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KDOQI CLINICAL PRACTICE GUIDELINE FOR NUTRITION IN CKD: 2020 UPDATE

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Abstract

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) has provided evidence-based guidelines for nutrition in kidney diseases since 1999. Since the publication of the first KDOQI nutrition guideline, there has been a great accumulation of new evidence regarding the management of nutritional aspects of kidney disease and sophistication in the guidelines process. The 2020 update to the KDOQI Clinical Practice Guideline for Nutrition in CKD was developed as a joint effort with the Academy of Nutrition and Dietetics (Academy). It provides comprehensive up-to-date information on the understanding and care of patients with chronic kidney disease (CKD), especially in terms of their metabolic and nutritional milieu for the practicing clinician and allied health care workers. The guideline was expanded to include not only patients with end-stage kidney disease or advanced CKD, but also patients with stages 1-5 CKD who are not receiving dialysis and patients with a functional kidney transplant. The updated guideline statements focus on 6 primary areas: nutritional assessment, medical nutrition therapy (MNT), dietary protein and energy intake, nutritional supplementation, micronutrients, and electrolytes. The guidelines primarily cover dietary management rather than all possible nutritional interventions. The evidence data and guideline statements were evaluated using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria. As applicable, each guideline statement is accompanied by rationale/background information, a detailed justification, monitoring and evaluation guidance, implementation considerations, special discussions, and recommendations for future research.

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Disclaimer

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon the best information available as of April 2017.* It is designed to provide information and assist decision making. It is not intended to define a standard of care and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

Kidney Disease Outcomes Quality Initiative (KDOQI) and The Academy of Nutrition and Dietetics (Academy) make every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the work group. All members of the work group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. All reported information is provided in the "Biographic and Disclosure Information" section of this journal supplement and is on file at the National Kidney Foundation (NKF).

*Commissioned evidence review included articles published through April 2017. Consensus opinion statements use literature published though August 2018.

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Abbreviations and Acronyms

25(OH)D	25-Hydroxyvitamin D
$1,25(OH)_2D$	1,25-Dihydroxyvitamin D
Academy	Academy of Nutrition and Dietetics
ACE	Angiotensin-converting enzyme
AGREE	Appraisal of Guidelines for Research and Evaluation
ALA	α-Linolenic acid
APD	Animal-based protein diet
AV	Arteriovenous
BF	Body fat
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BP	Blood pressure
BPI	Body protein index
BW	Body weight
CAPD	Continuous ambulatory peritoneal dialysis
CI	Confidence interval
CK	Creatine kinase
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-MBD	Chronic kidney disease–mineral and bone disorder
cPENS	Composite score of Protein Energy Nutrition Status
CRIC	Chronic Renal Insufficiency Cohort
CRP	C-Reactive protein
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DHA	Docosahexaenoic acid
DKD	Diabetic kidney disease
DOPPS	Dialysis Outcomes and Practice Patterns Study
DXA	Dual-energy x-ray absorptiometry
eGFR	Estimated glomerular filtration rate
EAAs	Essential amino acids
EPA	Eicosapentaenoic acid
ERT	Evidence Review Team
ESKD	End-stage kidney disease
FGF-23	Fibroblast growth factor 23
FM	Fat mass
FFM	Fat-free mass
FSA	Four-site skinfold anthropometry
GFR	Glomerular filtration rate
GNRI	Geriatric Nutrition Risk Index
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HD	Hemodialysis
HDL-C	High-density lipoprotein cholesterol
HGS	Handgrip strength
HR	Hazard ratio
hsCRP	High-sensitivity C-reactive protein
IBW	Ideal body weight
IDPN	Intradialytic parenteral nutrition
IL-6	Interleukin 6
IMT	Intima media thickening
IOM	Institute of Medicine
IPAA	Intraperitoneal amino acids
ISRMN	International Society of Renal Nutrition and Metabolism
IV	Intravenous
KA	Ketoacid analogue
KDIGO	Kidney Disease: Improving Global Outcomes
KDQOL-SF	Kidney Disease Quality of Life Short Form
KDOQI	Kidney Disease Outcomes Quality Initiative
LBM	Lean body mass
LC n-3 PUFA	Long chain omega-3 polyunsaturated fatty acids
LDL-C	Low-density lipoprotein cholesterol
LPD	Low-protein diet
MAMC	Midarm muscle circumference
MDRD	Modification of Diet in Renal Disease
MF-BIA	Multifrequency bioelectrical impedance analysis
MGP	Matrix Gla protein

MHD	Maintenance hemodialysis
MHDE	Maintenance Hemodialysis Equation
MI	Myocardial infarction
MIS	Malnutrition Inflammation Score
MNA	Mini Nutrition Assessment
MNA-SF	Mini-Nutrition Assessment-Short Form
MNT	Medical nutrition therapy
MST	Malnutrition Screening Tool
MUST	Malnutrition Universal Screening Tool
NAM	National Academy of Medicine
NEAAs	Nonessential amino acids
NEAP	Net endogenous acid production
NF-κB	Nuclear factor-κB
NHANES	National Health and Nutrition Examination Survey
NIS	Nutrition Impact Symptoms
NKF	National Kidney Foundation
NPV	Negative predictive value
NRCT	Nonrandomized controlled trial
nPCR	Normalized protein catabolic rate
nPNA	Normalized protein nitrogen appearance
NS	Nonsignificant
NST	Nutrition Screening Tool
ONS	Oral nutritional supplement
OR	Odds ratio
PCR	Protein catabolic rate
PD	Peritoneal dialysis
PEW	Protein-energy wasting
PIVKA-II	Protein induced by vitamin K absence/antagonist-II
PNA	Protein nitrogen appearance
PNI	Protein Nutrition Index
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PTH	Parathyroid hormone
QoL	Quality of life
RBC	Red blood cell
RCTs	Randomized controlled trials
RDA	Recommended Dietary Allowance
RDN	Registered dietitian nutritionist
REE	Resting energy expenditure
REIN	Ramipril Efficacy in Nephropathy
R-NST	Renal-Nutrition Screening Tool
RR	Risk ratio
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SD	Standard deviation
SGA	Subjective Global Assessment
SKF	Skinfold thickness
SMD	Standardized mean difference
TBF	Total-body fat
TC	Total cholesterol
TG	Triglycerides
TNF-α	Tumor necrosis factor α
TPN	Total parenteral nutrition
TSF	Triceps skinfold thickness
VPD	Vegetable protein diet
VLPD	Very low-protein diet
vs	Versus
WHO	World Health Organization

FOREWORD

It has been 20 years since the National Kidney Foundation (NKF) published the first Kidney Disease Outcomes Quality Initiative (KDOQI) nutrition guideline for patients with end-stage renal disease. The treatment of chronic kidney disease (CKD) has changed dramatically since the original nutrition guideline was published. This guideline update reflects the many changes in both guideline development and the management of nutritional aspects of CKD during that period.

There are several firsts with the *KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update*. First, this guideline was developed as a joint effort with the Academy of Nutrition and Dietetics (Academy). The Academy served as the Evidence Review Team (ERT) for this guideline; this group had previously developed a CKD guideline in 2010 and has developed an extensive evidence analysis library in nutrition. The ERT conducted 2 comprehensive literature reviews that identified more than 15,000 studies for possible inclusion into the guideline. After conducting a thorough review of these studies, the ERT provided the review results in systematic form for the work group to evaluate and incorporate into the guideline document. Second, the evidence data and guideline statements were evaluated using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria, an evidence review process that did not exist when the original guideline was published in 2000. The GRADE criteria have been adopted by most organizations that write guidelines on a regular basis and are considered a state-of-the-art method to grade guideline statements. Third, this extensively rewritten guideline has been reorganized into 6 primary topics, namely nutritional assessment, medical nutrition therapy, dietary protein and energy intake, nutritional supplementation, micronutrients, and electrolytes. This grouping should make it easier for the practitioner to identify best standards of care in particular aspects of nutritional management of patients with CKD. Finally, the guideline was expanded to include not only patients with end-stage renal disease or advanced CKD, as presented in the 2000 guideline, but also patients with stages 1-5 CKD who are not receiving dialysis and patients with a functional kidney transplant. Thus, the guideline provides a comprehensive assessment of nutrition in all adult patients with CKD.

Implementation activities are a critical part of maximizing the value of a clinical practice guideline. Implementation activities will include both patient and professional educational resources and tools. Patient resources include the National Kidney Diet (developed by the NKF Council on Renal Nutrition and the Academy's Renal Practice Group), as well as the nutrition component of the NKF Kidney Pathways. Professional education opportunities will include sessions at professional conferences, online learning, and a speaker's guide. Additionally, ongoing research activities are being done to understand the barriers and facilitators related to implementation of the guidelines and their impact on outcomes.

This document is the culmination of a 5-year process that included members of both the ERT and work group, as well as public reviews by a number of individuals and groups, including the International Society of Renal Nutrition and Metabolism. Both the NKF and the Academy are deeply appreciative of the work performed by these volunteers who helped craft the final guideline document. We would like to specifically recognize the work group chairs, T. Alp Ikizler, MD, and Lilian Cuppari, PhD, for their tireless efforts to lead the work group in performing this extensive update. It is the commitment and dedication of these volunteers to the KDOQI process that has made this guideline document possible.

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INTRODUCTION

Background

During progression of chronic kidney disease (CKD), the requirements and utilization of different nutrients change significantly. These changes ultimately place patients with kidney disease at higher risk for nutritional and metabolic abnormalities. Understanding the applicable nutritional principles, the available methods for assessing nutritional status, establishing patient-specific dietary needs, and preventing or treating potential or ongoing nutritional deficiencies and derangements is therefore essential for optimal care of the patients with CKD. The original National Kidney Foundation (NKF)–Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline for nutrition in CKD was published in 2000 and provided in-depth information regarding these principles. Since then, there have been significant improvements in the understanding and care of patients with CKD, especially in terms of their metabolic and nutritional milieu. This 2020 update of the KDOQI clinical practice guideline for nutrition in CKD is aimed at providing the most up-to-date information on these issues for the practicing clinician and allied health care workers.

The 2020 guideline differs from the previous publication in multiple ways. The development process included involvement of multiple groups, including NKF, the Academy of Nutrition and Dietetics (Academy), and the International Society of Renal Nutrition and Metabolism (ISRNM), with each entity contributing in a different but significant fashion. The initiative was funded solely by resources provided through NKF and the Academy. ISRNM provided intellectual and scientific support throughout the process. The work group members were chosen through an application and review process and specific attention was paid to geographic spread and diversity in the final selection of work group members. The systematic evidence review and grading were completed by the Academy Evidence Review Team (ERT).

The updated guideline statements focus on 6 primary areas: nutritional assessment, medical nutrition therapy (MNT), dietary protein and energy intake, nutritional supplementation, micronutrients, and electrolytes. The primary emphasis in the updated guideline is to provide information on dietary management rather than covering all possible nutritional intervention strategies. The rationale for having specific areas of emphasis was that nutrition is a vast subject, comprising many components of dietary intake. It is not possible to cover every single component of diet and we are aware that the guideline does not cover certain areas that might be important to many patients and caregivers. The work group members thought that this long-waited update should be more focused and could be followed by additional guidelines for other components of nutritional care of patients with CKD. The work group members also recognized that CKD is a continuum and decided to include patients with CKD stages 1-5, including those receiving maintenance dialysis and kidney transplant recipients. However, it was recognized that patients with acute kidney injury represented a significantly different nutritional and metabolic profile such that they were excluded from the updated guideline. In addition, we elected not to provide recommendations in certain guidelines for patients with stages 1-2 CKD, mainly due to lack of clinical relevance and limited data.

Several important caveats need to be considered when interpreting and implementing the 2020 updated clinical practice guideline for nutrition in CKD. There are no guideline statements provided in this update on certain nutritional management aspects of patients with CKD, including but not limited to obesity, exercise, and anabolic pharmacotherapy. We hope that these areas of significant clinical importance can be covered soon. We would also note that the guideline does not stratify patients based on their ethnic or racial backgrounds, which could have obvious implications. It is our expectation that this much-needed adjustment and consideration is taken upon by researchers and clinicians for more personalized and precise guidelines. Finally, it is important that the uptake and implementation of these guidelines is continuously surveilled. These data are much needed for further refinement and recalibration for the best care of patients with CKD.

This guideline is the result of more than 5 years of work with a substantial amount of voluntary commitment from many dedicated individuals. We believe it is a much-needed update given the advancements in the care of patients with CKD during the last 2 decades. We are also aware that this is a dynamic process and there is much more that needs to be accomplished, especially given the pace of advancements in science and technology that we are experiencing. We still hope that the guideline will be helpful to our colleagues in its current format so that they can implement these guideline recommendations in the most effective way to improve the lives of those with CKD.

The Guideline Development Process

According to the National Academy of Medicine (NAM; formerly the Institute of Medicine [IOM]), "Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[1(p4)] This chapter describes the process and methods used to conduct comprehensive systematic reviews and how the findings from these systematic reviews were used to develop clinical practice nutrition guidelines for patients with CKD. This guideline was developed according to the Standards for Developing Trustworthy Clinical Practice Guidelines as stated by the NAM.

Development of these guidelines was a collaborative process between the NKF and the Academy. Nutrition and its management are an integral aspect of care for patients with kidney disease. Due to recent developments in the literature regarding treatment and assessment of CKD, the Academy and NKF collaborated to merge, update, and expand the current 2010 Evidence Analysis Library CKD guidelines and the KDOQI nutrition guideline. Hence, the objective of this initiative is to provide MNT guidelines for patients with CKD to assess, prevent, and treat protein-energy wasting (PEW), mineral and electrolyte disorders, and other metabolic comorbid conditions associated with CKD.

Overview of the Guideline Development Process

Guideline development is a detailed and comprehensive process. The steps followed to develop this guideline are as follows (some steps were completed concurrently):

1. Select the work group or expert panel that works with the ERT.
2. Orient the work group to the 5-step systematic review process of the Academy Evidence Analysis Center.
3. Develop research questions, inclusion and exclusion criteria, and a detailed search plan, as well as identify interventions and outcomes of interest.
4. Search multiple databases based on search plan.
5. Screen abstracts and full-text articles based on a priori eligibility criteria.
6. Extract data and critically assess the quality of included studies (risk of bias of studies).
7. Synthesize evidence narratively (evidence summary and conclusion statements) and in table format. Grade the quality of evidence for each outcome and provide Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tables.
8. Develop recommendation statements based on the findings of the systematic review and other important considerations and assign "strength of recommendation."
9. Write a guideline manuscript.
10. Conduct internal, external, and public review of the guideline.
11. Respond to reviewer comments and update the guideline before publication.

Work Group Selection Process

The Academy led the process of work group member recruitment. To ensure appropriate expertise and limit bias, the Evidence Based Practice Committee Work Group Selection subcommittee followed a transparent process of selecting work group members. An open recruitment message with a link to online application was circulated via stakeholders for experts in the topic area of CKD.

Interested candidates provided signed disclosure and conflict-of-interest forms, curriculum vitae, and personal statements indicating interest and qualifications that related to the topic. The work group selection committee then evaluated each candidate based on set criteria. Higher-scoring candidates were considered for the position of work group chair/co-chair. A total of 15 work group members were selected to develop these guidelines. Two co-chairs were appointed, and the work group consisted of physicians, registered dietitians or nutritionists, researchers, and methodologists with expertise in the renal nutrition field. According to their experiences and skill sets, the selected members were assigned to corresponding subtopics. The work group participated in all steps of the systematic review process, which included developing research questions, agreeing on inclusion and exclusion criteria, developing the search plan, evaluating the evidence, and approving and grading the evidence and developing recommendation statements. All work group members and the ERT met twice for 2-day face-to-face meetings, as well as teleconference calls once a month for the duration of the project.

Guideline Focus

During the first meeting the work group defined the scope for the guideline. The co-chairs developed the first draft of the scope, which was discussed and refined by the work group members. It was determined that the guideline would focus on nutrition in all stages of CKD in adults and would cover the subtopics of macronutrient, micronutrient, and electrolyte management in CKD. Both assessment and intervention questions under these subtopics were proposed. Three work groups were developed, with 5 members assigned to each work group and a Chair appointed to help lead the work group.

Systematic Review Process

This guideline followed the Academy's systematic review methodology. An analytical framework was developed by the ERT and refined by the work group members to help guide question development. During the initial teleconference calls and first face-to-face meeting, the work group developed a list of questions that were deemed important for clinicians and patients (Table 1). The work group developed the a priori inclusion and exclusion criteria as listed in Table 2.

A comprehensive search of the literature was conducted using PubMed, MEDLINE, EMBASE, and CINAHL search engines. A first literature search was conducted to identify studies addressing assessment questions and a second search was conducted to identify studies addressing intervention questions to identify studies that answered more than 1 question. Inclusion criteria included in the search plan included human adults with CKD aged 19 years and older published between 1985 and December 2016. Search terms included terms to identify relevant nutrition interventions assessment tools in adult patients with CKD.

The first literature search focused on assessment questions identified 4,857 potential studies. The Preferred Reporting Items for Systematic Reviews and Meta-analyses

Table 1. Key Questions for Evidence Review

Topics	Questions
Assessment: nutritional status	What composite nutritional indices should be used to assess nutritional status and/or PEW in adults with CKD 1-5D, nondialysis and transplant?
	What technical devices and anthropometric measures should be used to assess body composition in adults with CKD 1-5D, nondialyzed and transplant?
	What laboratory measures should be used to assess nutritional status in adults with CKD 1-5D, nondialysis and transplant?
	Is there evidence to support the use of handgrip strength for assessing nutritional status in adults with CKD 1-5D, nondialysis and transplant?
Assessment: macronutrients	What methods should be used to assess dietary intake of energy and protein in adults with CKD 1-5D, nondialysis and transplant?
	What methods should be used assess energy and protein requirements in adults with CKD 1-5D, nondialysis and transplant?
Assessment: micronutrients	What methods should be used to assess micronutrient intake in adults with CKD 1-5D, nondialysis and transplant?
	What methods should be used to assess micronutrient needs in adults with CKD 1-5, nondialysis and transplant?
	What methods should be to assess micronutrient status in adults with CKD 1-5, nondialysis and transplant?
Assessment: electrolytes	What methods should be used to assess dietary electrolyte intake in adults with CKD 1-5D, nondialysis and transplant?
	What methods should be used to assess electrolyte needs in adults with CKD 1-5, nondialysis and transplant?
	What methods should be used to assess electrolyte status in adults with CKD 1-5, nondialysis and transplant?
MNT	What is the effect of MNT provided by a registered dietitian or international equivalent on outcomes in adult patients with CKD 1-5D, nondialysis and transplant?
Macronutrient: protein restriction and type	What is the effect of protein restriction, with or without ketoanalogues of amino acids, intake on outcomes in adults with CKD 1-5D, nondialysis and transplant?
	What is the effect of protein type (animal vs plant) intake on outcomes in adults with CKD 1-5D, nondialysis and transplant?
Macronutrient: dietary patterns	What is the effect of specific dietary patterns on outcomes in patients with CKD 1-5, nondialysis and transplant?
Macronutrient: omega-3 supplementation	What is the effect of omega 3 supplementation on outcomes in adults with CKD 1-5D, nondialysis and transplant?
Macronutrient: oral nutrition supplements	What is the effect of oral nutritional supplementation on outcomes in adults with CKD 1-5, nondialysis and transplant?
Macronutrient: dialysate supplements	What is the effect of nutritional supplementation via dialysate on outcomes in adults with CKD 1-5D, nondialysis and transplant?
Macronutrient: IDPN supplements	What is the effect of nutritional supplementation via IDPN on outcomes in adults with CKD 1-5D, nondialysis and transplant?
Micronutrients: intervention questions	What is the effect of micronutrient intake (B vitamins; vitamins C, D, E, and K; selenium; and zinc) on outcomes in adults with CKD 1-5D, nondialysis and transplant?
Electrolytes: intervention questions	What is the effect of dietary intake of (acid-base, calcium, phosphorus, potassium, magnesium, and sodium) on (electrolyte) biomarkers and other health outcomes in adults with CKD 1-5D, nondialysis and transplant?

Abbreviations: CKD, chronic kidney disease; IDPN, intradialytic parenteral nutrition; MNT, medical nutrition therapy; PEW, protein-energy wasting.

(PRISMA) diagram illustrating the study selection process is presented in Figure 1. The second comprehensive search to answer all the intervention questions in order identified 11,017 potential studies. The PRISMA diagram illustrating study selection process for intervention questions is in Figure 2.

