fiber content (e.g., whole-wheat breads, multigrain cereal, oatmeal, and mixed fruits and vegetables) to help reduce dietary phosphorus and protein as well as urea and creatinine generation.[70] Such a diet is thought to promote a more favorable microbiome[71] with less constipation.[65] Nonsaturated fat is the preferred lipid in the diet. Replacement of butter with flaxseed, canola, or olive oil, all of which are rich in n–3 fatty acids, may be worthwhile.[47] For example, a recent study suggested that dietary n–3 fatty acid supplementation in patients with diabetes and hypertriglyceridemia may reduce albuminuria and preserve renal function.[72] There is currently no evidence that low-fat diets, recommended by some guidelines, improve kidney disease outcomes. In a low-protein diet, fat and carbohydrate should together account for more than 90% of the daily energy intake requirement of 30 to 35 kcal per kilogram to avoid protein–energy wasting.[27] Obviously, in patients with diabetic kidney disease, proper glycemic control should be maintained, but adequate energy intake is needed to mitigate the risk of protein–energy wasting and hypoglycemia, which increases with worsening kidney function.

DIETARY MANAGEMENT OF ACIDOSIS IN KIDNEY DISEASE

Daily acid production results from bicarbonate losses in the gut (20 to 30 mmol of bicarbonate per day), breakdown of amino and nucleic acids from proteins (20 to 30 mmol per day), and oxidation of carbohydrates and fats to lactic acid and ketoacids (10 to 20 mmol per day).[73] The kidneys regenerate the bicarbonate used for buffering by excretion of both net acid and acid

buffers, including phosphate, and by ammoniagenesis through deamination of glutamine in the proximal tubule and its synthesization to ammonium in the collecting ducts, with subsequent urinary excretion (Fig. 2).[73] Hence, kidney disorders, including renal tubular defects, are often associated with chronic metabolic acidosis, which leads to glucocorticoid overproduction with resultant muscle wasting, worsens uremia-associated insulin resistance, and increases parathyroid hormone release.[74] An increase in the dietary acid load may be associated with glomerular hyperfiltration.[75] Metabolic acidosis is associated with more rapid kidney disease progression and an increase in the overall risk of death. Hyperparathyroidism, along with chronic buffering of acid by bone, leads to progressive loss of bone mineral and worsening renal osteodystrophy. Hence, reduced protein intake with a greater proportion of diet from plant-based foods to correct acidosis improves bone mineralization and may slow protein breakdown and disease progression.[76] Adjunctive alkali therapy can also be considered to mitigate acidosis in patients with chronic kidney disease.[77]

TRACE ELEMENTS AND VITAMINS

Patients with kidney disease often have an imbalance of several critical trace elements and vitamins. Inadequate food intake may result in insufficient ingestion of antioxidant vitamins, including vitamins C and E and carotenoids, and in patients with advanced renal disease, folate, vitamin K, and calcitriol become deficient.[78] A micronutrient imbalance in patients with kidney disease may contribute to a higher burden of oxidative stress, inflammation, and cardiovascular disease.[78,79] Among the trace elements, iron deficiency is most problematic, given the high frequency of gastrointestinal blood loss in patients with chronic kidney disease.[80] Deficiencies of zinc, copper, and selenium may occur, whereas aluminum and magnesium levels may increase.[78] A recent study showed that 800 μg of folic acid per day, when added to enalapril, led to slower disease progression than enalapril given alone.[81] Experimental models of chronic kidney disease suggest that vitamin K supplementation may blunt the development of vascular calcification.[82] Daily intake of other vitamins and trace elements at conventional doses is often recommended both for persons at high risk for kidney disease and for those with established renal insufficiency.[78,79]

PRACTICE STRATEGIES

Dietary protein, energy, and micronutrient intakes should be assessed regularly. Also, 24-hour urine collections should be performed to estimate dietary intakes of protein (based on urinary urea nitrogen), sodium, and potassium; to measure creatinine clearance and proteinuria; and to evaluate adherence to dietary recommendations, with suggestions for improving adherence if necessary (Fig. S4 in the Supplementary Appendix). Excessive restrictions may be harmful and should be avoided.