After the search was completed, studies were systematically screened based on additional a priori inclusion/exclusion criteria. For intervention questions, only randomized controlled trials (RCTs) that had at least 6 individuals per arm were included. Included studies investigated an intervention of interest (eg, protein

Table 2. Evidence Review Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Assessment Research Questions		
Age	Adults (aged ≥18 y)	Young adults aged ≤18 y, infants, children, and adolescents
Setting	Clinical or outpatient	Other than clinical or outpatient
Health status	CKD of any stage, nephrotic syndrome, maintenance HD, long-term PD, and kidney transplant with different CKD stages, with or without dyslipidemia and diabetes; kidney transplant recipients	Cancer or any other terminal condition or serious condition
Nutrition-related problem/condition	CKD	None
Study design preferences	• Diagnostic, validity, reliability studies, prediction, and/or correlation studies • Studies need to have a comparative tool/method included	• Review article; meta-analysis (pertinent review articles will be hand searched) • Not a research study: poster session, commentary, letter to editor, "grey" literature: technical reports from government agencies or scientific research groups, working papers from research groups or committees, white papers, position papers, abstracts, conference reports, or preprints
Outcomes	• Evaluates validity, agreement, and reliability of the screening tool • Reports ≥1 of the following outcomes: - Validity (eg, construct [convergent, divergent] criterion [concurrent or predictive]) - Reliability (eg, inter- or intrarater) - Sensitivity/specificity - Positive and/or negative predictive value - Agreement (κ)	• No evaluation of validity, agreement, or reliability of the screening tool • Does not report on at least 1 of the outcomes of interest • Tools evaluated as predictors of morbidity and mortality outcomes
Study dropout rate	20% for studies <1 y and 30% for studies > 1 y	>20% for studies < 1 y and >30% for studies > 1 y
Year range	1985 to December 2016	Published before 1985
Authorship	• If an author is included on >1 primary research article that is similar in content, the most recent review or article will be accepted, and earlier versions will be rejected • If an author is included on >1 review article or primary research article and the content is different, both reviews may be accepted	Studies by same author similar in content
Language	Limited to articles in English	Languages other than English
Subjects	Humans	Animals
Publication	Published in peer-reviewed journal	Not published in peer-reviewed journal
Intervention Research Questions		
Age	Adults (aged ≥18 y)	Young adults aged ≤18 y, infants, children, and adolescents
Setting	Clinical or outpatient	Other than clinical or outpatient
Health status	CKD of any stage, nephrotic syndrome, maintenance HD, long-term PD, and kidney transplant with different CKD stages, with or without dyslipidemia and diabetes; kidney transplant recipients	Cancer or any other terminal condition or serious condition
Nutrition-related problem/condition	CKD	None
Study design preferences	RCT or clinical controlled studies	• Observational studies • Review article; meta-analysis (pertinent review articles will be hand searched) • Not a research study: poster session, commentary, letter to editor, "grey" literature: technical reports from government agencies or scientific research groups, working papers from research groups or committees, white papers, position papers, abstracts, conference reports, or preprints

(Continued)

Table 2 (Cont'd). Evidence Review Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Outcomes	Mortality, renal replacement therapy, quality of life, nutritional status outcomes, dietary intake outcomes, inflammation outcomes, anthropometrics, micronutrient biomarkers, electrolyte biomarkers, CKD progression, comorbid condition outcomes (lipid profile, blood pressure)	• Does not report on at least 1 of the outcomes of interest
Size of study groups	For controlled trials, at least 6 participants in each arm	<6 individuals for each study group
Study dropout rate	20% for studies < 1 y and 30% for studies > 1 y	>20% for studies < 1 y and >30% for studies > 1 y
Year range	1985 to December 2016	Published before 1985
Authorship	• If an author is included on >1 primary research article that is similar in content, the most recent review or article will be accepted, and earlier versions will be rejected • If an author is included on >1 review article or primary research article and the content is different, both reviews may be accepted.	Studies by same author similar in content
Language	Limited to articles in English	Languages other than English
Subjects	Humans	Animals
Publication	Published in peer-reviewed journal	Not published in peer-reviewed journal

Abbreviations: CKD, chronic kidney disease; HD, hemodialysis; PD, peritoneal dialysis; RCT, randomized controlled trial.

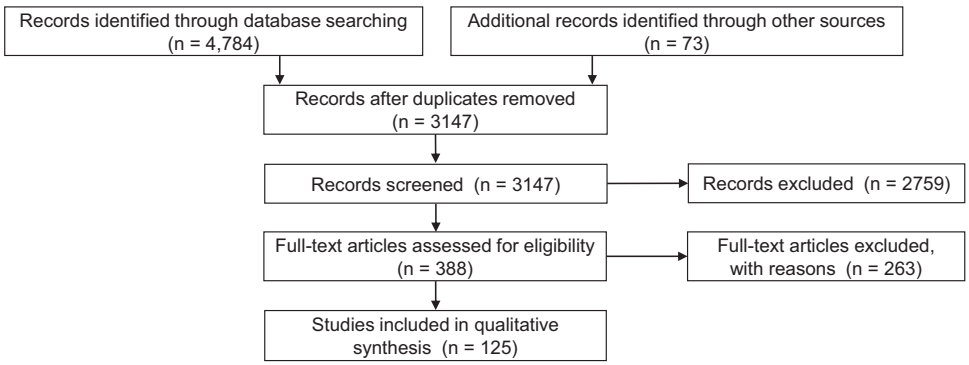

Figure 1. Flow diagram of identified studies for assessment questions.

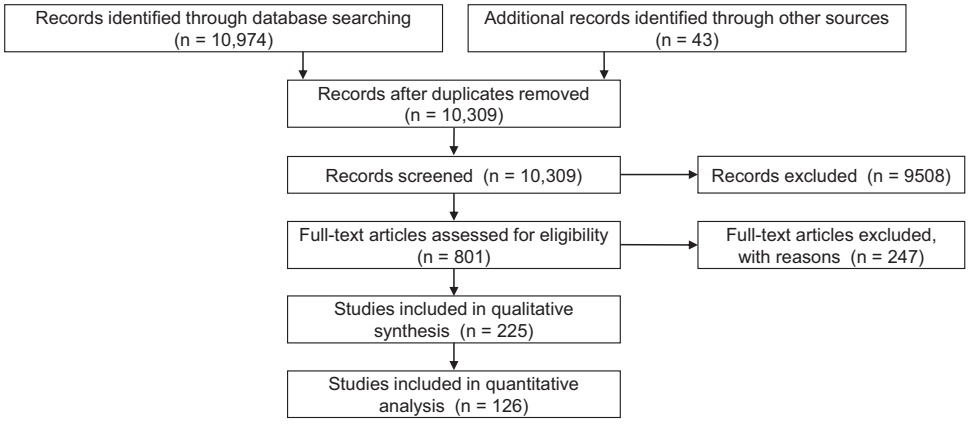

Figure 2. Flow diagram of identified studies for intervention questions.

Table 3. Quality of Evidence Grades

Grade	Definition
High (A)	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate (B)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low (C)	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low (D)	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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restrictions, phosphorus intake, and sodium intake) in comparison with no intervention or minimal intervention. For assessment questions, only studies that tested the validity, reliability, or relationship of an assessment tool against a comparative tool (reference standard) or mortality were included in this review.

The list of titles and abstracts was independently reviewed and marked for inclusion or exclusion (along with the reason) and any differences were resolved by discussion with a third reviewer. The full text of articles meeting inclusion criteria were ordered and reviewed for inclusion: 225 studies met the inclusion criteria for intervention questions, and 125, for assessment articles. A list of excluded articles with reason for exclusion was also created to maintain transparency (available on the Academy Evidence Analysis Center website).

Data Extraction and Study Quality Assessment

Relevant data were extracted from the included articles using a standardized online data extraction tool. Key information extracted from each study included author information, year of publication, type of study design, details of intervention (type of intervention, intervention duration, who delivered the intervention, setting, and number of centers), participant information (sample size, mean age, age range, sex, study inclusion and exclusion criteria, and comorbid conditions), intervention information (intervention details, comparison group details, and medication use), outcome information (reported primary and secondary outcomes and time points of reported outcomes), and other details such as funding source.

All included studies were critically appraised for risk of bias. Two independent reviewers assessed the quality of studies using the Academy's online risk-of-bias tool, the Quality Criteria Checklist. The questions of the Quality Criteria Checklist are based on quality constructs and risk of bias domains identified by the Cochrane Collaboration and the Agency for Healthcare Research and Quality. Questions examine sampling bias, performance bias, detection bias, attrition bias, and reporting bias. Any discrepancies between the 2 reviewers were resolved by consensus or by a third reviewer.

Data Synthesis and Grading the Evidence

Descriptive synthesis of evidence was conducted for all identified outcomes for which there were included studies. When possible, meta-analysis was conducted using a random-effects model. For continuous data, results were summarized as mean difference between treatment groups (intervention vs control/placebo) with 95% confidence intervals (CIs) or standardized mean difference (SMD). Dichotomous outcomes were reported as odds ratio (OR) or risk ratio (RR) with 95% CI. The I^2 statistic was used to determine the degree of heterogeneity in the calculated effect size, and 25%, 50%, and 75% were considered low, moderate, and high, respectively. Subgroup analysis was conducted as appropriate to manage clinical heterogeneity.

Table 4. Implications of Strong and Weak Recommendations for Different Users of Guidelines

	Strong Recommendation (level 1 = we recommend)	Weak Recommendation (level 2 = we suggest)
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
For policy makers	The recommendation can be adapted as policy in most situations, including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Source: Reproduced with permission from the GRADE handbook.[3]

After completion of the data extraction and data synthesis, the ERT provided the systematic review results in 3 formats for the work group to review, edit, and approve:

1. Evidence summary: a narrative summary of all included trials for each identified outcome was drafted for each research question in the systematic review. A conclusion statement was developed for each proposed question/outcome. The conclusion statement is a clear, simple, and to-the-point answer to the proposed questions.
2. Study characteristics provided information regarding study characteristics, sample size, population, intervention details, and quality of each included study (see Tables S1-S28).
3. Quality of evidence (strength of evidence): each of the conclusion statements were assigned a GRADE[2] to reflect the quality of studies, inconsistency of results, imprecision, indirectness of the evidence, and publication bias. Using this method, the evidence for each outcome of interest was graded as A (high), B (moderate), C (low), or D (very low). A GRADE table was generated using GradePro and demonstrated how the strength of evidence (GRADE) was derived for each outcome of interest.

Guideline Development

The work group members drafted comprehensive recommendations for nutrition care for adults with CKD. During this phase, the role of the work group member was to translate the available evidence into action statements that were clear, concise, and ready to be implemented by practitioners. The work group and ERT used the GRADE method for development of recommendations. The GRADE method involves 2 major components: a rating for the quality of evidence (described above) and a rating of the strength of recommendations. The evidence grades are reported at the end of the recommendation statements (eg, A, B, C, or D) and reflect the confidence in the estimated effects (Table 3[3]). The second component is rating the strength of the recommendation statement. This rating reflects the extent to which one is confident that desirable effects of an intervention outweigh undesirable effects. The grade for strength of the recommendation can be assigned Level 1 or Level 2. Table 4 shows the implication of each level for practitioners, clinicians, and policy makers. Level 1 recommendations use the terminology "We recommend," which means that this course of action should be applied to most people and practitioners can have confidence that implementing this recommendation has more benefit than risk. Level 2 recommendations use the terminology "We suggest."

When providing the level for the strength of the recommendation, a number of factors besides the quality of evidence are taken into consideration, including patient values and preferences, quality of evidence, benefits and harms, cost/resources to implement the recommendation, acceptability, feasibility, and health equity. In addition to evidence-based recommendations, in certain scenarios "Opinion" statements were developed. These statements were developed when there was not enough evidence or evidence had too low of quality to write a graded recommendation, but the work group determined it was important to provide some guidance to patients and practitioners. These recommendations are ungraded and usually refer to general or routine practice.

When the full draft of recommendation statements was ready, it was reviewed and edited multiple times by all work group members and the ERT. The work group participated in a final blinded vote of recommendation statements, and a majority of votes approving the statement was necessary for each statement to be accepted into the final guideline.

Draft Report With Supporting Rationale

After the recommendation statements were developed, the work group members drafted a guideline manuscript that included the supporting materials for each topic, including rationale, detailed justification (evidence summary), special discussions, implementation considerations, risks and harms, costs, and need for future research. In these sections the work group members also cited additional references important to the respective topic, including discussion of studies published after our search dates or other systematic reviews on the topic.

Peer Review Process

These guidelines underwent a systematic peer review process. The first phase of review was an internal review conducted by KDOQI leadership and the NKF Scientific Advisory Board. Feedback from this internal review was reviewed and incorporated in the guideline as appropriate. The second phase of the review was an external review conducted by 12 experts in this field. The AGREE II tool (Appraisal of Guidelines for Research and Evaluation) criteria were used to assess the quality of guideline reporting. The third phase was an open public review phase. Reviewer comments from all phases were collated by staff and sent to work group members for discussion and possible edits. Work group chairs coordinated the final revision of the guideline document based on review comments.

SUMMARY OF GUIDELINE STATEMENTS

Guideline 1: Nutrition Assessment

1.0 Statements on Usual Care

Routine Nutrition Screening

1.0.1 In adults with CKD 3-5D or posttransplantation, it is reasonable to consider routine nutrition screening at least biannually with the intent of identifying those at risk of protein-energy wasting (*OPINION*).

Nutrition Screening Tools

1.0.2 In adults with CKD 3-5D or posttransplantation, there is limited evidence to suggest the use of one tool over others for identifying those at risk of protein-energy wasting (PEW) (*2D*).

Routine Nutrition Assessment

1.0.3 In adults with CKD 3-5D or posttransplantation, it is reasonable that a registered dietitian nutritionist (RDN) or an international equivalent conduct a comprehensive nutrition assessment (including but not limited to appetite, history of dietary intake, body weight and body mass index, biochemical data, anthropometric measurements, and nutrition-focused physical findings) at least within the first 90 days of starting dialysis, annually, or when indicated by nutrition screening or provider referral (*OPINION*).

1.1 Statements on Technical Devices and Anthropometric Measurements to Assess Body Composition

Bioelectrical Impedance for Patients on Maintenance Hemodialysis (MHD)

1.1.1 In adults with CKD 5D on MHD, we suggest using bioimpedance and preferably multi-frequency bioelectrical impedance (MF-BIA) to assess body composition when available. Bioimpedance assessments should ideally be performed a minimum of 30 minutes or more after the end of the hemodialysis session to allow for redistribution of body fluids (*2C*).

Bioelectrical Impedance for CKD Patients Not on Dialysis or on Peritoneal Dialysis (PD)

1.1.2 In adults with CKD 1-5 or CKD 5D on PD, there is insufficient evidence to suggest using bioelectrical impedance to assess body composition (*2D*).

Dual-Energy X-Ray Absorptiometry (DXA) for Body Composition Assessment

1.1.3 In adults with CKD 1-5D or posttransplantation, it is reasonable to use DXA when feasible as it remains the gold standard for measuring body composition despite being influenced by volume status (*OPINION*).

Body Composition and Body Weight/BMI

1.1.4 In adults with CKD 1-5D or posttransplantation, it is reasonable to consider assessing body composition in combination with body weight/BMI at the first visit and to monitor overall nutrition status periodically over time (*OPINION*).

Frequency of Body Weight/BMI and Body Composition Assessment

1.1.5 In adults with CKD 1-5D or posttransplantation who are clinically stable, it is reasonable to measure body weight and BMI and to monitor for changes in body weight/BMI and body composition as needed (*OPINION*):

- At least monthly in MHD and PD patients
- At least every 3 months in patients with CKD 4-5 or posttransplantation
- At least every 6 months in patients with CKD 1-3

Assessment of Body Weight

1.1.6 In adults with CKD 1-5D or posttransplantation, it is reasonable for registered dietitian nutritionist (RDN) or an international equivalent or physicians to use clinical judgment to determine the method for measuring body weight (eg, actual measured weight; history of weight changes; serial weight measurements; adjustments for suspected impact of edema, ascites, and polycystic organs) due to absence of standard reference norms (*OPINION*).

BMI as a Predictor of Mortality

1.1.7 In adults with CKD 5D on PD, we suggest that underweight status (based on BMI) can be used as a predictor of higher mortality (*2C*).

1.1.8 In adults with CKD 5D on MHD, we suggest that overweight or obesity status (based on BMI) can be used as a predictor of lower mortality, whereas, underweight status and morbid obesity (based on BMI) can be used as a predictor of higher mortality (*2B*).

1.1.9 In adults with CKD 1-5, it is reasonable to consider using underweight status (based on BMI) as a predictor of higher mortality, though the mortality risk associated with overweight or obesity status (based on BMI) is not clear (*OPINION*).

1.1.10 In adults with CKD posttransplantation, it is reasonable to consider using underweight and overweight or obesity status (based on BMI) as a predictor of higher mortality (*OPINION*).

BMI and PEW

1.1.11 In adults with CKD 1-5D or posttransplantation, BMI alone is not sufficient to establish a diagnosis of PEW unless the BMI is very low (<18 kg/m^2) (*OPINION*).

Skinfold Thickness

1.1.12 In adults with CKD 1-5D (*1B*) or posttransplantation (*OPINION*), in the absence of edema, we suggest using skinfold thickness measurements to assess body fat.

Waist Circumference

1.1.13 In adults with CKD 5D, we suggest that waist circumference may be used to assess abdominal obesity, but its reliability in assessing changes over time is low (*2C*).

Conicity Index

1.1.14 In adults with CKD 5D on MHD, we suggest that the conicity index may be used to assess nutritional status (*OPINION*) and as a predictor of mortality (*2C*).

Creatinine Kinetics

1.1.15 In adults with CKD 5D, we suggest that creatinine kinetics may be used to estimate muscle mass, though very high or very low dietary intake of meat and/or creatine supplements will influence accuracy of this measurement (*2C*).

1.2 Statements on Assessment With Laboratory Measurements

Single Biomarker Measurements

1.2.1 In adults with CKD 1-5D or posttransplantation, biomarkers such as normalized protein catabolic rate (nPCR), serum albumin, and/or serum prealbumin (if available) may be considered complementary tools to assess nutritional status. However, they should not be interpreted in isolation to assess nutritional status as they are influenced by non-nutritional factors (*OPINION*).

Serum Albumin Levels

1.2.2 In adults with CKD 5D on MHD, serum albumin may be used as a predictor of hospitalization and mortality, with lower levels associated with higher risk (*1A*).

1.3 Statement on Handgrip Strength

1.3.1 In adults with CKD 1-5D, we suggest that handgrip strength may be used as an indicator of protein-energy status and functional status when baseline data (prior measures) are available for comparison (*2B*).

1.4 Statements on Methods to Assess Energy Requirements

Assessment of Resting Energy Expenditure

1.4.1 In adults with CKD 1-5D or posttransplantation, it is reasonable to use indirect calorimetry to measure resting energy expenditure when feasible and indicated, as it remains the gold standard for determining resting energy expenditure (*OPINION*).

Resting Energy Expenditure Equations

1.4.2 In adults with CKD 5D who are metabolically stable, we suggest that in the absence of indirect calorimetry, disease-specific predictive energy equations may be used to estimate resting energy expenditure as they include factors that may influence the metabolic rate in this population (*2C*).

1.5 Statements on Composite Nutritional Indices

7-Point Subjective Global Assessment (SGA)

1.5.1 In adults with CKD 5D, we recommend the use of the 7-point Subjective Global Assessment as a valid and reliable tool for assessing nutritional status (*1B*).

Malnutrition Inflammation Score (MIS)

1.5.2 In adults with CKD 5D on MHD or posttransplantation, Malnutrition Inflammation Score may be used to assess nutritional status (*2C*).

1.6 Statements on Tools/Methods Used to Assess Protein and Calorie Intake

Considerations When Assessing Dietary Intake

1.6.1 In adults with CKD 3-5D or posttransplantation, it is reasonable to assess factors beyond dietary intake (eg, medication use, knowledge, beliefs, attitudes, behavior, access to food, depression, cognitive function) to effectively plan nutrition interventions (*OPINION*).

3-Day Food Records to Assess Dietary Intake

1.6.2 In adults with CKD 3-5D, we suggest the use of a 3-day food record, conducted during both dialysis and nondialysis treatment days (when applicable), as a preferred method to assess dietary intake (*2C*).

Alternative Methods of Assessing Dietary Intake

1.6.3 In adults with CKD 3-5 (*OPINION*) or CKD 5D (*2D*), 24-hour food recalls, food frequency questionnaires, and nPCR may be considered as alternative methods of assessing dietary energy and protein intake (*2D*).

Guideline 2: Medical Nutrition Therapy

2.0 Statements on Medical Nutrition Therapy (MNT)

MNT to Improve Outcomes

2.1.1 In adults with CKD 1-5D, we recommend that a registered dietitian nutritionist (RDN) or an international equivalent, in close collaboration with a physician or other provider (nurse practitioner or physician assistant), provide MNT. Goals are to optimize nutritional status, and to minimize risks imposed by comorbid conditions and alterations in metabolism on the progression of kidney disease (*1C*) and on adverse clinical outcomes (*OPINION*).

MNT Content

2.1.2 In adults with CKD 1-5D or posttransplantation, it is reasonable to prescribe MNT that is tailored to the individuals' needs, nutritional status, and comorbid conditions (*OPINION*).

MNT Monitoring and Evaluation

2.1.3 In adults with CKD 3-5D or posttransplantation, it is reasonable for the registered dietitian nutritionist (RDN) or an international equivalent to monitor and evaluate appetite, dietary intake, body weight changes, biochemical data, anthropometric measurements, and nutrition-focused physical findings to assess the effectiveness of MNT (*OPINION*).

Guideline 3: Protein and Energy Intake

3.0 Statements on Protein Amount

Protein Restriction, CKD Patients Not on Dialysis and Without Diabetes

3.0.1 In adults with CKD 3-5 who are metabolically stable, we recommend, under close clinical supervision, protein restriction with or without keto acid analogs, to reduce risk for end-stage kidney disease (ESKD)/death (*1A*) and improve quality of life (QoL) (*2C*):

- a low-protein diet providing 0.55–0.60 g dietary protein/kg body weight/day, or
- a very low-protein diet providing 0.28–0.43 g dietary protein/kg body weight/day with additional keto acid/amino acid analogs to meet protein requirements (0.55–0.60 g/kg body weight/day)

Protein Restriction, CKD Patients Not on Dialysis and With Diabetes

3.0.2 In the adult with CKD 3-5 and who has diabetes, it is reasonable to prescribe, under close clinical supervision, a dietary protein intake of 0.6-0.8 g/kg body weight per day to maintain a stable nutritional status and optimize glycemic control (*OPINION*).

Dietary Protein Intake, MHD and PD Patients Without Diabetes

3.0.3 In adults with CKD 5D on MHD (*1C*) or PD (*OPINION*) who are metabolically stable, we recommend prescribing a dietary protein intake of 1.0-1.2 g/kg body weight per day to maintain a stable nutritional status.

Dietary Protein Intake, Maintenance Hemodialysis and Peritoneal Dialysis Patients With Diabetes

3.0.4 In adults with CKD 5D and who have diabetes, it is reasonable to prescribe a dietary protein intake of 1.0-1.2 g/kg body weight per day to maintain a stable nutritional status. For patients at risk of hyper- and/or hypoglycemia, higher levels of dietary protein intake may need to be considered to maintain glycemic control (*OPINION*).

3.1 Statement on Energy Intake

3.1.1 In adults with CKD 1-5D (*1C*) or posttransplantation (*OPINION*) who are metabolically stable, we recommend prescribing an energy intake of 25-35 kcal/kg body weight per day based on age, sex, level of physical activity, body composition, weight status goals, CKD stage, and concurrent illness or presence of inflammation to maintain normal nutritional status.

3.2 Statement on Protein Type

3.2.1 In adults with CKD 1-5D (*1B*) or posttransplantation (*OPINION*), there is insufficient evidence to recommend a particular protein type (plant vs animal) in terms of the effects on nutritional status, calcium or phosphorus levels, or the blood lipid profile.

3.3 Statements on Dietary Patterns

Mediterranean Diet

3.3.1 In adults with CKD 1-5 not on dialysis or posttransplantation, with or without dyslipidemia, we suggest that prescribing a Mediterranean Diet may improve lipid profiles (*2C*).

Fruits and Vegetables

3.3.2 In adults with CKD 1-4, we suggest that prescribing increased fruit and vegetable intake may decrease body weight, blood pressure, and net acid production (NEAP) (*2C*).

Guideline 4: Nutritional Supplementation

4.1 Statements on Oral, Enteral, and Intradialytic Parenteral Nutrition Supplementation

Oral Protein-Energy Supplementation

4.1.1 In adults with CKD 3-5D (*2D*) or posttransplantation (*OPINION*) at risk of or with protein-energy wasting, we suggest a minimum of a 3-month trial of oral nutritional supplements to improve nutritional status if dietary counseling alone does not achieve sufficient energy and protein intake to meet nutritional requirements.

Enteral Nutrition Supplementation

4.1.2 In adults with CKD 1-5D, with chronically inadequate intake and whose protein and energy requirements cannot be attained by dietary counseling and oral nutritional supplements, it is reasonable to consider a trial of enteral tube feeding (*OPINION*).

Total Parenteral Nutrition (TPN) and Intradialytic Parenteral Nutrition (IDPN) Protein-Energy Supplementation

4.1.3 In adults with CKD with protein-energy wasting, we suggest a trial of TPN for CKD 1-5 patients (*2C*) and IDPN for CKD 5D on MHD patients (*2C*), to improve and maintain nutritional status if nutritional requirements cannot be met with existing oral and enteral intake.

4.2 Statement on Nutrition Supplementation – Dialysate

Dialysate Protein-Energy Supplementation

4.2.1 In adults with CKD 5D on PD with protein-energy wasting, we suggest not substituting conventional dextrose dialysate with amino acid dialysate as a general strategy to improve nutritional status, although it is reasonable to consider a trial of amino acid dialysate to improve and maintain nutritional status if nutritional requirements cannot be met with existing oral and enteral intake (*OPINION*).

4.3 Statements on Long Chain Omega-3 Polyunsaturated Fatty Acids (LC n-3 PUFA)

LC n-3 PUFA Nutritional Supplements for Mortality and Cardiovascular Disease

4.3.1 In adults with CKD 5D on MHD or posttransplantation, we suggest not routinely prescribing LC n-3 PUFA, including those derived from fish or flaxseed and other oils, to lower risk of mortality (*2C*) or cardiovascular events (*2B*).

4.3.2 In adults with CKD 5D on PD, it is reasonable to not routinely prescribe LC n-3 PUFA, including those derived from fish or flaxseed and other oils, to lower risk of mortality or cardiovascular events (*OPINION*).

LC n-3 PUFA Nutritional Supplements for Lipid Profile

4.3.3 In adults with CKD 5D on MHD, we suggest that 1.3-4 g/d LC n-3 PUFA may be prescribed to reduce triglycerides and LDL cholesterol (*2C*) and raise HDL levels (*2D*).

4.3.4 In adults with CKD 5D on PD, it is reasonable to consider prescribing 1.3-4 g/d LC n-3 PUFA to improve the lipid profile (*OPINION*).

4.3.5 In adults with CKD 3-5, we suggest prescribing ~2 g/d LC n-3 PUFA to lower serum triglyceride levels (*2C*).

LC n-3 PUFA Nutritional Supplements for Arteriovenous (AV) Graft and Fistula Patency

4.3.6 In adults with CKD 5D on MHD, we suggest not routinely prescribing fish oil to improve primary patency rates in patients with AV grafts (*2B*) or fistulas (*2A*).

LC n-3 PUFA Nutritional Supplements for Kidney Allograft Survival

4.3.7 In adults with CKD posttransplantation, we suggest not routinely prescribing LC n-3 PUFA to reduce the number of rejection episodes or improve graft survival (*2D*).

Guideline 5: Micronutrients

5.0 Statements for General Guidance

Dietary Micronutrient Intake

5.0.1 In adults with CKD 3-5D or posttransplantation, it is reasonable for the registered dietitian nutritionist (RDN) or an international equivalent to encourage eating a diet that meets the recommended dietary allowance (RDA) for adequate intake for all vitamins and minerals (*OPINION*).

Micronutrient Assessment and Supplementation

5.0.2 In adults with CKD 3-5D or posttransplantation, it is reasonable for the registered dietitian nutritionist (RDN) or an international equivalent, in close collaboration with a physician or physician assistant, to assess dietary vitamin intake periodically and to consider multivitamin supplementation for individuals with inadequate vitamin intake (*OPINION*).

Micronutrient Supplementation, Dialysis

5.0.3 In adults with CKD 5D who exhibit inadequate dietary intake for sustained periods of time, it is reasonable to consider supplementation with multivitamins, including all the water-soluble vitamins, and essential trace elements to prevent or treat micronutrient deficiencies (*OPINION*).

5.1 Statements on Folic Acid

Folic Acid Supplementation for Hyperhomocysteinemia

5.1.1 In adults with CKD 3-5D or posttransplantation who have hyperhomocysteinemia associated with kidney disease, we recommend not to routinely supplement folate with or without B-complex since there is no evidence demonstrating reduction in adverse cardiovascular outcomes (*1A*).

Folic Acid Supplementation for Folic Acid Deficiency and Insufficiency

5.1.2 In adults with CKD 1-5D (*2B*) or posttransplantation (*OPINION*), we suggest prescribing folate, vitamin B12, and/or B-complex supplement to correct for folate or vitamin B12 deficiency/insufficiency based on clinical signs and symptoms (*2B*).

5.2 Statement on Vitamin C

Vitamin C Supplementation

5.2.1 In adults with CKD 1-5D or posttransplantation who are at risk of vitamin C deficiency, it is reasonable to consider supplementation to meet the recommended intake of at least 90 mg/d for men and 75 mg/d for women (*OPINION*).

5.3 Statements on Vitamin D

Vitamin D Supplementation for Vitamin D Deficiency and Insufficiency

5.3.1 In adults with CKD 1-5D (*2C*) or posttransplantation (*OPINION*), we suggest prescribing vitamin D supplementation in the form of cholecalciferol or ergocalciferol to correct 25-hydroxyvitamin D (25(OH)D) deficiency/insufficiency.

Vitamin D Supplementation With Proteinuria

5.3.2 In adults with CKD 1-5 with nephrotic-range proteinuria, it is reasonable to consider supplementation of cholecalciferol, ergocalciferol, or other safe and effective 25(OH)D precursors (*OPINION*).

5.4 Statement on Vitamins A and E

Vitamins A and E Supplementation and Toxicity

5.4.1 In adults with CKD 5D on MHD or CKD 5D on PD, it is reasonable to not routinely supplement vitamin A or E because of the potential for vitamin toxicity. However, if supplementation is warranted, care should be taken to avoid excessive doses, and patients should be monitored for toxicity (*OPINION*).

5.5 Statement on Vitamin K

Anticoagulant Medication and Vitamin K Supplementation

5.5.1 In adults with CKD 1-5D or posttransplantation, it is reasonable that patients receiving anticoagulant medicines known to inhibit vitamin K activity (eg, warfarin compounds) do not receive vitamin K supplements (*OPINION*).

5.6 Statement on Trace Minerals – Selenium and Zinc

Selenium and Zinc Supplementation

5.6.1 In adults with CKD 1-5D, we suggest to not routinely supplement selenium or zinc since there is little evidence that it improves nutritional, inflammatory, or micronutrient status (*2C*).

Guideline 6: Electrolytes

6.1 Statements on Acid Load

Dietary Management of Net Acid Production (NEAP)

6.1.1 In adults with CKD 1-4, we suggest reducing net acid production (NEAP) through increased dietary intake of fruits and vegetables (*2C*) in order to reduce the rate of decline of residual kidney function.

Bicarbonate Maintenance

6.1.2 In adults with CKD 3-5D, we recommend reducing net acid production (NEAP) through increased bicarbonate or a citric acid/sodium citrate solution supplementation (*1C*) in order to reduce the rate of decline of residual kidney function.

6.1.3 In adults with CKD 3-5D, it is reasonable to maintain serum bicarbonate levels at 24-26 mmol/L (*OPINION*).

6.2 Statements on Calcium

Total Calcium Intake

6.2.1 In adults with CKD 3-4 not taking active vitamin D analogs, we suggest that a total elemental calcium intake of 800-1,000 mg/d (including dietary calcium, calcium supplementation, and calcium-based phosphate binders) be prescribed to maintain a neutral calcium balance (*2B*).

6.2.2 In adults with CKD 5D, it is reasonable to adjust calcium intake (dietary calcium, calcium supplements, or calcium-based binders) with consideration of concurrent use of vitamin D analogs and calcimimetics in order to avoid hypercalcemia or calcium overload (*OPINION*).

6.3 Statements on Phosphorus

Dietary Phosphorus Amount

6.3.1 In adults with CKD 3-5D, we recommend adjusting dietary phosphorus intake to maintain serum phosphate levels in the normal range (*1B*).

Dietary Phosphorus Source

6.3.2 In adults with CKD 1-5D or posttransplantation, it is reasonable when making decisions about phosphorus restriction treatment to consider the bioavailability of phosphorus sources (eg, animal, vegetable, additives) (*OPINION*).

Phosphorus Intake With Hypophosphatemia

6.3.3 For adults with CKD posttransplantation with hypophosphatemia, it is reasonable to consider prescribing high-phosphorus intake (diet or supplements) in order to replete serum phosphate (*OPINION*).

6.4 Statements on Potassium

Dietary Potassium Amount

6.4.1 In adults with CKD 3-5D or posttransplantation, it is reasonable to adjust dietary potassium intake to maintain serum potassium within the normal range (*OPINION*).

Dietary and Supplemental Potassium Intake for Hyperkalemia or Hypokalemia

6.4.2 In adults with CKD 3-5D (*2D*) or posttransplantation (*OPINION*) with either hyperkalemia or hypokalemia, we suggest that dietary or supplemental potassium intake be based on a patient's individual needs and clinician judgment.

6.5 Statements on Sodium

Sodium Intake and Blood Pressure

6.5.1 In adults with CKD 3-5 (*1B*), CKD 5D (*1C*), or posttransplantation (*1C*), we recommend limiting sodium intake to less than 100 mmol/d (or <2.3 g/d) to reduce blood pressure and improve volume control.

Sodium Intake and Proteinuria

6.5.2 In adults with CKD 3-5 we suggest limiting sodium intake to less than 100 mmol/d (or <2.3 g/d) to reduce proteinuria synergistically with available pharmacologic interventions (*2A*).

Sodium Intake and Dry Body Weight

6.5.3 In adults with CKD 3-5D, we suggest reduced dietary sodium intake as an adjunctive lifestyle modification strategy to achieve better volume control and a more desirable body weight (*2B*).

KDOQI CLINICAL PRACTICE GUIDELINE FOR NUTRITION IN CKD

Guideline 1: Nutritional Assessment

1.0 Statements on Usual Care

Routine Nutrition Screening

1.0.1 In adults with CKD 3-5D or posttransplantation, it is reasonable to consider routine nutrition screening at least biannually with the intent of identifying those at risk of protein-energy wasting (*OPINION*).

Nutrition Screening Tools

1.0.2 In adults with CKD 3-5D or posttransplantation, there is limited evidence to suggest the use of one tool over others for identifying those at risk of protein-energy wasting (PEW) (*2D*).

Routine Nutrition Assessment

1.0.3 In adults with CKD 3-5D or posttransplantation, it is reasonable that a registered dietitian nutritionist (RDN) or an international equivalent conduct a comprehensive nutrition assessment (including but not limited to appetite, history of dietary intake, body weight and body mass index, biochemical data, anthropometric measurements, and nutrition-focused physical findings) at least within the first 90 days of starting dialysis, annually, or when indicated by nutrition screening or provider referral (*OPINION*).

1.1 Statement on Technical Devices and Anthropometric Measurements to Assess Body Composition

Bioelectrical Impedance for Patients on Maintenance Hemodialysis (MHD)

1.1.1 In adults with CKD 5D on MHD, we suggest using bioimpedance and preferably multi-frequency bioelectrical impedance (MF-BIA) to assess body composition when available. Bioimpedance assessments should ideally be performed a minimum of 30 minutes or more after the end of the hemodialysis session to allow for redistribution of body fluids (*2C*).

Bioelectrical Impedance for CKD Patients Not on Dialysis or on Peritoneal Dialysis (PD)

1.1.2 In adults with CKD 1-5 or CKD 5D on PD, there is insufficient evidence to suggest using bioelectrical impedance to assess body composition (*2D*).

Dual-Energy X-Ray Absorptiometry (DXA) for Body Composition Assessment

1.1.3 In adults with CKD 1-5D or posttransplantation, it is reasonable to use DXA when feasible as it remains the gold standard for measuring body composition despite being influenced by volume status (*OPINION*).

Body Composition and Body Weight/BMI

1.1.4 In adults with CKD 1-5D or posttransplantation, it is reasonable to consider assessing body composition in combination with body weight/BMI at the first visit and to monitor overall nutrition status periodically over time (*OPINION*).

Frequency of Body Weight/BMI and Body Composition Assessment

1.1.5 In adults with CKD 1-5D or posttransplantation who are clinically stable, it is reasonable to measure body weight and BMI and to monitor for changes in body weight/BMI and body composition as needed (*OPINION*):

- At least monthly in MHD and PD patients
- At least every 3 months in patients with CKD 4-5 or posttransplantation
- At least every 6 months in patients with CKD 1-3

Assessment of Body Weight

1.1.6 In adults with CKD 1-5D or posttransplantation, it is reasonable for registered dietitian nutritionist (RDN) or an international equivalent or physicians to use clinical judgment to determine the method for measuring body weight (eg, actual measured weight; history of weight changes; serial weight measurements; adjustments for suspected impact of edema, ascites, and polycystic organs) due to absence of standard reference norms (*OPINION*).

BMI as a Predictor of Mortality

1.1.7 In adults with CKD 5D on PD, we suggest that underweight status (based on BMI) can be used as a predictor of higher mortality (*2C*).

1.1.8 In adults with CKD 5D on MHD, we suggest that overweight or obesity status (based on BMI) can be used as a predictor of lower mortality, whereas, underweight status and morbid obesity (based on BMI) can be used as a predictor of higher mortality (*2B*).

1.1.9 In adults with CKD 1-5, it is reasonable to consider using underweight status (based on BMI) as a predictor of higher mortality, though the mortality risk associated with overweight or obesity status (based on BMI) is not clear (*OPINION*).

1.1.10 In adults with CKD posttransplantation adults, it is reasonable to consider using underweight and overweight or obesity status (based on BMI) as a predictor of higher mortality (*OPINION*).

BMI and PEW

1.1.11 In adults with CKD 1-5D or posttransplantation, BMI alone is not sufficient to establish a diagnosis of PEW unless the BMI is very low (<18 kg/m^2) (*OPINION*).

Skinfold Thickness

1.1.12 In adults with CKD 1-5D (*1B*) or posttransplantation (*OPINION*), in the absence of edema, we suggest using skinfold thickness measurements to assess body fat.

Waist Circumference

1.1.13 In adults with CKD 5D, we suggest that waist circumference may be used to assess abdominal obesity, but its reliability in assessing changes over time is low (*2C*).

Conicity Index

1.1.14 In adults with CKD 5D on MHD, we suggest that the conicity index may be used to assess nutritional status (*OPINION*) and as a predictor of mortality (*2C*).

Creatinine Kinetics

1.1.15 In adults with CKD 5D, we suggest that creatinine kinetics may be used to estimate muscle mass, though very high or very low dietary intake of meat and/or creatine supplements will influence accuracy of this measurement (*2C*).

Rationale/Background

Methods of assessing body composition, including anthropometric measurements, are components of the nutrition assessment in CKD. Anthropometric measurements are practical, inexpensive, and noninvasive techniques that describe body mass, size, shape, and levels of fatness and leanness; they are the most basic and indirect methods of assessing body composition. These include height, weight, skinfolds, circumferences, bioelectrical impedance analysis (BIA), creatinine kinetics, and near-infrared. Dual-energy x-ray absorptiometry (DXA) is a direct method that is considered the gold standard for assessing body composition in patients with CKD; however, this measure is labor intensive, invasive, and expensive and can be influenced by a number of CKD-related factors such as hydration status.

Timing of body composition assessments is important in CKD because assumptions of hydration are required for accurate interpretation of the results, and fluid/electrolyte balance is likely to be altered significantly in patients with CKD. For these reasons, in adults undergoing dialysis, assessments are best obtained after treatment when body fluid compartments levels are balanced.[4,5]

Regardless of the method selected to assess body composition, none are perfect, and the errors surrounding them should not be ignored. Errors may have clinical relevance, especially if the individual is treated and observed over time.[5] Moreover, the results of the measures are only as useful as the availability of suitable reference data from a group of persons of at least the same age, race, sex, and disease status.