CONCLUSIONS

Given the high incidence and prevalence of chronic kidney disease and an urgent need for alternative disease management strategies, nutritional interventions with disease-specific dietary ranges that are patient-centered and cost-effective may help increase longevity and prolong the dialysis-free interval for millions of people worldwide. Additional studies are needed to ensure a more robust, evidence-based approach to the nutritional management of chronic kidney disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011;80:17-28.
2. Armstrong JE, Laing DG, Wilkes FJ, Kainer G. Smell and taste function in children with chronic kidney disease. Pediatr Nephrol 2010;25:1497-504.
3. Vaziri ND, Yuan J, Norris K. Role of urea in intestinal barrier dysfunction and disruption of epithelial tight junction in chronic kidney disease. Am J Nephrol 2013;37:1-6.
4. Bello AK, Levin A, Tonelli M, et al. Assessment of global kidney health care status. JAMA 2017;317:1864-81.
5. Hostetter TH, Meyer TW, Rennke HG, Brenner BM. Chronic effects of dietary protein in the rat with intact and reduced renal mass. Kidney Int 1986;30:509-17.
6. Tovar-Palacio C, Tovar AR, Torres N, et al. Proinflammatory gene expression and renal lipogenesis are modulated by dietary protein content in obese Zucker fa/fa rats. Am J Physiol Renal Physiol 2011;300:F263-F271.

7. Brenner BM, Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA. The role of glomerular hyperfiltration in the initiation and progression of diabetic nephropathy. Acta Endocrinol Suppl (Copenh) 1981;242:7-10.
8. Wrone EM, Carnethon MR, Palaniappan L, Fortmann SP. Association of dietary protein intake and microalbuminuria in healthy adults: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:580-7.
9. Sällström J, Carlström M, Olerud J, et al. High-protein-induced glomerular hyperfiltration is independent of the tubuloglomerular feedback mechanism and nitric oxide synthases. Am J Physiol Regul Integr Comp Physiol 2010;299:R1263-R1268.
10. Cirillo M, Lombardi C, Chiricone D, De Santo NG, Zanchetti A, Bilancio G. Protein intake and kidney function in the middle-age population: contrast between cross-sectional and longitudinal data. Nephrol Dial Transplant 2014;29:1733-40.
11. Ruilope LM, Casal MC, Praga M, et al. Additive antiproteinuric effect of converting enzyme inhibition and a low protein intake. J Am Soc Nephrol 1992;3:1307-11.
12. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. N Engl J Med 1994;330:877-84.
13. Levey AS, Greene T, Beck GJ, et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? J Am Soc Nephrol 1999;10:2426-39.
14. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. Am J Kidney Dis 1998;31:954-61.
15. Haring B, Selvin E, Liang M, et al. Dietary protein sources and risk for incident chronic kidney disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. J Ren Nutr 2017;27:233-42.
16. Kaysen GA, Gambertoglio J, Jimenez I, Jones H, Hutchison FN. Effect of dietary protein intake on albumin homeostasis in nephrotic patients. Kidney Int 1986;29:572-7.
17. Maroni BJ, Staffeld C, Young VR, Manatunga A, Tom K. Mechanisms permitting nephrotic patients to achieve nitrogen equilibrium with a protein-restricted diet. J Clin Invest 1997;99:2479-87.
18. D'Amico G, Gentile MG, Manna G, et al. Effect of vegetarian soy diet on hyperlipidaemia in nephrotic syndrome. Lancet 1992;339:1131-4.
19. Weiner ID, Mitch WE, Sands JM. Urea and ammonia metabolism and the control of renal nitrogen excretion. Clin J Am Soc Nephrol 2015;10:1444-58.
20. Protein and amino acids. Washington, DC: National Academy of Sciences, Institute of Medicine, Food and Nutrition Board, 2005.
21. Berg AH, Drechsler C, Wenger J, et al. Carbamylation of serum albumin as a risk factor for mortality in patients with kidney failure. Sci Transl Med 2013;5:175ra29.
22. Patel KP, Luo FJ, Plummer NS, Hostetter TH, Meyer TW. The production of p-cresol sulfate and indoxyl sulfate in vegetarians versus omnivores. Clin J Am Soc Nephrol 2012;7:982-8.