Detailed Justification

Technical Devices to Measure Body Composition. Multifrequency BIA. Twelve studies reported on the use of multifrequency BIA (MF-BIA) to assess fat mass (FM) and fat-free mass (FFM) in maintenance hemodialysis (MHD), peritoneal dialysis (PD), and CKD patients not receiving dialysis. Four of these studies were validity/reliability studies: 2 in MHD patients,[6,7] 1 in PD patients,[8] and 1 in CKD patients not receiving dialysis.[9]

Three were prediction studies: 2 in MHD patients and 1 in MHD and PD patients.[10-12]

Eight were correlation studies; 5 in MHD patients,[6,8,13-16] 1 in PD patients, 1 in MHD and PD patients,[17] and 1 in CKD patients not receiving dialysis.[9]

MHD patients. FM and FFM measured using MF-BIA had good agreement with DXA in 2 studies,[6,7] had high correlations with several markers of nutritional status in 4 studies,[6,15-17] and predicted hard outcomes in 3 studies.[10-12] Furstenberg and Davenport concluded that MF-BIA was a more robust tool than DXA for measuring body composition in MHD patients.[7] Donadio et al found that MF-BIA yielded a smaller prediction error in MHD patients.[6]

Body composition determined using MF-BIA was found to be predictive of hospitalization[11] and survival.[10-12] In Rodrigues et al, BIA underestimated FM and overestimated FFM when compared with air displacement plethysmography in MHD patients.[16] PEW determined using MF-BIA was positively related to body mass index (BMI) and negatively associated with serum albumin level.[15] In Mancini et al, bioimpedance vector analysis was predicted by normalized protein catabolic rate (nPCR) and albumin level in MHD patients with normal nutritional status, but the predictive effects were not accurate in undernourished patients.[14] In MHD patients, a body protein index (BPI) score calculated from MF-BIA protein mass and height significantly correlated with blood protein levels in men receiving MHD, but there was no relationship in women receiving MHD.[17]

PD patients. FM and FFM measured using MF-BIA showed wide limits of agreement with DXA in 1 study, which was affected by hydration status,[8] and was an independent risk factor for survival in another study.[10] In continuous ambulatory PD (CAPD) patients, lean body mass (LBM) measured using MF-BIA and the creatinine kinetic method were highly correlated but there was no difference in LBM using BIA in patients with or without

peritoneal dialysate.[13] A BPI score calculated from MF-BIA protein mass and height significantly correlated with blood protein levels in men receiving MHD, but there was no relationship in women receiving MHD or CAPD patients. The findings varied according to sex and dialysis treatment.[17]

CKD patients not receiving dialysis. In diabetic patients, percent LBM measured using DXA was greater than that predicted by BIA ($P < 0.05$). Bland-Altman analysis demonstrated biases by BIA, but the mean of the results obtained by combined anthropometry and BIA demonstrated no bias from DXA measurements.[9]

Anthropometric and Other Measurements to Measure Body Composition. Skinfold measurements. Ten studies reported on the use of skinfold measurements to assess body composition, including 4 agreement/validity/reliability studies,[18-21] 1 prediction study,[22] and 6 correlation studies.[19,23-27]

MHD patients. Bross et al used DXA as the reference test and showed that triceps skinfold thickness (TSF), BIA (Kushner),[28] and near-infrared interactance were the most accurate of the index tests in estimating total-body fat (TBF) percent, although the BIA (Segal)[29] and BIA (Lukaski)[30] equations overestimated TBF percent.[19] These results were not affected by skin color. In Bross et al, there were significant correlations (all $P < 0.001$) between DXA measurements and triceps skinfold measures of body fat (BF) in MHD participants.[19] Kamimura et al compared skinfold thickness (SKF) using DXA and BIA and found that BF estimates using SKF and BIA were not significantly different from those obtained using DXA in the total group.[20] There were significant intraclass correlations between DXA with SKF ($r = 0.94$) and BIA ($r = 0.91$). DXA showed relatively good agreement with both SKF (mean difference ± standard deviation [SD], 0.47 ± 2.8 [95% limits of agreement, −5.0 to 6.0] kg) and BIA (mean difference ± SD, 0.39 ± 3.3 [95% limits of agreement, −6.9 to 6.1] kg) in the total group, but BIA showed greater mean prediction error for both men and women. This study indicated that SKF was preferable over BIA, which showed sex-specific variability in the assessment of BF.

A prediction study by Araujo et al showed that TSF < 90% was not associated with higher odds of mortality.[22] In MHD patients, Oe et al found a significant correlation in LBM ($r = 0.69$; $P < 0.025$) between 4-site skinfold anthropometry (FSA) and BIA. BF-FSA was positively correlated with BF-BIA ($r = 0.65$; $P < 0.005$).[26] Both techniques are comparable for LBM and BF measurements; however, FSA is less affected by change in fluid status. Malnutrition score was significantly correlated with bicep skinfolds ($r = -0.32$) in MHD patients in a study by Kalantar-Zadeh et al.[24] Aatif et al showed that fat tissue index and TSF had a positive significant correlation ($r = 0.61$; $P < 0.001$).[23] Kamimura et al found a strong correlation between BIA and SKF ($r = 0.87$) and near-infrared interactance and SKF ($r = 0.78$).[20] This study confirmed that the most simple, long-established, and inexpensive method of skinfold thickness measurement is very useful for assessing BF in patients on long-term MHD therapy.

PD patients. Stall et al examined 5 different tools to assess BF percent. BF percent measurements were different between all methods ($P < 0.001$), although there were differences according to sex.[27] For men, all techniques were significantly different from each other ($P < 0.05$) except BIA and DXA, as well as the Steinkamp method[31] (SKF) and total-body potassium. For women, all techniques were significantly different from each other ($P < 0.05$) except DXA and the 2 methods for measuring SKF (Durnin and Womersley[32] and Steinkamp[31]). Despite the differences between modalities, all techniques were found to correlate significantly with each other ($P < 0.01$ or better for men and $P < 0.001$ or better for women).

Hemodialysis and PD patients. Woodrow et al compared SKF using DXA and BIA.[21] Bland-Altman analysis demonstrated no observed differences in 95% levels of agreement for TBF percent and FFM from skinfold-BIA or skinfold anthropometry compared with DXA (percent TBF BIA-DXA, −13.7% to +8.3%; percent TBF skinfold anthropometry–DXA, −13.0% to +9.4%; FFM BIA-DXA, −5.1 to +9.6 kg; FFM skinfold anthropometry–DXA, −5.6 to +9.1 kg). There were considerable variations in agreement between the measures.

CKD patients not receiving dialysis. Avesani et al used a Bland-Altman plot analysis for BF percent and showed that the best agreement was between SKF and DXA compared with other measures.[18] SKF also had significant intraclass correlations with BF percent and it significantly correlated with FFM as measured using DXA ($r = 0.74$; $r = 0.85$), indicating moderate and good reproducibility, respectively. This study indicated that SKF may be a good method to determine BF percent in CKD patients not receiving dialysis and patients with mild to advanced CKD.

Serum creatinine/creatinine kinetics. Seven studies examined the relationship between serum creatinine level or creatinine kinetics and comparative measures of muscle mass in MHD, PD, and CKD patients not receiving dialysis.

MHD patients. One study in MHD patients showed that creatinine kinetics correlated with creatinine levels and other traditional measures of muscle mass (eg, computed tomographic scan and anthropometric measurements).[33] Another 3 studies in MHD patients showed that predialysis, interdialytic change, and weekly creatinine clearance levels predicted mortality.[33-35]

PD patients. In PD patients, creatinine kinetics was correlated with other body composition measurements in 1 study.[36] However, significant differences existed between creatinine levels and anthropometric measures for LBM/FFM in another.[37] A study in PD examined creatinine clearance and relative risk for mortality.[38] Evidence was limited in CKD patients not receiving dialysis to 1 study.[18] Creatine kinase level was significantly correlated with BF percent and FFM from DXA ($r = 0.47$ and $r = 0.57$, respectively, indicating moderate reproducibility, though there were significant differences in adjusted

means of BF percent and FFM between creatine kinase level and DXA ($P < 0.05$).[18]

Waist circumference. Two studies reported on the use of waist circumference to assess nutritional status in dialysis patients.[39,40]

MHD patients. Cordeiro et al[40] examined risk for PEW, inflammation, and mortality according to waist circumference tertile in MHD patients. As waist circumference increased, indicating increased abdominal fat, patients had increased odds of PEW (assessed using subjective global assessment [SGA]) and inflammation (assessed using interleukin 6 [IL-6] level). In the fully adjusted model, there was no increased risk for mortality according to waist circumference tertile.[40]

PD patients. Bazanelli et al found a strong correlation between waist circumference and trunk fat ($r = 0.81$; $P < 0.001$) for both men and women and a significant association with BMI ($r = 0.86$; $P < 0.001$).[39] There was moderate agreement between waist circumference and trunk fat ($\kappa = 0.59$) and area under the curve was 0.90. In a prospective evaluation of the same study, changes in waist circumference were also correlated with changes in trunk fat ($r = 0.49$; $P < 0.001$) and $\kappa = 0.48$ indicated moderate agreement between the tools. The authors concluded that waist circumference is a reliable marker of abdominal adiposity in PD patients.

Body mass index. Twenty-four studies reported on the use of BMI to assess nutritional status, including 17 prediction studies[22,34,41-55] and 9 correlation studies.[17,19,23,48,56-60] There were no studies examining the validity or reliability of using BMI in this population to classify nutritional status.

MHD patients. Eight studies examined MHD patients only. Seven studies examined mortality risk according to BMI category. In 3 studies,[42,54,55] the authors examined mortality risk according to traditional weight categories (underweight, normal weight, overweight, and obese), although in a study with Taiwanese participants,[55] these categories were defined differently. In 5 additional studies, the authors examined risk according to 5 to 11 BMI categories.[41,45,47,61,62]

In one study that only compared 2 groups (BMI < 25 or >25 kg/m^2), the authors found no association between BMI and mortality at 10 years.[22] However, in the remaining studies in which BMI was examined according to traditional weight status groups or by 5 to 11 categories, there was consistently a higher risk for mortality for participants who were underweight and lower risk for participants who were overweight or obese.[41,42,45,47,54,55] Length of follow-up for these studies ranged from 1.34 to 10 years. There was an inverse relationship with mortality when BMI was measured as a continuous variable in 3 studies,[47,53,54] but Harrell C statistic was not significant in de Roij van Zuijdewijn et al.[34]

Findings from correlation studies indicated that BMI was positively associated with albumin level, FM, and LBM measured using a variety of methods in hemodialysis (HD) patients. Beberashvili et al showed that serum albumin level was significantly and positively correlated with BMI and FM in MHD patients.[56] The higher BMI group had greater LBM ($P = 0.001$) and FM ($P = 0.0001$) and higher phase angle and extracellular mass to body cell mass ratio ($P < 0.05$). MHD patients with elevated BMI demonstrate better nutritional status compared with patients with normal BMI or overweight patients. Severity of inflammation was not related to BMI in MHD patients.

Bross et al indicated that BMI had a strong linear correlation with TBF percent measured using near-infrared radiation and BIA (Segal) ($r \geq 0.85$) in MHD patients.[19] Fat tissue index, as estimated using BIA, was significantly correlated with BMI in the study by Aatif et al.[23] In another study, Kadiri et al showed that BMI was positively correlated with FM ($r = 0.493$; $P = 0.002$), serum albumin level ($r = 0.340$; $P = 0.04$), and anemia in MHD patients.[57] BMI was negatively correlated with C-reactive protein (CRP) level ($r = -0.065$; $P = 0.702$) but had no correlation with LBM ($r = 0.278$; $P = 0.085$). Kahraman et al studied the relationship between CRP level and BMI status and found that CRP levels were significantly higher in obese and underweight MHD patients compared with normal and overweight patients ($P < 0.05$).[58]

Steiber et al[59] found that mean BMI was significantly different across the 5 categories of SGA ($P < 0.05$) in MHD patients. Visser et al[60] demonstrated that there was a strong correlation between the 7-point SGA scale and BMI in MHD patients ($r = 0.79$; $P < 0.001$) and percent fat ($r = 0.77$; $P < 0.001$).

MHD and PD patients. Three studies reported on the relationship between BMI and mortality in a combination of MHD and PD patients (Badve et al[41] reported results for MHD and PD patients separately). In Mathew et al,[51] participants who survived had higher baseline BMI compared with the group that did not survive, but BMI category was not a significant predictor. Hoogeveen et al[44] demonstrated that underweight and obesity were risk factors in a combination of MHD/PD patients younger than 65 years, but for those who were at least 65 years old, there was no relationship between BMI and mortality. Lievense et al[49] demonstrated that PD patients had lower mortality risk compared with MHD patients. Leinig et al[48] showed that there was a positive correlation between BMI and FM in predialysis ($r = 0.67$; $P = 0.0002$), MHD ($r = 0.67$; $P = 0.0002$), and PD ($r = 0.79$; $P < 0.0001$) patients. Nakao et al[17] indicated that BMI was significantly correlated with BPI score in MHD and PD patients (r values ranging from 0.778 to 0.886; $P < 0.0001$). Hoogeveen et al[44] followed up dialysis patients younger than 65 or 65 years and older for 7 years. In the multivariable-adjusted model, compared with those with "normal" weight status, those who were categorized as underweight (hazard ratio [HR], 2.00 [95% CI, 1.30-3.07]) and obese (HR, 1.57 [95% CI, 1.08-2.28]) had a significantly higher hazard of mortality for those who were younger than 65 years, but

there was no significant relationship between weight status and mortality for those 65 years and older.[44]

PD patients. Four studies reported on the relationship between BMI and mortality in PD patients. Badve et al[41] found that underweight increased mortality risk at 2.3 years, but results regarding higher BMI categories were not consistent. Leinig et al[48] found no difference in mortality risk according to whether PD patients had BMI < 23 or >23 kg/m^2 at 2 years. McDonald et al[52] found that in adjusted analysis, PD patients who were obese had higher risk for mortality (up to 10 years) compared with patients with normal weight status. In the study by Kim et al,[48] the group with the lowest quartile of BMI had the highest mortality risk at 2 years, but there were no other significant associations. In a systematic review performed by Ahmadi et al,[3] the authors confirmed an increased risk for 1-year mortality for people with CKD who were underweight, but this relationship did not persist for 2-, 3- and 5-year mortality. Conversely, Ahmadi et al[63] found that overweight or obesity status decreased mortality risk at 1, but not 2, 3, or 5 years.

CKD patients not receiving dialysis. Finally, 2 studies examined the relationship between BMI and mortality in CKD patients not receiving dialysis. Madero et al[50] examined risk according to BMI quartile and found no relationship.[64] Hanks et al[43] took a different approach and examined risk not only according to traditional BMI categories, but also according to whether participants were metabolically healthy. Of those who were metabolically healthy, there was decreased risk for overweight/obese participants compared with those with normal BMI. However, there was no difference in mortality risk according to weight status in those who were metabolically unhealthy. These findings were consistent with a systematic review by Ahmadi et al.[64]

Posttransplant patients. A systematic review by Ahmadi et al[65] examined the relationship between BMI and mortality in more than 150,000 adults with CKD with a kidney transplant. The authors conclude that compared with participants with "normal" weight status at baseline, those who were underweight (HR, 1.09 [95% CI, 1.02-1.20]) or overweight/obese (HR, 1.20 [95% CI, 1.14-1.23]) were at increased hazard of mortality.[65]

Near-Infrared. Evidence examining the validity of near-infrared radiation as a measure of body composition was too limited to make recommendations.

Special Discussions

The guidelines for MF-BIA, DXA, and skinfold measurements require specialized equipment.

Bioelectrical impedance or DXA is not routinely available at all facilities and could cause undo financial burden on the client and the facility.

Good-quality calipers are needed to obtain an accurate measurement of SKF. However, the measurer must be trained to obtain accurate results. To obtain waist circumference, only a measuring tape is required. Again, the measurer must be trained on how to obtain this measurement. MF-BIA is becoming more widely available as the technology advances. However, training is needed to understand and to appropriately interpret the output from the device and how to utilize the data for clinical practice and treatment alterations.

In patients initiating maintenance dialysis, a comprehensive nutrition assessment should be completed as quickly as possible (ie, 2-4 weeks), best to be completed within 90 days of dialysis initiation.

Implementation Considerations

Multifrequency BIA.

- The guideline for MF-BIA applies to all adult patients receiving MHD. The measurement must be obtained postdialysis on a nonconducting surface for an accurate assessment.
- When bioimpedance is performed in patients treated by PD, measurements should be done with an empty abdominal cavity (following PD fluid drainage) and bladder. For individuals receiving MHD with residual kidney function, the bladder should be empty.
- There are no potential risks or harms associated with the application of the guideline for MF-BIA in adult patients receiving MHD.
- The logistics of obtaining BIA 30 minutes postdialysis could be complicated. In certain circumstances, predialysis BIA can be considered if monitored over time.

Body Mass Index.

- BMI is not an ideal marker of obesity because it cannot differentiate between higher weights due to increased adiposity versus muscularity and it cannot identify visceral adiposity, which has negative metabolic effects.
- To ensure the accuracy of BMI, height should be measured periodically.
- There are no potential risks or harms associated with the application of the guideline for BMI.
- The standard weight status categories that have been defined by the World Health Organization (WHO) according to BMI ranges for adults should be used in the CKD population; these include <18.5 kg/m^2 for underweight, 18.5 to 24.9 kg/m^2 for normal weight, 25.0 to 29.9 kg/m^2 for overweight, and ≥30 kg/m^2 for obese. Population-specific BMI cutoffs to define weight status may be lower for Asian populations.
- Limited evidence suggested that obesity (BMI ≥ 30 kg/m^2) may be a risk factor for higher mortality in individuals who are receiving dialysis and younger than 65 years. Therefore, practitioners should consider patient age when determining mortality risk according to BMI.
- In patients receiving dialysis, weight to calculate BMI should be measured following dialysis treatment to improve accuracy.

- For certain patients, such as those with polycystic kidney disease, nutrition screening using standard BMI (and waist circumference) measurements is not suitable.

Skinfold Measurements.

- The guideline for skinfold measurements applies to all adult patients with CKD, including posttransplant. However, for the measurements to be useful to the practitioner, longitudinal assessments must be done to provide meaningful information about changes in BF percent for that patient.
- There are no potential risks or harms associated with the application of the guideline for skinfold measurements in all adult patients with CKD.
- Skinfold measurements may not be accurate for obese patients because calipers may have upper limits that do not accommodate high levels of adiposity.

Creatinine Kinetics.

- The guideline for using creatinine kinetics to measure muscle mass applies to all adult patients with CKD. However, the procedure requires the patient to collect his or her urine for a 24-hour period and preferably to keep the collection on ice, which may make the procedure inconvenient for some patients. Furthermore, intake of meat or protein supplements containing creatine may contribute to urinary creatinine excretion and this must be considered when calculating creatinine kinetics. In MHD patients, creatinine kinetics based on pre- and post-HD serum creatinine measurements is more reliable for patients who are anuric.
- There are no potential risks or harms associated with the application of the guideline for creatinine kinetics in adult patients with CKD.

Dual-Energy X-ray Absorptiometry.

- DXA is a valid technique for measuring body composition in adult patients with CKD, including posttransplant patients. In MHD and PD patients, this is despite the measurement being influenced by overhydration.
- DXA is associated with very small amounts of radiation and this should be considered when weighing the benefits and risks of this method for a particular individual. Ten screenings with DXA result in a similar amount of radiation exposure as 1 chest x-ray.

Measuring Body Weight. Body weight is a complicated measurement in CKD and requires careful clinical interpretation. Regardless of stage of CKD, body weight should be measured serially, and any sudden changes in body weight (eg, unintentional weight loss or weight gain) can indicate serious changes in health status. A patient's weight history and comparison to his or her usual body weight over time assists in determining risk for PEW, as well as establishing optimal health goals. When using published weight norms in the anthropometric assessment of adult patients with CKD, caution must be used because each norm has significant drawbacks (Table 5[66-71]).

- Ideal body weight (IBW) is the body weight associated with the lowest mortality for a given height, age, sex, and frame size and is based on the Metropolitan Life Insurance Height and Weight Tables. (Caution: not generalizable to the CKD population and data-gathering methods were not standardized.)
- The Hamwi method can be used to estimate IBW. (Caution: a quick and easy method for determining optimal body weight but has no scientific data to support its use.)
- Standard body weight as used in the original KDOQI nutrition guideline is the median body weight of average Americans from 1976 to 1980 for height, age, sex, and frame size as determined by the Second National Health and Nutrition Examination Survey (NHANES II). (Caution: Although data are validated and standardized and use a large database of ethnically diverse groups, data are provided only on what individuals weigh, not what they should weigh to reduce morbidity and mortality.)
- BMI often defines generalized obesity in the general population. Studies in maintenance dialysis patients have identified that patients at higher BMI have lower mortality risk. (Caution: the researchers may not have statistically adjusted for all confounders related to comorbid conditions occurring in CKD on maintenance dialysis [diabetes, malignancy, etc] and it is unclear how it may relate to patients with CKD not receiving dialysis.)
- Adjusted body weight is based on the theory that 25% of the excess body weight (adipose tissue) in obese patients is metabolically active tissue. (Caution: this has not been validated for use in CKD and may either over- or underestimate energy and protein requirements.)

Monitoring and Evaluation

- Anthropometric measurements for assessment of body composition should be done routinely in patients with CKD; these include skinfold measurements, waist circumference, and creatinine kinetics.
- BMI should be used routinely to assess weight status in patients with CKD because it is useful in predicting mortality. However, in isolation, BMI is not sufficient to establish a diagnosis of PEW unless it is very low (<18 kg/m^2).
- However, because of the cost associated with some of these measures (eg, MF-BIA and DXA), there is insufficient evidence for the work group to suggest the use of these measurements on a routine basis in clinical practice.
- Although absolute body weight and BMI are useful indicators of nutritional status, percent change in usual body weight (dry weight in maintenance dialysis patients) may be a more reliable measure for determining risk for PEW.

Table 5. Measuring Body Weight

Ideal BW[66] (Hamwi method[a])	• Women: 100 lb (45.36 kg) for first 5'0" (127 cm) and add 5 lb (2.27 kg) for each additional inch (25.4 cm) > 5'0" • Men: 106 lb (48.08 kg) for first 5'0" (127 cm) and add 6 lb (2.72 kg) for each additional inch (25.4 cm) > 5'0"
Standard BW[67]	• Average 50th percentile weights for men and women by age, height, and frame size in the US (based on NHANES II date). Tables are published in KDOQI 2000 Nutrition Guideline.[67]
Desirable BW[68]	• Based on body mass index
Adjusted BW[69]	• Adjusted BW = ideal BW + [(actual BW − ideal BW) × 0.25] • It is recommended that BW should be adjusted for calculation of nutrient recommendation if patient's weight is <95% or >115% of ideal/standard BW: adjusted BW = edema-free BW + [(standard BW − edema-free BW) × 0.25]
Edema-free BW[70]	• Analogous to estimated dry weight in the patient being treated by renal replacement therapies
Percent of usual BW[71]	• Percent usual BW = (usual BW − current BW)/usual BW) × 100

Abbreviations: BW, body weight; KDOQI, Kidney Disease Outcomes Quality Initiative; NHANES II, Second National Health and Nutrition Examination Survey; US, United States.
[a]Can subtract 10% for small frame and add 10% for large frame.

Future Research

Multifrequency BIA.

- Determine the frequency with which MF-BIA measurements should be performed in patients with CKD, particularly in individuals who are nondialyzed, treated with PD, or posttransplant.
- Determine the validity and reliability of these measurements compared with DXA and anthropometric markers of nutritional status in PD patients, posttransplant patients, and CKD patients not receiving dialysis.
- Determine how to use the data from body composition to assist daily clinical practice and treatment alterations.
- Determine how data from body composition assessment and serial changes over time may predict clinical outcomes.

Body Mass Index.

- Examine the predictive value of BMI with mortality and other markers of nutritional status in maintenance dialysis patients of different racial and ethnic backgrounds. Determine whether the BMI categories for dialysis patients are similar to the general population.

Creatinine Kinetics.

- Determine the frequency with which creatinine kinetics should be measured and monitored.

Skinfold Measurements.

- Determine the frequency with which skinfold measurements should be obtained and monitored in the CKD population.

- Obtain a reference data set for maintenance dialysis patients of the same age, race, and sex.

Waist Circumference.

- Determine the frequency with which waist circumference should be measured and monitored in the CKD population.
- Obtain a reference data set for maintenance dialysis patients of the same age, race, and sex.
- Define the criteria or threshold of waist circumference in the CKD population in defining obesity/overweight and whether the criteria in the general population also apply to patients with CKD and dialysis and transplant patients.

1.2 Statements on Assessment With Laboratory Measurements

Single Biomarker Measurements

1.2.1 In adults with CKD 1-5D or posttransplantation, biomarkers such as normalized protein catabolic rate (nPCR), serum albumin, and/or serum prealbumin (if available) may be considered complementary tools to assess nutritional status. However, they should not be interpreted in isolation to assess nutritional status as they are influenced by nonnutritional factors (*OPINION*).

Serum Albumin Levels

1.2.2 In adults with CKD 5D on MHD, serum albumin may be used as a predictor of hospitalization and mortality, with lower levels associated with higher risk (*1A*).

Background/Rationale

Assessments of nutritional status in patients with CKD have traditionally relied on biochemical or other related calculated indices such as serum albumin, prealbumin, and nPCR as diagnostic tools. Albumin is a major circulating protein that plays a number of biological roles, such as maintaining osmotic pressure and transporting a variety of molecules. Serum prealbumin, also known as transthyretin, is another circulating protein produced by the liver with a shorter half-life than albumin; it is therefore

more sensitive to rapid changes in nutritional status. nPCR is a common tool used to estimate protein intake and is calculated using the intradialytic increase in serum urea nitrogen level in MHD patients and from urinary urea from 24-hour urine collection in CKD patients not receiving dialysis. The advantages of such markers include the fact that they are easily quantifiable and available for each patient. However, these markers are known to be heavily influenced by inflammation, illness, liver failure, volume expansion, and urinary or dialysate protein losses (or in the case of nPCR, protein balance and other factors). Serum albumin level is one of the best predictors of illness or death in patients with end-stage kidney disease (ESKD). In light of this, their utility in assessing nutritional status has been re-evaluated in recent years. Existing data suggest that such markers are not sufficiently reliable or valid to use in isolation for assessing nutritional status. Instead, it should be used as part of a more comprehensive and inclusive evaluation as used for screening purposes.

Detailed Justification

Serum Albumin. Sixteen observational studies that compared serum albumin concentration with other methods used to assess nutritional status, including 12 studies with MHD patients, 2 studies with PD patients, and 2 studies with both MHD and PD patients, were included in this review

MHD patients. Among the MHD studies, 1 was a prospective cohort study,[34] 2 were retrospective cohort studies,[22,72] and 7 were cross-sectional studies.[23,56,57,73-76] Two studies were diagnostic validity or reliability studies.[14,77]

Gurreebun et al determined that serum albumin concentration was a sensitive method for identifying patients at risk for PEW defined by the 7-point SGA score.[77] In a study by Mancini et al,[14] albumin level independently predicted bioimpedance vector analysis in patients with normal values for other nutritional indices, but the association was not significant in patients with worse nutritional values.[14] Araujo et al[22] demonstrated that serum albumin concentration < 3.5 g/dL was associated with higher odds of mortality over 10 years (OR, 2.34 [95% CI, 1.33-4.10]; P = 0.002). Campbell and MacLaughlin[72] found that low albumin concentration (<38 g/L) was significantly associated with higher mortality and morbidity (length of hospital stay), but there was no adjustment for comorbid conditions.[22] de Roij van Zuijdewijn et al[34] determined that albumin concentration predicted all-cause mortality and was the most predictive of 8 other nutrition measures.

In Yelken et al,[76] serum albumin concentration was significantly correlated with high-sensitivity CRP (hsCRP) level, TSF, midarm circumference, and midarm muscle circumference (MAMC). Serum albumin concentrations were associated with nPCR and inflammatory markers,[73,75] BMI,[57] 7-point SGA score,[74] and lean tissue index values, but not fat tissue index from bioimpedance spectroscopy[23] BMI and FM.[56]

PD patients. Of the 2 studies in PD, one was a prospective cohort study[38] and the other was a retrospective cohort study.[78] Leinig et al[78] demonstrated that hypoalbuminemia was a significant independent predictor of mortality (HR, 2.3 [95% CI, 1.1-5.0]) after 24 months of follow-up. Churchill et al[38] described that for every 1-g/L increase in serum albumin level, there was a 2-year relative mortality risk of 0.94 (95% CI, 0.90-0.97).

MHD and PD patients. Both MHD and PD patients were evaluated in 2 prospective cohort studies.[51,79] Mathew et al[51] found that serum albumin concentration did not predict mortality and was not correlated with lean tissue index. de Mutsert et al[79] demonstrated that a 1-g/dL decrease in serum albumin level was associated with increased mortality risks of 47% in MHD patients and 38% in PD patients. After adjusting for systemic inflammation or for SGA score and nPCR, these mortality RRs were not statistically significant, indicating potential confounding effects of systemic inflammation.

In summary, 1 study showed that serum albumin concentration was a sensitive measure of nutritional status defined by 7-point SGA scores in MHD patients. Seven studies indicated that serum albumin level was associated with other common markers of nutritional status in MHD patients. The preponderance of evidence suggested that lower serum albumin concentration predicts mortality in both MHD and PD patients.

Inflammatory Markers. There were no studies examining the validity and/or reliability of using inflammatory markers to measure nutritional status. Thirteen studies examined correlations between inflammatory marker levels and other nutrition indices, including 7 studies in MHD patients, 1 study in PD patients, 2 studies in both MHD and PD patients, 1 study in patients with a kidney transplant, and 2 studies in CKD patients not receiving dialysis.

MHD patients. Among the MHD studies, all 7 were cross-sectional studies.[56-58,73,75,78,80] hsCRP levels were positively associated with FM[80] and negatively associated with LBM,[80] serum albumin level,[73,75,76,81] and serum prealbumin level.[75] hsCRP level was not associated with SGA score, nPCR, anthropometric indices, or BIA measurements.[80] Although CRP level was not associated with BMI in Vannini et al,[80] there was a negative correlation in Kadiri et al.[57] Kahraman et al[57] found that CRP levels were highest in obese and underweight participants compared with their counterparts. Beberashvili et al[56] found no relationship between proinflammatory cytokine level and BMI.

PD patients. de Araujo Antunes et al[82] conducted a cross-sectional study in PD patients. Compared with patients with CRP levels < 1 mg/dL, those with CRP levels ≥ 1 mg/dL had higher BMI (29.4 ± 6.1 vs 24.4 ± 4.5 kg/m^2; P = 0.009), percent standard body weight (124.5% ± 25.4% vs 106.8% ± 17.9%; P = 0.012), and percent BF

measured using skinfold-BIA (38.9% ± 6.3% vs 26.2% ± 12.6%; P < 0.001).[82]

MHD and PD patients. Isoyama et al[83] demonstrated that low handgrip strength (HGS), rather than low muscle mass measured with DXA, was associated with inflammatory markers, including hsCRP, IL-6, and tumor necrosis factor α (TNF-α). In addition, CRP levels were negatively associated with BIA phase angle.[10]

Posttransplant patients. Only 1 cross-sectional study was identified for kidney transplant recipients. In this study, malnutrition inflammation score (MIS) was positively correlated with IL-6 (r = 0.231; P < 0.001), TNF-α (r = 0.102; P < 0.001), and CRP levels (r = 0.094; P = 0.003).[84]

CKD patients not receiving dialysis. Both studies in CKD patients not receiving dialysis were cross-sectional in nature.[85,86] In a study by Wing et al,[86] hsCRP levels were higher in the highest BMI quartile, but results with other cytokines were mixed. In men with stages 2-4 CKD, CRP levels were negatively associated with testosterone distribution.[86]

In summary, many studies found correlations between higher inflammatory marker levels and suboptimal nutritional status; findings varied according to comparison measure. The relationship between BMI and inflammatory marker levels was unclear, and a U-shaped relationship may exist. MIS was associated with inflammation in kidney transplant patients.

Normalized Protein Catabolic Rate.

This evidence review included 7 studies that examined the relationships between nPCR and comparative measures in patients with CKD.

MHD patients. Of the 3 studies with MHD patients, 1 was a prospective cohort study[34] and the other 2 were cross-sectional studies.[73,75] In the study by de Roij van Zuijdewijn et al,[34] normalized protein nitrogen appearance (nPNA [nPCR]) was a significant predictor of all-cause mortality (Harrell C statistic = 0.56; P < 0.01), but the authors reported that MIS and serum albumin level had the best predictive value.[34] Jones et al[73] and Molfino et al[75] found that nPCR was a significant predictor of serum albumin and prealbumin levels.

PD patients. Both prospective and cross-sectional studies were conducted in PD patients. The former showed that nPCR was negatively correlated with anthropometric measures of body composition and positively correlated with composite nutritional index scores (r = 0.32; P < 0.001), but there was no relationship between nPCR and serum albumin level.[87] The latter study demonstrated that protein catabolic rate (PCR) was not correlated with LBM measured using the creatinine kinetic method or MF-BIA.[13]

MHD and PD patients. A cross-sectional study demonstrated that SGA score was associated with nPCR (r = −0.29; P = 0.027) in a group of MHD and PD patients.[88]

CKD patients not receiving dialysis. A cross-sectional study by Cigarran et al indicated that nPNA (nPCR) levels were progressively reduced across decreasing tertiles of testosterone distribution (P < 0.05) in male patients with stages 2-4 CKD.[85]

In summary, nPCR was a predictor of albumin concentration and mortality in MHD patients. In PD patients, the relationship between nPCR and body composition measurements was unclear, and the relationships with other measures of nutritional status varied.

Serum Prealbumin.

This evidence review included 4 studies that examined relationships between prealbumin concentration and comparative measures in patients with CKD.

MHD patients. Of the 3 studies in MHD, 1 was a prospective cohort study[9] and the other 2 were cross-sectional studies.[23,75] In the study by Molfino et al, prealbumin concentrations were associated with nPCR and IL-6 levels.[75] Prealbumin level increased by 20.8 mg/dL for each 1-g/kg increase in nPCR (P < 0.001), and there was a decrease in prealbumin concentration of 0.94 mg/dL for each increase in IL-6 concentration of 1 pg/mL. In the multiple regression model, prealbumin concentration increased by 1.8 mg/dL for each 1-kg increase in visceral adipose tissue (P = 0.015). Fiedler et al determined that prealbumin concentration was predictive of 3-year mortality and hospitalizations.[11] CRP level was correlated with prealbumin (r = −0.45; P < 0.001) concentration. Additionally, Aatif et al demonstrated that lean and fat tissue indices derived using bioimpedance spectroscopy were significantly correlated with prealbumin concentration.[23]

PD patients. In a cross-sectional study, Cigarran et al found that prealbumin concentration was progressively reduced across decreasing tertiles of testosterone in men with stages 2-4 CKD (P < 0.05).[85]

In summary, serum prealbumin concentration was associated with nPCR, inflammatory marker levels, lean and fat tissue indices, mortality, and hospitalizations in MHD patients. However, there were no studies examining the validity and/or reliability of this measure compared to a gold standard.

Special Discussions

The biochemical markers must be obtained predialysis for maintenance dialysis patients.

Implementation Considerations

- A number of considerations must be made on the unique situation of patients with CKD for appropriate screening and assessment of their nutritional status. Some of these include fluid status, which could alter body composition and biochemical markers; the presence of systemic inflammation, which could change serum concentrations of acute-phase proteins; the presence and extent of proteinuria, a major determinant of serum albumin concentrations; and level of residual kidney function, which could influence serum

concentrations of some biochemical markers, such as prealbumin, that are cleared by the kidneys.
- The guideline for serum albumin applies to all adult patients with CKD receiving maintenance dialysis.
- There are no potential risks or harms associated with application of the guideline for measuring/monitoring serum albumin levels in adult patients with CKD receiving maintenance dialysis.
- The gold-standard method for measuring serum albumin is nephelometry, which is not commonly used in practice due to cost and time. In patients with CKD 3-5D, the bromocresol green method should be used to estimate albumin level, whereas in patients without CKD or CKD 1-2, the bromocresol purple method is more accurate.

Future Research

General.

- Determine the incremental value of using 1 or more nutritional markers for better nutritional assessment and risk prediction.
- Develop risk prediction models using multiple nutritional markers.
- Determine the effects of established or promising nutritional interventions on nutritional markers and whether changes in nutritional marker levels correlate with outcomes as a marker of efficacy.

Inflammatory Markers.

- Determine whether systemic inflammatory markers may be useful in assessing nutritional status in adult patients with CKD stages 3-5, including those receiving maintenance dialysis and with kidney transplants.

Normalized PCR.

- Determine frequency with which nPCR should be measured/calculated.

Serum Prealbumin Concentration.

- Determine the frequency with which serum prealbumin concentration should be measured.

1.3 Statement on Handgrip Strength

1.3.1 In adults with CKD 1-5D, we suggest that handgrip strength may be used as an indicator of protein-energy status and functional status when baseline data (prior measures) are available for comparison (2B).

Rationale/Background

HGS is a simple and reliable method to evaluate muscle function in patients with CKD. In addition, it can be used as an indirect measure of nutritional status in maintenance dialysis patients and CKD patients not receiving dialysis.

Detailed Justification

Five studies examined relationships between HGS and comparative measures in patients with CKD, including 1 study with CKD patients not receiving dialysis,[89] 1 study with incident dialysis patients,[83] 2 studies with MHD patients,[90,91] and 1 study with PD patients.[8] Overall, HGS was a valid measure of nutritional status compared to MIS in MHD patients (sensitivity, 70%-87%; specificity, 43%-66%)[91] and was negatively associated with MIS in CKD patients not receiving dialysis ($r = 0.42$; $P < 0.001$),[89] but results may vary according to confounding variables. HGS was correlated with LBM assessed using other methods, but there was no correlation with other markers of body composition or nutritional status in PD patients.[8] In incident dialysis patients, HGS had higher correlations with nutritional status and inflammatory marker levels and was more predictive of mortality than muscle mass measured using DXA.[83]

Special Discussions

There is a cost associated with purchasing the equipment to measure HGS.

Implementation Considerations

- The guideline for HGS applies to all adult MHD patients, PD patients, and CKD patients not receiving dialysis.
- The potential risk or harm associated with the application of the guideline for HGS in MHD patients involves the side of the body assessed. The measurement should be obtained on the opposite side of the vascular access. In all other patients (ie, PD and predialysis), there are no potential risks or harms. Staff need to be properly trained on performing the measurement and interpreting the results.
- Many individuals with CKD also have type 2 diabetes, a consequence of which may include peripheral neuropathy. Practitioners should account for potential loss in HGS due to peripheral neuropathy in patients with type 2 diabetes when comparing measurements over time.[92]

Monitoring and Evaluation

Measuring HGS is simple; however, it is not routinely used in clinical practice.

Future Research

The work group recommends further research on HGS to determine:

- the timing of the measurement (eg, pre or post HD session or nondialysis day),
- the cutoff values that are correlated with other measures of muscle function used as surrogate measures of nutritional status,
- the best method to standardize the technique (eg, position of the arm, the evaluation period, and choice of arm side),
- the reliability and validity of the measurement in comparison to a gold standard used as the preferred

instrument to obtain the muscle function measurement,
- the association between HGS and other markers of physical function.

1.4 Statement on Methods to Assess Energy Requirements

Assessment of Resting Energy Expenditure

1.4.1 In adults with CKD 1-5D or posttransplantation, it is reasonable to use indirect calorimetry to measure resting energy expenditure when feasible and indicated, as it remains the gold standard for determining resting energy expenditure (*OPINION*).

Resting Energy Expenditure Equations

1.4.2 In adults with CKD 5D who are metabolically stable, we suggest that in the absence of indirect calorimetry, disease-specific predictive energy equations may be used to estimate resting energy expenditure as they include factors that may influence the metabolic rate in this population (2C).

Rationale/Background

Achieving energy balance is critical in persons diagnosed with CKD so that protein-energy malnutrition and PEW can be prevented or treated in susceptible persons. Thus, obtaining reliable data regarding dietary energy intake, as well as having a valid measure for energy expenditure, is paramount.

Indirect calorimetry remains as the best-practice measure for determining resting energy expenditure (REE) in adults diagnosed with CKD stages 1-5, including renal replacement therapy (RRT) patients (MHD or PD patients or transplant recipients). More research is needed to demonstrate whether handheld indirect calorimetric devices may be a suitable alternative in this population.

In the absence of indirect calorimetry, there are more than 200 predictive energy equations available that may be able to estimate REE in patients diagnosed with CKD. Several have been shown to either over- or underestimate REE in earlier stages of CKD, as well as patients treated with maintenance dialysis. There have been several cross-sectional studies that suggest that the energy requirements of patients with earlier stages of CKD may not be substantially different than for healthy adults, but the evidence is limited. Recent research has shown that predictive energy equations specifically designed for patients with CKD receiving maintenance dialysis have lower bias and greater precision.

Even the best predictive models designed for CKD do not account for the contribution of physical activity or structured exercise. Reliance on current estimates for physical activity may not determine total energy requirements accurately in this population.

Detailed Justification

There were 6 studies that tested REE equations in patients with CKD and compared them to a reference standard of indirect calorimetry.[93-98] Two of the 6 studies used indirect calorimetry data to derive a disease-specific equation.[93,98] The Harris-Benedict equation overestimated REE in 4 studies across the spectrum of CKD; for example, Dias Rodrigues et al[94] (MHD), Kamimura et al[95] (nondialyzed, MHD, and PD), Lee et al[96] (CAPD), and Neyra et al[97] (chronic renal failure, MHD, and PD), but the Harris-Benedict equation underestimated REE in MHD participants in Vilar et al[98] (MHD). Similarly, the Schofield equation overestimated REE in Dias Rodrigues et al[94] (MHD) and Kamimura et al[95] (nondialyzed, MHD, and PD), but underestimated REE in Vilar et al[98] (MHD). Byham-Gray et al[93] demonstrated that the Maintenance Hemodialysis Equation (MHDE) more accurately predicted REE than the Mifflin-St. Joer equation. Vilar et al[98] also found that their created equation for REE was the best predictor of REE when compared with traditional predictive energy equations. Generally, agreement between equations and methods was low to moderate.