23. Walser M, Hill S. Can renal replacement be deferred by a supplemented very low protein diet? J Am Soc Nephrol 1999;10:110-6.
24. Brunori G, Viola BF, Parrinello G, et al. Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly: a prospective randomized multicenter controlled study. Am J Kidney Dis 2007;49:569-80.
25. Garneata L, Stancu A, Dragomir D, Stefan G, Mircescu G. Ketoanalogue-supplemented vegetarian very low-protein diet and CKD progression. J Am Soc Nephrol 2016;27:2164-76.
26. Ko GJ, Obi Y, Tortorici AR, Kalantar-Zadeh K. Dietary protein intake and chronic kidney disease. Curr Opin Clin Nutr Metab Care 2017;20:77-85.
27. Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy. Am J Clin Nutr 2013;97:1163-77.
28. Wu HL, Sung JM, Kao MD, Wang MC, Tseng CC, Chen ST. Nonprotein calorie supplement improves adherence to low-protein diet and exerts beneficial responses on renal function in chronic kidney disease. J Ren Nutr 2013;23:271-6.
29. Paes-Barreto JG, Silva MI, Qureshi AR, et al. Can renal nutrition education improve adherence to a low-protein diet in patients with stages 3 to 5 chronic kidney disease? J Ren Nutr 2013;23:164-71.
30. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med 2014;371:601-11.
31. He FJ, Li J, Macgregor GA. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev 2013;4:CD004937.
32. O'Donnell M, Mente A, Yusuf S. Sodium intake and cardiovascular health. Circ Res 2015;116:1046-57.
33. Kwakernaak AJ, Krikken JA, Binnenmars SH, et al. Effects of sodium restriction and hydrochlorothiazide on RAAS blockade efficacy in diabetic nephropathy: a randomised clinical trial. Lancet Diabetes Endocrinol 2014;2:385-95.
34. McMahon EJ, Bauer JD, Hawley CM, et al. A randomized trial of dietary sodium restriction in CKD. J Am Soc Nephrol 2013;24:2096-103.
35. Smyth A, Dunkler D, Gao P, et al. The relationship between estimated sodium and potassium excretion and subsequent renal outcomes. Kidney Int 2014;86:1205-12.
36. He J, Mills KT, Appel LJ, et al. Urinary sodium and potassium excretion and CKD progression. J Am Soc Nephrol 2016;27:1202-12.
37. Mills KT, Chen J, Yang W, et al. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. JAMA 2016;315:2200-10.
38. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA 2011;305:1777-85.
39. Kovesdy CP, Lott EH, Lu JL, et al. Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. Circulation 2012;125:677-84.
40. Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int 2008;73:391-8.
41. Sontrop JM, Dixon SN, Garg AX, et al. Association between water intake, chronic kidney disease, and cardiovascular disease: a cross-sectional analysis of NHANES data. Am J Nephrol 2013;37:434-42.
42. Palmer BF, Clegg DJ. Achieving the benefits of a high-potassium, paleolithic diet, without the toxicity. Mayo Clin Proc 2016;91:496-508.
43. Araki S, Haneda M, Koya D, et al. Urinary potassium excretion and renal and cardiovascular complications in patients with type 2 diabetes and normal renal function. Clin J Am Soc Nephrol 2015;10:2152-8.
44. Water, potassium, sodium, chloride, and sulfate. Washington, DC: National Academy of Sciences, Institute of Medicine, Food and Nutrition Board, 2004.
45. Noori N, Kalantar-Zadeh K, Kovesdy CP, et al. Dietary potassium intake and mortality in long-term hemodialysis patients. Am J Kidney Dis 2010;56:338-47.
46. Chen Y, Sang Y, Ballew SH, et al. Race, serum potassium, and associations with ESRD and mortality. Am J Kidney Dis 2017;70:244-51.
47. Khoueiry G, Waked A, Goldman M, et al. Dietary intake in hemodialysis patients does not reflect a heart healthy diet. J Ren Nutr 2011;21:438-47.
48. St-Jules DE, Goldfarb DS, Sevick MA. Nutrient non-equivalence: does restricting high-potassium plant foods help to prevent hyperkalemia in hemodialysis patients? J Ren Nutr 2016;26:282-7.
49. Sim JJ, Bhandari SK, Smith N, et al. Phosphorus and risk of renal failure in subjects with normal renal function. Am J Med 2013;126:311-8.
50. Gutiérrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and