Special Discussions

Among patients with stage 5 CKD receiving MHD or PD, there are several factors that may influence energy expenditure beyond the traditional determinants (age, sex, and FFM), such as hyperparathyroidism, hyperglycemia, and chronic inflammation, that should be considered in the overall energy prescription. Energy needs will be variable depending on the health status of the patient (eg, acutely vs chronically ill) and overall health goals (eg, weight maintenance, repletion, or loss). Energy needs may be different depending on the stage of CKD and its respective treatment (dialysis vs transplant). In the context of these recommendations, "metabolically stable" indicates the absence of any active inflammatory or infectious diseases, no hospitalization within 2 weeks, absence of poorly controlled diabetes and consumptive diseases such as cancer, absence of antibiotics or immunosuppressive medications, and absence of significant short-term loss of body weight.

Implementation Considerations

- The registered dietitian nutritionist (RDN) should consider a number of factors when determining the energy requirements for adults diagnosed with CKD, and these include the patient's overall health status, CKD diagnosis and associated therapies, level of physical activity, age, sex, weight status, disease-specific determinants, metabolic stressors, and treatment goals.
- Disease-specific equations should be used when estimating energy requirements for the different patient populations, such as those treated by HD or PD (ie, MHDE).
- Thermal effects of food may be decreased in individuals who are nondialyzed compared with dialyzed due to lower protein intake.

Monitoring and Evaluation

Patients should be monitored routinely to assess whether energy requirements are being met satisfactorily. Changes in nutritional status should be treated and the energy prescription modified accordingly.

Future Research

- Determine the energy requirements across the spectrum of kidney disease and evaluate for the contribution of exercise and physical activity; that is, indexing total energy expenditure in CKD.
- Uncover the key determinants of energy expenditure in CKD, enabling practitioners to account for them in the energy prescription.
- Develop and test predictive energy equations in CKD that can more accurately or precisely determine the individual's unique energy requirements.

1.5 Statements on Composite Nutritional Indices

7-Point Subjective Global Assessment (SGA)

1.5.1 In adults with CKD 5D, we recommend the use of the 7-point Subjective Global Assessment as a valid and reliable tool for assessing nutritional status (1B).

Malnutrition Inflammation Score (MIS)

1.5.2 In adults with CKD on MHD or posttransplantation, Malnutrition Inflammation Score may be used to assess nutritional status (2C).

Rationale/Background

Assessment of nutritional status in adults diagnosed with CKD stages 1-5D must occur on a routine basis to prevent and/or treat malnutrition and wasting. The Nutrition Care Process begins with a nutrition screening, whereby key nutritional indicators may trigger further assessment and intervention. There are several nutrition screening mechanisms in clinical practice, but few are specific to CKD and there are limited data for their validity and reliability. Most of the existing tools focus on identification of malnutrition risk; only 1 currently screens for PEW. Regardless of the mechanism used, the nutritional assessment conducted subsequent to the screening should be comprehensive and include the routine monitoring of nutrition care outcomes. The main components of the comprehensive nutrition assessment comprise anthropometric measurements, biomarkers, clinical symptoms exhibited on physical examination, dietary intake assessment, and medical/psychosocial history. The availability of composite nutritional indices (eg, the SGA or MIS) that collect such data and therefore assist the clinician in deciding about the individual's nutritional status and eventual plan of care. Therefore, these nutritional indices are specific to the unique nutritional requirements of this patient population.

Detailed Justification

Composite Nutritional Indices: Screening Tools. ***Geriatric Nutrition Risk Index.*** Three studies reported on the use of the Geriatric Nutrition Risk Index (GNRI) to assess nutritional status, including 2 validity/reliability studies[99,100] and 1 prediction study in MHD patients.[34] In 1 study, GNRI had the greatest area under the curve (using MIS as a reference) of the nutrition screening tools.[100] GNRI showed a significantly negative correlation with the MIS ($r = -0.67$; $P < 0.0001$), and the most accurate GNRI cutoff to identify a malnourished patient according to the MIS was 91.2. The GNRI's sensitivity, specificity, and accuracy of a score of 91.2 in predicting malnutrition according to the MIS were 73%, 82%, and 79%, respectively. Another study reported that GNRI had a high interobserver agreement score ($\kappa = 0.98$) and high intraobserver reproducibility ($\kappa = 0.82$).[99] In another study, GNRI was a significant predictor for mortality at 2.97 years ($P < 0.001$) but had lower predictive value for all-cause mortality compared with MIS and albumin levels.[34]

Malnutrition Universal Screening Tool/Malnutrition Screening Tool. Two validity/reliability studies reported on the use of Malnutrition Universal Screening Tool (MUST) and Malnutrition Screening Tool (MST) to assess nutritional status in MHD patients.[100,101] A study by Lawson et al[101] reported on the validity and reliability of both MUST and MST in MHD patients. The sensitivity of both the MUST and MST was low (53.8% for MUST; 48.7% for MST), indicating that they are not particularly sensitive at identifying individuals with malnutrition in this group, compared to SGA. Both tools have high specificity (MUST, 78.3%; MST, 85.5%), so they are good at excluding individuals who are not malnourished. Reliability assessed using κ was 0.58 for MUST (95% CI, 0.20-0.80) and 0.33 for MST (95% CI, 20.03-0.54). Both tools had a negative predictive value (NPV) of 60%, and positive predictive value (PPV) for MUST was 73.7% and for MST was 78.7%. Though these tools are not sensitive enough to identify all malnourished renal in-patients, they are still fairly reliable and related to other nutrition status markers. In Yamada et al,[100] the authors compared results from various malnutrition assessment tools to the reference standard of MIS. MUST and MST scores were both significantly associated with MIS ($P < 0.0001$ for each). The receiver operation characteristic curves of the MUST and MST compared to MIS were the smallest of the tools measured, and sensitivity, specificity, and accuracy to detect hypoalbuminemia were among the lowest of all tools considered, indicating that these may not be the best tools to discriminate nutritional risk in patients on MHD.

Mini Nutrition Assessment. Four studies reported on the use of Mini Nutrition Assessment (MNA) to assess nutritional status in MHD patients: 3 were validity/reliability studies[100,102,103] and 1 was a correlational study.[104] Afsar et al[102] reported on the reliability of the MNA tool compared to the SGA 3-point scale. The reliability

coefficient (alpha) for MNA was 0.93 (good degree of reproducibility). MNA might underestimate the nutritional status of patients receiving MHD who are not in an inflammatory state. Hence, MNA may not be as reliable as SGA in detecting PEW in the MHD population. Erdogan et al[104] compared MNA with BIA and reported a significant correlation between MNA score and single frequency-BIA ($r = 0.2$; $P = 0.045$), muscle mass ($r = 0.382$; $P < 0.001$), and visceral fat ratio ($r = 0.270$; $P = 0.007$). The authors concluded that BIA is not as sensitive as MNA to detect early effects of secondary causes for malnutrition. Santin et al[103] (2016) compared SGA (7-point), MIS, and MNA-Short Form (MNA-SF) with HGS, albumin level, CRP level, and skinfolds. SGA and MNA-SF had fair agreement ($\kappa = 0.24$; $P < 0.001$). The worst agreement was found between MIS and MNA-SF ($\kappa = 0.14$, none to slight; $P < 0.004$). Again, both SGA and MIS had good concurrent and predictive validity for the CKD population, whereas MNA-SF validity results were more comparable to elderly individuals without CKD. Yamada et al[100] compared MNA with other nutritional tools and reported that MNA had lower area under curve (0.73) than GNRI and Nutritional Risk Score but higher than MUST and MST.

Nutrition Impact Symptoms. One validity study reported on the use of the Nutrition Impact Symptoms (NIS) score for identifying those at risk for malnutrition in patients receiving HD and concluded that NIS score is a useful nutrition screening tool for identifying who is at risk for malnutrition.[105] NIS score > 2 had the strongest predictive value for mortality and for predicting poor nutritional outcomes, behind the rating of malnourished by SGA. Concurrent validity indicated similar agreement between each of the malnutrition risk tools (patient-generated SGA, an abbreviated patient-generated SGA, and NIS). Serum albumin level was negatively correlated with NIS (Spearman $\rho = -0.161$; $P = 0.018$).

Nutrition Screening Tool. One validity study reported on the use of Nutrition Screening Tool (NST) to assess nutritional status in PD patients. In this study, NST had a sensitivity of 0.84 (range, 0.74-0.94; $P < 0.05$) and specificity of 0.9 (range, 0.82-0.99; $P < 0.05$), which is clinically acceptable.[106]

Renal NST. In another study by Xia et al[107] in PD patients, the Renal NST (R-NST) was compared to the SGA 7-point scale. The authors determined that the R-NST when compared to the SGA 7-point scale is valid to detect risk for malnutrition (sensitivity, 97.3% [95% CI, 90.7%-99.7%]; specificity, 74.4% [95% CI, 57.9-87.0]; PPV, 88.0% [95% CI, 79.0%-94.1%], and NPV, 93.6% [95% CI, 78.6%-99.2%]). These results indicate that R-NST is a good tool for identifying renal in-patients at risk for undernutrition.

PEW score. Two predictive studies reported on the use of PEW score to assess nutritional status. Leinig et al[78] identified that SGA and albumin level were significant predictors of mortality, but BMI, MAMC, and PEW score did not predict mortality at 24 months in PD patients. However, Moreau-Gaudry et al,[108] in a study conducted in patients receiving MHD, recorded that PEW score predicts survival. Each 1-unit decrease in score was related to a 5% to 7% reduction in survival ($P < 0.01$). This score can be helpful in identifying subgroups of patients with a high mortality rate and recommend nutrition support.

Composite Nutritional Indices: Assessment Tools. Subjective Global Assessment. Eleven studies examined the relationship between the 7-point SGA score and comparative measures, including 3 validity/reliability studies[59,60,103] and 6 additional prediction and/or correlation studies.[34,74,80,109-111]

Three studies examined the validity and/or reliability of the 7-point SGA score in MHD patients. In Visser et al,[60] the 7-point SGA score demonstrated fair interobserver reliability (intraclass correlation, 0.72) and good intraobserver reliability (intraclass correlation, 0.88) in MHD patients. In Santin et al,[103] the 7-point SGA score had good agreement with MIS ($\kappa = 0.43$; $P < 0.001$) and MNA-SF ($\kappa = 0.24$; $P < 0.001$). In a study by Steiber et al,[59] SGA score had fair inter-rater reliability ($\kappa = 0.5$; Spearman $\rho = 0.7$) and substantial intrarater reliability ($\kappa = 0.7$; Spearman $\rho = 0.8$; $P < 0.001$).

Three cohort studies examined whether the 7-point SGA score was predictive of hard outcomes in patients receiving MHD. In Perez Vogt et al,[110] SGA was a significant predictor of mortality at 2 years after adjustments for significant confounders. In a study by de Roij van Zuijdewijn et al,[34] SGA was a significant predictor ($P < 0.001$) for mortality at 2.97 years, but had lower predictive value for all-cause mortality compared with MIS and albumin levels. de Mutsert et al[79] reported that the hazard of mortality increased with SGA in a dose-dependent manner among patients receiving dialysis. Compared with normal nutritional status, persons who had an SGA score of 4 to 5 had an increased HR at 7-year mortality of 1.6 (95% CI, 1.3-1.9) and SGA score of 1 to 3 had an HR of 2.1 (95% CI, 1.5-2.8) at 7-year mortality. The strength of association increased in time-dependent models. Finally, in a study with PD patients, every 1-unit increase in the 7-point SGA score adapted for patients with ESKD/CAPD patients, there was 25% decreased 2-year mortality risk ($P < 0.05$).[38]

Six studies examined correlations between the 7-point SGA score and other measures of nutritional status. In Visser et al,[60] there was a strong correlation between the 7-point SGA score and BMI ($r = 0.79$), percent fat ($r = 0.77$), and midarm circumference ($r = 0.71$; all $P < 0.001$) in MHD patients. In a study by Steiber et al,[59] there were statistically significant differences in mean BMI and serum albumin levels according to SGA score in MHD patients ($P < 0.05$). Tapiawala et al[111] assessed the 7-point SGA score in patients with CKD or ESKD, including those receiving all types of dialysis. SGA scores were not correlated with dietary protein and energy intake or serum albumin levels, but anthropometric measures correlated with SGA scores (skinfolds, $r = 0.2$; midarm

circumference, r = 0.5; and MAMC, r = 0.5). The authors concluded that the 7-point SGA is a reliable method of assessing nutritional status. Malgorzewicz et al[74] compared near-infrared measurements and albumin levels with the SGA 7-point score in MHD patients. LBM measured using near-infrared was significantly decreased in malnourished patients ($P < 0.05$) and there was a correlation between SGA score and LBM ($r = 0.5$; $P < 0.05$), as well as SGA score and albumin concentration ($r = 0.7$; $P < 0.05$). In Vannini et al,[80] SGA scores were associated with traditional nutritional markers, reinforcing the validity for use among patients receiving MHD. SGA score was not associated with CRP level. Jones et al[109] examined the relationship between 3-point SGA score and a composite nutritional score that included SGA (3 point and 7 point), BMI, percent of reference weight, skinfold and MAMC measurements, and albumin levels in patients treated by MHD. Compared with the composite score, the SGA score misclassified a "large number of subjects" and score was not associated with many nutrition parameters such as dietary intake, BMI, or albumin levels.

In one study,[112] the authors used a version of the SGA that was adapted for patients receiving MHD, and in 2 studies,[78,113] the version of the SGA tool used was unclear. Garagarza et al[112] compared bioimpedance spectroscopy measurements with SGA scores from a version modified for MHD that included a 5-point score comprising weight changes, eating habits, gastrointestinal symptoms, functional activity, and comorbid conditions. PEW measured using bioimpedance spectroscopy extracellular weight to body weight ratio was positively associated with CRP level ($P = 0.009$) and SGA score ($P = 0.03$). Leinig et al[78] examined the relationship between SGA score and mortality risk at 24 months in PD patients, but the version of the SGA used was unclear. SGA score was a significant predictor of mortality in PD patients. Passadakis et al[113] compared BIA measurements with SGA scores in CAPD patients, but the version of SGA used was uncertain. SGA score was significantly correlated with impedance index ($r = 0.48$; $P = 0.0038$) and phase angle ($r = 0.43$; $P = 0.0048$).

Malnutrition Inflammation Score. Nine studies reported on the use of MIS to assess nutritional status, including 2 validity/reliability studies,[99,103] 4 prediction studies,[11,34,110] and 3 correlation studies.[84,89,114]

One study by Beberrashavili et al[99] reported that MIS had moderate interobserver agreement ($\kappa = 0.62$) and interobserver reproducibility ($\kappa = 0.77$) and is a valid tool for longitudinal assessment of nutritional status of patients receiving MHD. Another study by Santin et al[103] indicated that MIS had good agreement with SGA score ($\kappa = 0.43$; $P < 0.001$) and worse agreement with MNA-SF ($\kappa = 0.14$; $P < 0.004$). MIS also had good concurrent and predictive validity for the MHD population.

Four studies reported on the use of MIS as a predictor of mortality.[11,34,103,110] Three of the studies reported that in patients receiving MHD, MIS is a significant predictor of mortality.[11,34,110] In 1 study, MIS was a significant predictor for mortality at 2.97 years ($P < 0.001$) and the best predictive tool for all-cause mortality and secondary end points such as cardiovascular events in patients receiving MHD.[34] Another study by Fiedler et al[11] also reported that MIS was predictive of both mortality and hospitalizations in patients treated by MHD, with survival analysis indicating that MIS was one of the best predictors of mortality (HR, 6.25 [95% CI, 2.82-13.87]; $P < 0.001$). Perez Vogt et al[110] also indicated that MIS was a significant predictor for 2-year mortality in MHD patients. Finally, in Santin et al,[103] although mild MIS did not predict mortality, severe MIS was a significant predictor of mortality in adjusted analysis (HR, 5.13 [95% CI, 1.19-13.7]).

Three studies reported on the use of MIS and correlation with other tools. Amparo et al[89] indicated that there was a significant negative correlation between HGS and MIS ($r = -0.42$; $P < 0.001$) in CKD patients not receiving dialysis. Hou et al[114] indicated that MIS was strongly correlated with modified quantitative SGA score ($r = 0.924$) and inversely correlated with BIA ($r = -0.213$) in MHD patients. Molnar et al[84] reported that MIS showed significant negative correlations with abdominal circumference ($r = -0.144$; $P < 0.001$) and prealbumin level ($r = -0.165$; $P < 0.001$), whereas significant positive correlation was seen with IL-6 ($r = 0.231$; $P < 0.001$), TNF-α ($r = 0.102$; $P < 0.001$), and CRP levels ($r = 0.094$; $P = 0.003$) in kidney transplant recipients. All studies show that MIS is a useful tool to assess nutritional status in patients with CKD.

Other Composite Nutritional Indices. ***Nutrition Risk Score.*** A prediction study reported that Nutrition Risk Score was a good predictor of mortality (HR, 4.24 [95% CI, 1.92-9.38]; $P < 0.001$) in patients receiving MHD and was superior when compared with laboratory markers and BIA in predicting mortality.[11]

Protein Nutrition Index. A reliability study investigated Protein Nutrition Index (PNI) as a predictor of survival in PD patients. Compared with the reference standard (nPNA [nPCR] $\leq$ 0.91 as malnutrition), the sensitivity, specificity, PPV, and NPV of PNI were 0.4, 0.978, 0.901, and 0.783, respectively.[115] This study indicated that PNI is a good predictor of mortality (even after adjusting for age and comorbid conditions). An increase in PNI score by 1 led to a 16% decrease in mortality risk.

Composite Score of Protein Energy Nutrition Status. de Roij van Zuijdewijn et al[34] studied 8 nutrition assessment tools used to predict all-cause mortality. The Composite Score of Protein Energy Nutrition Status (cPENS) had Harrell C statistics of 0.63 (95% CI, 0.61-0.66) for predicting mortality. However, the study indicated that it had inadequate discrimination and calibration or a lower predictive value for mortality.

Other measures. Blumberg Benyamini et al[116] compared the integrative score with the SGA 7-point scale in MHD patients. Integrative clinical nutrition dialysis

score is based on biochemical measures of albumin, creatinine, urea, cholesterol, CRP, dialysis adequacy, and weight change. With every unit increase in integrative score, the odds of death were significantly decreased (HR, 0.929; 95% CI, 0.885-0.974; $P < 0.002$). SGA and integrative scores were significantly correlated ($n = 69$; $r = 0.853$; $P < 0.01$), and according to the author, this is a useful prognostic tool to detect early nutrition deterioration.

A prediction study investigated which nutritional composed scoring system best predicts all-cause mortality in MHD patients.[110] This study indicated that SGA score and MIS are better predictors of all-cause mortality at 15.5 months in this study and ISRNM criteria were not able to predict mortality in this sample.

One correlation study investigated the relationship between body adiposity index, BIA, anthropometrics, and DXA.[117] The correlation coefficient was higher between DXA versus anthropometric measurements ($r = 0.76$) and body adiposity index ($r = 0.61$) when compared with BIA ($r = 0.57$) in the adjusted analysis ($P < 0.0001$). Results suggest that BIA estimates BF with limited accuracy in CKD patients not receiving dialysis compared with DXA.

Special Discussions. The large body of literature on nutritional assessment and composite nutritional indices has been completed in CKD 5D. Although some of these tools may be relevant and can be translated to earlier stages (1-4) of CKD, there is a need for the practitioner to conduct a comprehensive nutritional assessment comprising the main domains of the Nutrition Care Process.

PEW, a term supported by the ISRNM, describes the complexity of nutritional and metabolic alterations that exist in CKD. Although PEW definition is useful to identify patients with overt nutritional abnormalities, its sensitivity is low given its strict criteria. Although comprehensive nutritional indices have been validated for the recognition of a poor nutritional status (eg, malnutrition), it is unclear how well some of these same tools may be applied in the early identification of PEW.

Implementation Considerations.

- Routine nutrition screening of adults diagnosed with CKD stages 1-5D should occur to allow for the identification and further assessment and treatment of nutritional concerns.
- A comprehensive nutrition assessment, using a composite nutritional index, should be conducted at the initial visit and completed whenever there is suspicion of any change in health status or as per institutional or regulatory policies.

Monitoring and Evaluation. The comprehensive nutrition assessment will guide the nutrition intervention prescribed. The clinician should monitor key nutrition care outcomes, such as dietary nutrient intake, body composition, and serum biomarker levels, based on the treatment plan prescribed and re-assess and change the plan accordingly to achieve the goals established.

Future Research.

- More research is needed in trying to standardize the methods for nutrition screening so that early identification and referral can result.
- Additional investigations should focus on what composite nutritional indices, if any, can be used reliably in earlier stages of CKD.
- More research is needed to examine which composite nutritional indices are appropriate for nutrition screening or assessment in people with CKD who are nondialyzed.
- More research is needed examining the validity and reliability of the GNRI and SGA tools in elderly people with CKD.
- Further evaluation of screening and assessment tools for PEW are necessary, especially in terms of response to nutritional interventions.

1.6 Statements on Tools/Methods Used to Assess Protein and Calorie Intake

Considerations When Assessing Dietary Intake

1.6.1 In adults with CKD 3-5D or posttransplantation, it is reasonable to assess factors beyond dietary intake (eg, medication use, knowledge, beliefs, attitudes, behavior, access to food, depression, cognitive function) to effectively plan nutrition interventions (*OPINION*).

3-Day Food Records to Assess Dietary Intake

1.6.2 In adults with CKD 3-5D, we suggest the use of a 3-day food record, conducted during both dialysis and nondialysis treatment days (when applicable), as a preferred method to assess dietary intake (*2C*).

Alternative Methods of Assessing Dietary Intake

1.6.3 In adults with CKD 3-5 (*OPINION*) or CKD 5D (*2D*), 24-hour food recalls, food frequency questionnaires, and nPCR may be considered as alternative methods of assessing dietary energy and protein intake (*2D*).

Rationale/Background

Poor nutritional intake and obesity are prevalent among patients diagnosed with CKD and therefore it is important to monitor dietary intake that provides information on total energy and macro- and micronutrients, as well as overall food/liquid servings and eating patterns. In this context, it is important to identify reliable methods for estimating dietary intake in diverse care settings. Under- and overreporting of intake are a concern in this population.

Detailed Justification

A total of 6 studies reported on the use of methods to assess protein and energy intake in individuals with CKD.[118-124]

Food Records/Diary. Based on the findings of 4 studies, food records/diary for assessing dietary intake of protein and calories were reliable and correlated with reference standards. Food records can provide accurate information if patients are instructed and trained and food intake is recorded for at least 7 days.[120-122] Two studies used food diary/3-day food records to determine underreporting of energy intake in nondialyzed and PD patients.[118,119] Underreporting was noticed in 72.5% of CKD patients not receiving dialysis and 52.5% of PD patients. Both studies indicated that underreporting was more pronounced in overweight patients. Shapiro et al compared energy intake measured using 3-day food record (dietitian interview–assisted) and REE measured using indirect calorimetry. Energy intake reported by interview-assisted food records was lower than measured REE.[124]

Food Frequency Questionnaires. Delgado et al conducted a validation study comparing Block Brief 2000 food frequency questionnaire against 3-day food diary records[125] and found that the Block Brief 2000 food frequency questionnaire underestimated energy and macronutrient intake in patients receiving HD. However, simple calibration equations can be used to obtain intake similar to 3-day food diary records.

Protein Catabolic Rate. Three studies examined the use of PCR to assess protein intake in patients with CKD[123,126,127] and found significant correlations with reference standards for measuring dietary intake (eg, food records). However, PCR overestimated protein intake when daily protein intake was <1 g/kg, and when daily protein intake was >1 g/kg, it was underestimated using PCR. In PD patients, protein nitrogen appearance (PNA) (PCR) normalized to desirable body weight was correlated better with blood urea nitrogen level ($r = 0.702$) and Kt/V ($r = 0.348$).[127]

Special Discussions

Despite the food record/diary being the most reliable and valid measure of dietary intake among patients diagnosed with CKD, it relies on accurate reporting inclusive of portion sizes. The food record may be seen as cumbersome to complete for several days and is limited to individuals who are able to read and record intake reliably. With the generation of smartphone applications, there has been a burgeoning interest in recording dietary intake using technology, with limited success in its adoption among certain subgroups (eg, the elderly). In CKD patients not receiving dialysis, 24-hour urine collection to measure urinary urea nitrogen, sodium, and potassium is more reliable to yield estimates of dietary protein intake, sodium, and potassium.

Dietary intake methods may need to be simplified, modified, or combined with a few strategies to obtain reliable dietary intake data, with emphasis on them being culturally appropriate.

Implementation Considerations

- Routine dietary assessment among adults diagnosed with CKD stages 1-5D should occur to allow for identification and treatment of nutritional concerns related to nutrient intake.
- Assessing dietary intake using multiple complementary methods, such as food frequency questionnaire and 24-hour urine collection to measure urinary urea nitrogen, sodium, and potassium, may be useful to confirm the accuracy of dietary intake estimates.
- Dietary assessment should be conducted at the initial visit and completed whenever there is a change in health status or as per institutional or regulatory policies.

Monitoring and Evaluation

A thorough assessment of dietary intake will guide the nutrition intervention prescribed. The clinician should monitor key nutrition care outcomes based on the treatment plan and re-assess and change the plan accordingly to achieve the goals established.

Future Research

- Identify the best methods for dietary assessment among adults diagnosed with CKD stages 1-5D and those receiving a kidney transplant.
- Focus on how to better determine instances of under- and overreporting of dietary intake in this population.
- Further development and testing of dietary assessment tools that integrate technology to patient care and assist individuals with limited literacy and vision and are culturally appropriate.

Guideline 2: Medical Nutrition Therapy

2.1 Statements on Medical Nutrition Therapy (MNT)

MNT to Improve Outcomes

2.1.1 In adults with CKD 1-5D, we recommend that a registered dietitian nutritionist (RDN), or an international equivalent, in close collaboration with a physician, or other provider (nurse practitioner or physician assistant), provide MNT. Goals are to optimize nutritional status, and to minimize risks imposed by comorbid conditions and alterations in metabolism on the progression of kidney disease (1C) and on adverse clinical outcomes (OPINION).

MNT Content

2.1.2 In adults with CKD 1-5D or posttransplantation, it is reasonable to prescribe MNT that is tailored to the individuals' needs, nutritional status, and comorbid conditions (*OPINION*).

MNT Monitoring and Evaluation

2.1.3 In adults with CKD 3-5D or posttransplantation, it is reasonable for the registered dietitian nutritionist (RDN) or an international equivalent to monitor and evaluate appetite, dietary intake, body weight changes, biochemical data, anthropometric measurements, and nutrition-focused physical findings to assess the effectiveness of MNT (*OPINION*).

Rationale/Background

Individualized management of nutritional intake is a crucial aspect of care for individuals diagnosed with any stage of CKD, including those receiving maintenance dialysis and those who have received a kidney transplant. These patients are vulnerable for nutritional abnormalities, which are associated with higher risk for morbidity, mortality, and length of hospital stay. Nutritional needs change throughout the disease course, from the earlier stages of CKD to the posttransplant period. The metabolic abnormalities and comorbid diseases that often accompany CKD further emphasize the need for specialized nutrition health care. Therefore, it is essential that such individuals receive tailored nutrition assessment and counseling in the form of MNT. MNT is a collaborative approach that typically requires the medical expertise and prescription of MNT by a physician or other provider (nurse practitioner or physician assistant) and implementation by an RDN or international equivalent). These roles are not mutually exclusive and involve ongoing team-patient analysis and discussion. Participating providers and RDNs are recommended to have received specialized education and training in nutrition and CKD in accordance with the requirements set forth by local regulations.

Medical Nutrition Therapy. In 2002, the American Dietetic Association published a nutrition care model that provided evidence-based high-quality standardized care for patients with CKD, nondialyzed and posttransplant.[128] The document was later revised in 2010, which reported that nutrition care provided by a registered dietician up to twice monthly over a 1-year period can have a valuable role in the medical care of patients with CKD by:

- providing nutrition assessment and interventions to delay kidney disease progression in addition to comorbid conditions such as diabetes mellitus, cardiovascular disease (CVD), dyslipidemia, gout, and nephrolithiasis;
- using behavioral methods to individualize the approach and minimize barriers to individualized goals;
- providing individualized meal plans and follow-up on adherence and successful implementation. Interventions include but are not limited to weight management and maintenance/repletion of patient nutritional status;
- addressing inflammation, obtaining a euvolemic state, contributing to correction of electrolyte abnormalities, assisting in anemia management, and managing bone disease through nutrition assessment and dietary interventions including individualized meal plans;
- assisting in identifying medication errors and need for adjustment in collaboration with nephrology provider (medical doctor, nurse practitioner, or physician assistant);
- providing and updating nutrition therapy as new knowledge emerges.

Detailed Justification

MNT requires nutrition screening and assessment of nutritional status to provide individualized treatment for specific disease states. Patients with CKD are on a dynamic nutrition trajectory according to their disease stage and MNT is needed at each stage of CKD. Metabolic abnormalities and acid-base and fluid and electrolyte balances often change as CKD progresses. For example, a patient can be hypokalemic during stage 2 CKD, requiring potassium supplementation and a high-potassium diet. Months or years later, this same patient during stage 4 CKD might become hyperkalemic, requiring medication adjustment and dietary potassium restriction rather than supplementation. Should this same patient receive a kidney transplant, he or she might stabilize potassium balance and have no need for potassium supplementation or dietary potassium restriction. This type of complicated patient with CKD requires specialized nutrition health care and ongoing monitoring by a nephrology RDN.

Sixteen RCTs examining the effect of MNT on nutrition-related outcomes were identified in the systematic review (Table S7). However, these studies were heterogeneous in terms of the populations (5 studies included patients who were nondialyzed, 9 included patients receiving MHD, 1 included patients receiving CAPD, and 1 included patients posttransplant), interventions (eg, RDNs used various methods of nutritional counseling among the studies), and outcomes (ex: protein intake, serum phosphate level, serum albumin level, BMI, and dyslipidemia). Intervention durations ranged from 4 weeks to 2 years.

CKD Progression. In 4 of the studies ranging from 4 weeks to 4 months, the authors found no effect of MNT on CKD progression in CKD patients not receiving dialysis compared with participants receiving standard nutrition education for CKD, which may or may not have also been provided by an RDN. Interventions ranged from 1 in-person contact plus telephone contacts with the RDN for 12 weeks (stage 4 CKD)[129] to a multidisciplinary intervention including 4 weeks of weekly counseling with an RDN (stages 3-4 CKD)[130] to two 2-hour cooking classes and a

shopping tour (stages 2-4 CKD)[131] to nutrition counseling plus nutrition education for 4 months (stages 3-5 CKD).[132]

SGA Scores. Three RCTs, including 2 study populations, reported on the effect of MNT on SGA scores. Campbell et al demonstrated that malnourished patients with stage 4 CKD had SGA scores that significantly improved in the intervention group compared with the control group, for whom malnutrition by SGA score increased.[129] The intervention consisted of nutritional counseling from an RDN for 12 weeks, with an emphasis on self-management techniques, face-to-face consultation at baseline, and telephone consultation every 2 weeks for the first month and then monthly for the next 2 months. In Leon et al,[133] MHD participants received monthly consultation with an RDN for 12 months. RDNs assigned for intervention were trained to determine potential barriers to achieving normal albumin levels for each patient, to attempt to overcome the barriers, and to monitor for improvements in barriers. There was no difference in the percentage of participants who had improved or decreased SGA scores between groups.

Body Mass Index. Four RCTs examined the effect of MNT interventions on BMI, including 2 studies with CKD patients not receiving dialysis (stages 3-5),[130,132] 1 study with MHD participants,[133] and 1 with posttransplant patients.[134] Howden et al[130] examined the effect of a 12-month multidisciplinary lifestyle intervention on BMI in patients with stages 3-4 CKD. The intervention group received 4 weeks of group behavioral and lifestyle modification sessions provided by an RDN and a psychologist. Mean BMI significantly decreased in the intervention group compared with the standard-care group ($P < 0.01$). Paes-Barreto et al[132] examined the effect of MNT on BMI in participants with stages 3-5 CKD who received individualized dietary counseling monthly for 4 months. In addition to the routine counseling, the intervention group received intensive counseling, which included nutrition education materials emphasizing a low-protein and low-sodium diet. There was a significantly greater decrease in BMI in the intervention group compared with the standard-care group ($P < 0.01$). In Leon et al,[133] MHD participants received monthly consultation by an RDN to determine and address barriers to reaching normal serum albumin levels for 12 months. There was no effect on BMI, though this was not the objective of the intervention. Finally, in Orazio et al,[134] intervention participants received RDN counseling using a Mediterranean-style diet, which consisted of a low glycemic index and moderate energy deficit. MNT counseling was based on the Stages of Change Model.[134] There was no difference in change in BMI between groups after 2 years.

In a meta-analysis of 2 studies, participants who received MNT had a greater mean decrease in BMI compare with the control groups (−0.89 [95% CI, 1.52 to −0.25] kg/m^2].[132,134] Results regarding the effect of MNT on arm and waist circumference, as well as body composition, were limited and unclear.

Phosphate Levels. Eight studies examined the effect of MNT on phosphorus/phosphate levels in MHD patients for durations ranging from 8 weeks to 6 months. In Ashurst Ide and Dobbie[135] and Lou et al,[136] phosphorus-focused education, provided once and monthly for 6 months, respectively, significantly improved (decreased) mean serum phosphate levels. In Karavetian et al,[137] weekly education nutrition counseling for 2 months also decreased phosphate levels ($P < 0.01$). However, Morey et al[138] also used phosphorus-focused RDN counseling and education, monthly for 6 months, and found no difference in change in phosphate levels between groups at 6 months.

Participants receiving a multidisciplinary nutrition education program did not have any changes in phosphate levels compared with participants receiving an oral nutrition supplement (ONS).[139] In Reese et al,[140] participants who were coached by a trained RDN about dietary and medication adherence (≥3 times a week) for 10 weeks were compared with patients receiving a financial incentive or usual care. There were no between-group differences in change in phosphate levels. There was no effect of MNT in the form of dietary counseling in CAPD patients[141] or in the form of RDN counseling plus low-protein and low-sodium diet education in CKD patients not receiving dialysis[132] on phosphate levels, but the primary objectives of these studies were to improve energy, protein, and sodium intake.

Meta-analysis of 4 studies with comparable data revealed that mean phosphorus/phosphate levels were decreased (−0.715 [95% CI, −1.395 to −0.034] mg/dL); however, heterogeneity is high ($I^2 = 67.71\%$; $P = 0.015$). Thus, there was evidence that MNT decreased phosphorus/phosphate levels in MHD patients,[138,139,142] but the effect on phosphorus/phosphate levels, as well as the effect on calcium or potassium levels, in CKD patients not receiving dialysis[132] was unclear.

Lipid Profile. Three RCTs examined the effect of MNT from an RDN on lipid profile.[123,124,132] In Hernandez Morante et al,[139] MHD participants in the intervention group received a 12-session multidisciplinary Nutrition Education Program over 4 months, including group and individual therapy, while control participants received an ONS 3 days per week. Within-group analysis showed no significant changes in mean triglyceride (TG) and total cholesterol (TC) levels over 4 months. There was a significant increase in mean low-density lipoprotein cholesterol (LDL-C) and a significant decrease in mean high-density lipoprotein cholesterol (HDL-C) levels in both groups during the 4-month study period ($P < 0.001$ for each measure). Between-group analysis was not reported.

Both Howden et al[130] and Flesher et al[131] examined the effect of MNT in participants with stages 3-4 CKD. In Howden et al,[130] intervention participants received a

multidisciplinary lifestyle intervention for 12 months. It included 4 weeks of group behavioral and lifestyle modification by an RDN and a psychologist. No significant changes were observed in TG, TC, HDL-C, or LDL-C levels between the 2 groups. In Flesher et al,[131] in addition to the standard nutrition care for CKD, the intervention group received cooking classes over 4 weeks for 2 hours per session and a shopping tour led by an RDN. No significant difference was observed in mean TC levels between the 2 groups. Pooled analysis confirmed no effect of MNT on TC and TG levels. However, in pooled analysis, LDL-C levels were decreased by MNT (mean, −6.022 [95% CI, −7.754 to −4.290] mg/dL). There was no clear effect of MNT on blood pressure (BP).

Protein Intake. Six RCTs examined the effect of MNT on protein intake in patients with CKD. Two of those studies targeted protein intake as their primary outcome of the MNT provided to the participants.

Paes-Barreto et al[132] educated nondialysis patients on eating a low-protein diet (LPD), whereas Leon et al[133] counseled MHD participants on following a high-protein diet. Both studies showed high adherence to the recommended protein intake among participants in the intervention group as compared with the control group. The other 4 studies did not show any significant differences in protein intake between the intervention and control groups, but protein intake was not the primary outcome.

The use of MNT protocols has the potential to preserve nutritional status, modify risk factors for progression of kidney disease, and assist with living with CKD from a diet and lifestyle perspective through teaching patients healthy food choices in an individualized manner.

Special Discussions

The full utility and value of MNT provided by the RDN on both nutrition outcomes and risk for morbidity, mortality, and hospitalizations has not yet been fully identified. The impact of the RDN in many disease states and the value of repeated contacts with an RDN on specific nutrition parameters has been documented in the literature.[143] This is particularly true for patients with CKD, as well as in other disease states and metabolic phenotypes such as obesity that affect CKD risk and exacerbation of CKD progression. Although MNT outcomes research is still in its infancy, the studies that exist exhibit important relationships on nutrition parameters and other outcomes. An MNT database that monitors MNT intervention effectiveness on nutrition and overall outcome parameters would enable the formalization of this analysis. Studies that prove causality or significant association between MNT application and patient outcomes are currently in progress. In addition, the strength of the evidence in the studies reviewed prohibits strong recommendations due to the variability in study populations, protocols, and analyses. Therefore, this section included recommendations that are mostly opinion based.

MNT facilitates the delivery of Nutrition Practice Guidelines through a systemic approach of delivery that is based on scientific evidence and expert opinion. The education, content, and practice expertise for the provision of MNT individualized care is found within the scope of practice of the RDN with expertise in nephrology.

Implementation Considerations

- Evidence-based protocols are inherent to MNT but also require individualized modification.
- Implementation of MNT for patients with CKD requires the formation of a fiscal structure that will support the integration of MNT into routine medical management of patients with CKD. The interest level to integrate MNT into clinical practice exists by many nephrology and general medicine clinics; however, the lack of adequate reimbursement for RDN services may preclude the opportunity to pursue implementation.
- Demand for MNT is growing as the global prevalence of CKD increases. Reimbursement policies for disease prevention need to include MNT. Legislation awareness is needed to disseminate the value of MNT as part of the comprehensive CKD care.
- MNT may be delivered through telehealth options to improve patient education and successful maintenance of nutrition interventions and adherence to reduce health care manpower.

Monitoring and Evaluation

Monitoring and evaluation of MNT on patients' nutritional parameters is an essential component of treatment and includes assessment of patients' clinical status (body weight is the most straightforward and least costly and readily available test), laboratory tests, nutritional status, cause of kidney disease, lifestyle (stress, exercise, evaluation of smoking and alcohol use, etc), and patient-identified nutrition goals.

Future Research

- Development of an MNT database is imperative to the formalization of MNT outcomes research.
- Evaluation of the impact of MNT care on progression of kidney disease by analysis of association with risk factors of comorbid conditions is necessary.
- Patient outcomes pertaining to the individualized nutrition plan formulated for patients and/or group classes to evaluate the effectiveness and adherence of the therapy should be explored in future studies.
- Research examining access to MNT, as well as methods (fiscal, referral, etc) that support MNT access for individuals with CKD worldwide.

Guideline 3: Protein and Energy Intake

3.0 Statements on Protein Amount

Protein Restriction, CKD Patients Not on Dialysis and Without Diabetes

3.0.1 In adults with CKD 3-5 who are metabolically stable, we recommend, under close clinical supervision, protein restriction with or without keto acid analogs, to reduce risk for end-stage kidney disease (ESKD)/death (*1A*) and improve quality of life (QoL) (*2C*):

- a low-protein diet providing 0.55–0.60 g dietary protein/kg body weight/day, or
- a very low-protein diet providing 0.28–0.43 g dietary protein/kg body weight/day with additional keto acid/amino acid analogs to meet protein requirements (0.55–0.60 g /kg body weight/day)

Protein Restriction, CKD Patients Not on Dialysis and With Diabetes

3.0.2 In the adult with CKD 3-5 and who has diabetes, it is reasonable to prescribe, under close clinical supervision, a dietary protein intake of 0.6 - 0.8 g/kg body weight per day to maintain a stable nutritional status and optimize glycemic control (*OPINION*).

Dietary Protein Intake, MHD and PD Patients Without Diabetes

3.0.3 In adults with CKD 5D on MHD (*1C*) or PD (*OPINION*) who are metabolically stable, we recommend prescribing a dietary protein intake of 1.0-1.2 g/kg body weight per day to maintain a stable nutritional status.

Dietary Protein Intake, Maintenance Hemodialysis and Peritoneal Dialysis Patients With Diabetes

3.0.4 In adults with CKD 5D and who have diabetes, it is reasonable to prescribe a dietary protein intake of 1.0-1.2 g/kg body weight per day to maintain a stable nutritional status. For patients at risk of hyper- and/or hypoglycemia, higher levels of dietary protein intake may need to be considered to maintain glycemic control (*OPINION*).