mortality among patients undergoing hemodialysis. N Engl J Med 2008;359:584-92.
51. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. J Clin Invest 2011;121:4393-408.
52. Kalantar-Zadeh K, Gutekunst L, Mehrotra R, et al. Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. Clin J Am Soc Nephrol 2010;5:519-30.
53. Moorthi RN, Armstrong CL, Janda K, Ponsler-Sipes K, Asplin JR, Moe SM. The effect of a diet containing 70% protein from plants on mineral metabolism and musculoskeletal health in chronic kidney disease. Am J Nephrol 2014;40:582-91.
54. Sullivan C, Sayre SS, Leon JB, et al. Effect of food additives on hyperphosphatemia among patients with end-stage renal disease: a randomized controlled trial. JAMA 2009;301:629-35.
55. Lynch KE, Lynch R, Curhan GC, Brunelli SM. Prescribed dietary phosphate restriction and survival among hemodialysis patients. Clin J Am Soc Nephrol 2011;6:620-9.
56. Tonelli M, Pannu N, Manns B. Oral phosphate binders in patients with kidney failure. N Engl J Med 2010;362:1312-24.
57. Spiegel DM, Brady K. Calcium balance in normal individuals and in patients with chronic kidney disease on low- and high-calcium diets. Kidney Int 2012;81:1116-22.
58. Bushinsky DA. Clinical application of calcium modeling in patients with chronic kidney disease. Nephrol Dial Transplant 2012;27:10-3.
59. Hill KM, Martin BR, Wastney ME, et al. Oral calcium carbonate affects calcium but not phosphorus balance in stage 3-4 chronic kidney disease. Kidney Int 2013;83:959-66.
60. de Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet 2010;376:1543-51.
61. Powe CE, Evans MK, Wenger J, et al. Vitamin D–binding protein and vitamin D status of black Americans and white Americans. N Engl J Med 2013;369:1991-2000.
62. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. Kidney Int 2017;92:26-36.
63. Young VR, Pellett PL. Plant proteins in relation to human protein and amino acid nutrition. Am J Clin Nutr 1994;59:Suppl:1203S-1212S.
64. Chen X, Wei G, Jalili T, et al. The associations of plant protein intake with all-cause mortality in CKD. Am J Kidney Dis 2016;67:423-30.
65. Sumida K, Molnar MZ, Potukuchi PK, et al. Constipation and incident CKD. J Am Soc Nephrol 2017;28:1248-58.
66. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505:559-63.
67. Koppe L, Mafra D, Fouque D. Probiotics and chronic kidney disease. Kidney Int 2015;88:958-66.
68. Rossi M, Johnson DW, Xu H, et al. Dietary protein-fiber ratio associates with circulating levels of indoxyl sulfate and p-cresyl sulfate in chronic kidney disease patients. Nutr Metab Cardiovasc Dis 2015;25:860-5.
69. Schulman G, Berl T, Beck GJ, et al. Randomized placebo-controlled EPPIC trials of AST-120 in CKD. J Am Soc Nephrol 2015;26:1732-46.
70. Chiavaroli L, Mirrahimi A, Sievenpiper JL, Jenkins DJ, Darling PB. Dietary fiber effects in chronic kidney disease: a systematic review and meta-analysis of controlled feeding trials. Eur J Clin Nutr 2015;69:761-8.
71. Salmean YA, Segal MS, Palii SP, Dahl WJ. Fiber supplementation lowers plasma p-cresol in chronic kidney disease patients. J Ren Nutr 2015;25:316-20.
72. Han E, Yun Y, Kim G, et al. Effects of omega-3 fatty acid supplementation on diabetic nephropathy progression in patients with diabetes and hypertriglyceridemia. PLoS One 2016;11(5):e0154683.
73. Hood VL, Tannen RL. Protection of acid–base balance by pH regulation of acid production. N Engl J Med 1998;339:819-26.
74. Krapf R, Vetsch R, Vetsch W, Hulter HN. Chronic metabolic acidosis increases the serum concentration of 1,25-dihydroxyvitamin D in humans by stimulating its production rate: critical role of acidosis-induced renal hypophosphatemia. J Clin Invest 1992;90:2456-63.
75. So R, Song S, Lee JE, Yoon HJ. The association between renal hyperfiltration and the sources of habitual protein intake and dietary acid load in a general population with preserved renal function: the KoGES Study. PLoS One 2016;11(11):e0166495.
76. Goraya N, Simoni J, Jo C, Wesson DE. Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. Kidney Int 2012;81:86-93.
77. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol 2009;20:2075-84.
78. Swaminathan S. Trace elements, toxic metals, and metalloids in kidney disease. In: Kopple JD, Massry S, Kalantar-Zadeh K, eds. Nutritional management of renal disease. 3rd ed. London: Academic Press of Elsevier, 2013:339-49.
79. Clase CM, Ki V, Holden RM. Water-soluble vitamins in people with low glomerular filtration rate or on dialysis: a review. Semin Dial 2013;26:546-67.
80. Ishigami J, Grams ME, Naik RP, Coresh J, Matsushita K. Chronic kidney disease and risk for gastrointestinal bleeding in the community: the Atherosclerosis Risk in Communities (ARIC) Study. Clin J Am Soc Nephrol 2016;11:1735-43.
81. Xu X, Qin X, Li Y, et al. Efficacy of folic acid therapy on the progression of chronic kidney disease: the Renal Substudy of the China Stroke Primary Prevention Trial. JAMA Intern Med 2016;176:1443-50.
82. McCabe KM, Booth SL, Fu X, et al. Dietary vitamin K and therapeutic warfarin alter the susceptibility to vascular calcification in experimental chronic kidney disease. Kidney Int 2013;83:835-44.

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