3.1 Statement on Energy Intake

3.1.1 In adults with CKD 1-5D (*1C*) or post-transplantation (*OPINION*) who are metabolically stable, we recommend prescribing an energy intake of 25-35 kcal/kg body weight per day based on age, sex, level of physical activity, body composition, weight status goals, CKD stage, and concurrent illness or presence of inflammation to maintain normal nutritional status.

Rationale/Background

Protein metabolism in the body is responsible for adequate growth in children and maintenance of body protein mass such as muscle mass in adults. Every day, approximately 250 g of protein are catabolized, leading to protein catabolic products such as urea and many other known or unidentified compounds. Most of these degradation products are normally cleared by the kidneys and excreted in urine. When kidney function declines, there will be an accumulation of these by-products into the blood, which will progressively impair organ function.[144] This has been clearly identified for compounds such as p-cresyl sulfate, indoxyl sulfate, trimethyl aminoxide, and fibroblast growth factor 23 (FGF-23), which are now considered as uremic toxins. Second, protein intake is responsible for a major fraction of kidney workload, and much experimental and clinical research has confirmed the renal effects of a protein load and a deleterious role of the renal hyperfiltration response associated with protein intake. Therefore, in a situation of nephron reduction such as CKD, reducing protein intake will reduce hyperfiltration, with an additive effect to those of angiotensin-reducing drugs.[144] As a consequence of both actions, reducing uremia and uremic toxins on one hand and improving renal hemodynamics on the other hand, a reduction in protein intake may reduce clinical symptoms and postpone the need to start maintenance dialysis treatment.

In the context of these recommendations, "metabolically stable" indicates the absence of any active inflammatory or infectious diseases, no hospitalization within 2 weeks, absence of poorly controlled diabetes and consumptive diseases such as cancer, absence of antibiotic or immunosuppressive medications, and absence of significant short-term loss of body weight. Another consideration is determination of body weight for diet prescription. Because the body weight suggested (whether IBW, BMI, usual or current, or adjusted) depends on clinician judgment related to the patient's health goals (**Guideline Statement 1.1.6**), the specific weight formula used for prescription should be personalized to the patient.

Detailed Justification

Energy Intake. Energy metabolism may be impaired in patients with CKD. Hence, maintaining adequate energy intake is necessary to prevent PEW.

Evidence from 10 controlled trials in predialysis populations and from 3 studies in MHD patients indicates that energy intake ranging from 30 to 35 kcal/kg per day helps maintain neutral nitrogen balance and nutritional status.[145-157] However, it is important to remember that many other factors may influence energy expenditure beyond traditional determinants such as age, sex, and FFM. Some of these factors include hyperparathyroidism, hyperglycemia, and chronic inflammation that should be considered into the overall energy prescription; health

status (eg, acutely ill vs managed long term); overall health goals; and weight maintenance, repletion or loss.

There is still a paucity of controlled metabolic studies, as well as long-term well-designed outpatient clinical trials, studying energy intake in this population. Results from an old metabolic study examining energy requirements in MHD (sample size = 6) indicated that mean energy intake of 35 kcal/kg per day helped maintain neutral nitrogen balance and body composition.[158] Another similar study in 6 individuals indicated that average intake of 38 kcal was desirable to maintain neutral nitrogen balance.[159] Recent review articles not included in this evidence review also suggest that energy intake in the range of 30 to 35 kcal/kg per day is appropriate to maintain neutral nitrogen balance and nutritional status, although not based on additional research studies.[144,160]

Protein Intake. Reducing protein intake may impair nutritional status in individuals at risk for PEW. However, it is a well-known fact that adults in Western countries eat above their minimum daily requirement (1.35 g protein/kg per day) as compared with their optimal daily needs, estimated to be 0.8 g protein/kg per day. Further, metabolic balances in healthy adults and patients with CKD have confirmed that, provided there is sufficient energy intake (eg, >30 kcal/kg per day), the protein intake level can be safely decreased to 0.55 to 0.6 g protein/kg per day. A further reduction in protein intake to 0.3 to 0.4 g protein/kg per day can be achieved with the addition of pills of ketoacid analogues (KAs) to ensure a sufficient balance of the essential amino acids (EAAs) normally brought by animal proteins, which are basically absent in these low-protein vegan-like diets. Optimal metabolism of this lower range of protein intake requires adequate amount of caloric intake to promote protein sparing.

Protein restriction alone. In adults with CKD/kidney transplant, 13 RCTs reported the effect of protein restriction only (no supplementation) on outcomes of interest.[149,151,156,157,161-169] The duration of follow-up in the included studies ranged from 3 to 48 months (Table S8b).

Survival/renal death. Research reports a beneficial effect of protein restriction (0.55-0.6 g/kg per day) on ESKD/death in adults with CKD. In adults with CKD, 5 RCTs reported findings on the effect of protein restriction on survival/deaths. Three studies clearly indicated a beneficial effect of moderate restriction in dietary protein on the development of ESKD/death.[153,164,168] Rosman et al[168] indicated that people consuming 0.6 g/kg per day of protein had better survival (55%) compared with patients consuming free protein intake (40%). Hansen et al[164] indicated that death or ESKD was significantly lower in the low-protein-intake group (0.6 g/kg per day; 10%) compared with usual protein intake (27%). Locatelli et al[153] also showed that an LPD (0.6 g/kg per day) had fewer events (27/192) compared with usual protein intake (1 g/kg per day; 42/188), borderline significant ($P < 0.06$), whereas Cianciaruso et al[161] indicated that cumulative incidences of death and dialysis therapy start were unaffected by the diet regimen, and a low-protein-intake group (0.55 g/kg per day) does not seem to confer a survival advantage compared with a moderate-protein-intake group (0.80 g/kg per day) but may be explained by a relatively small sample size. Pooled together, results from the secondary analysis of the number of events of death/ESKD combined from the 3 studies indicated a beneficial effect of protein restriction on death/ESKD (OR, 0.621; 95% CI, 0.391-0.985).[153,161,164]

Quality of life. Research reports an improved quality of life (QoL) of a protein-restricted diet in one study. In adults with CKD, 1 RCT examined the effect of protein restriction on QoL.[156] QoL scores at the end of the study indicated that the protein-restricted group had significantly higher scores for general health (mean difference, 4.0; 95% CI, 3.1-4.86) and physical status (mean difference, 10.0; 95% CI, 9.1-10.9) compared with the control group (0.6 g/kg per day vs 1.0 g/kg per day; $P < 0.05$).

Glomerular filtration rate. In adults with CKD, 5 RCTs reported on the effect of protein-restricted diet on glomerular filtration rate (GFR). Results from all the studies indicated that an LPD (0.55-0.6 g/kg body weight) had no significant effect on GFR compared with the control group (0.8 g/kg protein). Hansen et al[164] indicated that at a 6-month follow-up time, there was a comparable and significant decline in GFRs in both groups. However, the difference between groups was not statistically significant ($P = 0.87$). Sanchez et al[156] indicated that GFRs decreased by 17.2% in the control group compared to only 6.9% in the low-protein group (not significant [NS] between groups). Cianciaruso et al[161] indicated that no effect of diet assignments was noted on estimated GFR (eGFR) and proteinuria (0.55 vs 0.80 g/kg per day). Jesudason et al[165] reported that dietary treatment had no effect on changes in eGFR. Meloni et al[170] (stage 3) also indicated no effect of protein restriction on eGFR decline (0.6 g/kg per day). Decline in GFR was reported by 3 studies, and a pooled analysis of these studies indicated no clear effect of protein restriction without supplementation on eGFR (SMD, −0.002; 95% CI, −0.192 to 0.188).

Phosphate levels. In adults with CKD, 2 RCTs reported mixed results regarding the effect of protein restriction on serum phosphate levels.[162,167] Rosman et al[167] indicated that patients in the protein-restriction group had significantly lower serum phosphate levels (used less phosphate binders; 0.4-0.6 vs 0.8 g; $P < 0.05$). By contrast Cianciaruso et al[162] reported that phosphate levels were similar in the 2 groups throughout the entire period of follow-up (0.55 vs 0.8 g protein/kg per day).

Dietary intake. Seven randomized controlled studies[149,156,157,163-165,170] and 1 nonrandomized controlled trial (NRCT)[151] reported on dietary intake. Dietary intake was used as a measure of adherence in most of the studies. These studies indicated that protein intake was lower in groups assigned to an LPD (0.6 g/kg per day) compared with control or standard

groups (0.8-1.3 g/kg per day). In 1 study, average protein intake during the entire duration of follow-up was higher than expected in both groups (control, 1.03 ± 0.18, and LPD, 0.78 ± 0.17 g protein/kg per day).[163] Follow-up of at least 1.5 year indicated that adherence to diet did not change in time in either group. Hansen et al[164] reported an estimated dietary protein intake at 4 years significantly lower in the LPD compared to the usual-protein-diet group ($P = 0.005$). Jesudason et al[165] showed that the moderate protein intake group increased their protein intake (NS) and the standard protein group decreased their protein intake. In the study by Kloppenburg et al,[149] protein intake during the high-protein diet was higher than during the regular-protein diet. Kuhlmann et al[151] reported that protein intake was not significantly different among the groups. However, total energy intake significantly differed among each other. In the Meloni et al[170] study, patients in the low-protein group were maintaining their intake at the 0.68–g protein/kg per day level, which was significantly lower than in the free-protein-diet group. Phosphate intake was also significantly lower in the LPD group. Sanchez et al[156] showed that protein intake in the LPD group decreased significantly from baseline to the end of the study ($P < 0.05$). Energy intake tended to decrease during the study duration in both groups but it was nonsignificant. In the Williams et al[157] study, compared with control, only the dietary protein and phosphate restriction group had a significantly lower protein intake level. Finally, Cianciaruso et al[161] reported that the 2 groups (LPD vs moderate protein diet) maintained significantly different protein intakes ($P < 0.05$), with a difference between the 2 groups of 0.17 ± 0.05 g/d, which lasted from month 6 until the study end. Dietary intake can be used as an index of adherence to the diet.

Nutritional status. Research findings indicated that protein restriction did not affect serum albumin levels or anthropometrics in adult patients with CKD. In adults with CKD, 2 RCTs reported no effect of protein restriction (0.55-0.9 g protein/kg per day) on serum albumin levels compared with the control group (0.8-1.3 g protein/kg per day).[149,161] In adults with CKD, 1 RCT reported no effect of protein restriction (55-70 g/d) on anthropometrics compared with the control group (90-120 g/d).[165]

Blood pressure. Two RCTs reported no effect of protein restriction (0.6 g/kg body weight vs usual) on BPs.[164,165] Hansen et al[164] reported that BP changes were comparable in the 2 groups during the follow-up period. BP was equally and significantly reduced during the study compared with baseline in both groups. Jesudason et al[165] reported no overall changes in BP for both groups. However, there was a time-by-treatment interaction ($P < 0.05$) for diastolic BP (DBP). DBP was lower throughout the follow-up period in the moderate-protein-intake group.

Lipid profile. Research reported an improvement in serum lipid profile during an LPD. Coggins et al[171] determined that an intervention diet providing 0.28 kg/kg per day showed significant decreases in TC, HDL-C, and LDL-C levels between baseline and the 6-month follow-up ($P < 0.05$). The diet providing 0.575 g/kg per day reported trends for decreases in TC and LDL-C levels between baseline and the 6-month follow-up ($P < 0.10$). Cianciaruso et al[162] showed a significant decrease in LDL-C values in the LPD group, but not in the moderate-protein-intake group.

Protein restriction plus KA supplement. In settings in which KAs are available, a very low-protein–controlled diet may be considered. Different compositions of KAAs and EAAs have been tested in the setting of CKD, with most of them containing 4 KAs (of the EAAs isoleucine, leucine, phenylalanine, and valine), 1 hydroxyacid (of the EAA methionine), and 4 amino acids considered essential in CKD (tryptophan, threonine, histidine, and tyrosine). Collectively, these supplements are referred as KAs.[172] For adults with CKD without diabetes, not receiving dialysis, with an eGFR < 20 mL/min/1.73 m^2, a very LPD (VLPD) providing 0.28 to 0.43 g protein/kg per day with the addition of KAs to meet protein requirements may be recommended.

In adults with CKD including kidney transplant, 14 studies reported the effect of protein restriction plus KA supplementation on outcomes of interest. One NRCT[145] and 13 RCTs were included.[146,148,150,152,154,155,171,173-178]

Survival/renal death. In adults with CKD (stages 3-5), 4 RCTs reported a mixed effect of a protein-restricted diet plus KA on renal survival/RRT.[147,154,176,177] Garneata et al[147] and Mircescu et al[154] indicated that a significantly lower percentage of patients in the VLPD plus KA group required RRT initiation throughout the therapeutic intervention, whereas Levey et al[176] and Malvy et al[177] indicated no effect, but the Malvy et al[177] study was underpowered. Pooled analysis of 2 studies that reported RRT incidence indicated that a protein-restricted diet plus KA has a lower RR for incidence of RRT (RR, 0.412; 95% CI, 0.219-0.773).[147,154] Levey et al[176] indicated that after controlling for protein intake from food and supplement from the studies evaluated, assignment to the VLPD did not have a significant effect on renal failure/death risk. Malvy et al[177] also indicated no effect of protein restriction plus KA on renal survival, whereas Mircescu et al[154] indicated that a statistically significantly lower percentage of patients in the VLPD plus KA group required RRT initiation throughout the therapeutic intervention (4% vs 27%)[154] and Garneata et al[147] also indicated a delay in dialysis initiation. Both Garneata et al[147] and Mircescu et al[154] are newer studies, and have shorter durations (12-15 months) compared with Levey et al[176] and Malvy et al[177] (Levey et al, 2.2 years). When pooled together, there is probably an overall benefit of dietary protein restriction plus KA supplementation on RRT/renal

survival in patients with CKD stages 3-5 (RR, 0.65; 95% CI, 0.49-0.85; P < 0.001).

Estimated GFR. A VLPD supplemented with KAs (0.28-0.4 g protein/kg per day) could help preserve kidney function in patients with stages 3-5 CKD. One study was conducted in PD patients and GFR was preserved. In adults with CKD, 1 NRCT[145] and 4 RCTs[147,154,155,175,176] reported on the effect of a protein-restricted diet plus KA (0.28-0.4 g/kg body weight) on eGFR. Results from all 6 studies indicated that a VLPD plus KA (0.3-0.4 g/kg body weight) supplementation helped preserve eGFR, whereas participants assigned to LPD only (0.58-0.68 g/kg protein) indicated a decline in eGFR. All studies were conducted in patients in stages 3-5. Pooled analysis for all 5 studies was not possible to conduct.

Bellizzi et al[145] reported that GFR significantly decreased in the control group. Garneata et al[147] indicated that the decrease in eGFR was less in the KA group compared with LPD. Klahr et al[175] indicated that compared with the usual-protein group, the low-protein group had a more rapid GFR decline in the first 4 months (P = 0.004) but slower decline from the first 4 months to the end (P = 0.009). Among patients with GFRs of 13 to 24 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD] Study 2), there was a trend for slower GFR decline in the VLPD group when compared with the low-protein group (P = 0.07). Levey et al[176] (post hoc analysis of MDRD Study) indicated that at a fixed level of protein intake from food only, assignment to a VLPD was associated with a decrease (trend) in the steepness of the mean GFR slope of 1.19 mL/min per year (P = 0.063). Similarly, after controlling for protein intake from food and supplement, assignment to the VLPD did not improve the rate of decline in GFR (P = 0.71). Mircescu et al[154] indicated that eGFR did not change significantly in patients receiving a VLPD plus KA but significantly decreased in the LPD group (P < 0.05), suggesting renal protection for VLPD plus KA. Prakash et al[155] also indicated that eGFR was unchanged in the KA-supplemented group; however, it significantly decreased in the placebo group (P = 0.015). A KA-supplemented diet during the 9-month period helped preserve eGFR.

Electrolyte levels. A VLPD supplemented with KAs (0.28-0.4 g protein/kg per day) could potentially decrease serum phosphate levels and improve some markers of bone metabolism (calcium and parathyroid hormone [PTH]). Four randomized controlled studies (stages 4-5)[146,154,167,177] indicated a decrease in serum phosphate levels at the end of intervention among the LPD-plus-KA groups. One study with MHD patients also demonstrated a decrease in serum phosphate levels in the LPD-plus-KA group.[152]

Feiten et al[146] indicated that serum phosphate levels did not change in the LPD group but tended to decrease in the VLPD-plus-KA group (within VLPD, P = 0.07). Serum PTH concentration did not significantly change in the VLPD-plus-KA group; however, it increased significantly in the LPD group (P = 0.01). Li et al[152] in MHD patients indicated that in the LPD-plus-KA group, no significant changes in serum calcium levels were observed; however, mean serum phosphate levels significantly decreased at the end of the study (P < 0.001) compared with the normal-protein diet group. Mircescu et al[154] in patients with stages 4 and 5 indicated that in the VLPD-plus-KA group, a significant increase was seen in serum calcium levels postintervention (P < 0.05) and serum phosphate levels decreased (P < 0.05), whereas no statistical changes were observed in the LPD group. In the study by Rosman et al,[167] patients in the LPD group showed significantly lower serum phosphate levels and used less phosphate binders (P < 0.05). In a recent meta-analysis, it was reported that serum phosphate levels were lower in patients with supplemented very low-protein intake in 2 randomized studies from China.[179]

Dietary intake. Research findings indicate that a VLPD supplemented with KAs (0.28-0.40 g protein/kg per day) can effectively be achieved. Dietary intake can be used as an index of adherence to the diet. Five randomized controlled studies and 1 NRCT (4 studies with patients with CKD stages 3-5 and 1 with PD patients) reported on dietary intake. These studies indicated that protein intake was lower in groups assigned to the LPD or VLPD groups compared with the control or standard groups. Dietary intake was used as a measure of adherence in most of the studies.

In Bellizzi et al[145] (stages 4 and 5), at 6 months, protein intake and salt intake were significantly lower in the VLPD than LPD group (P < 0.0001). Feiten et al[146] (stage 4) reported a reduction in protein intake in the VLPD supplemented group; energy intake did not change in either group during the entire study and was low (~23 kcal/kg per day). Phosphorus intake decreased significantly only in the VLPD-plus-KA group. Calcium intake was low and did not change during the intervention period for both groups. In the Herselma et al[148] study, protein intake during intervention was significantly reduced from baseline in both groups. In the study of Jiang et al[173] in PD patients, dietary protein intake between the low-protein and high-protein groups was different in months 6 and 10 (P < 0.05). Kopple et al[150] looked at both protein and energy intake (CKD stages 3 and 4); compared with a usual-protein diet, the LPD had significantly lower dietary protein intake in study A (P ≤ 0.001). Compared with the LPD, the VLPD had significantly lower dietary protein intake in study B (P ≤ 0.001). Dietary energy intake in the LPD was significantly lower in study A (P ≤ 0.001) compared with the usual-protein diet; however, there was no significant difference between the LPD and VLPD in study B (P > 0.05). The Mircescu et al[154] (CKD stages 4 and 5) results indicated that adherence to the prescribed diet was good throughout the study in both arms.

Nutritional status. Research reports that a VLPD supplemented with KAs (0.28-0.4 g protein/kg per day) had no significant effect on serum albumin levels and nutritional status as measured by SGA, and effects on anthropometry were inconclusive. In adults with CKD, 6 RCTs[146,147,150,154,155,173] and 1 NRCT[145] reported no effect of a VLPD and KA intervention on serum albumin levels. Jiang et al[173] and Garneata et al[147] were the only studies that studied the effect of protein restriction plus KA supplementation on SGA and no statistically significant effect was noticed. Both studies indicated that nutritional status was maintained.

In the study by Kopple et al[150] (MDRD Study B, CKD stages 3 and 4), no significant differences in anthropometric measurements were observed between groups ($P > 0.05$). Malvy et al[177] reported that for the patients in the VLPD group, significant weight loss was observed at the end of the study ($P < 0.01$) and lean mass and FM were reduced in this group at the end of study. The moderate-protein group indicated no difference for weight variables. Garneata et al,[147] in a larger and more recent study, reported no differences throughout the study period in both groups for BMI, MAMC, and TSF.

Blood pressure. The effects of a VLPD supplemented with KAs (0.28-0.40 g protein/kg per day) on BP are inconclusive. In adults with CKD, 1 NRCT[145] and 2 RCTs[148,154] reported mixed effect of a protein-restricted diet (0.3-0.4 g/kg per day) plus KA supplements on BP. Only 1 study showed a significant reduction in systolic BP (SBP) and DBP.[145] In this study, the VLPD had an antihypertensive effect in response to the reduction in sodium intake, type of protein intake, and KA supplements, independent of actual protein intake. The other 2 studies reported no effect of protein-restricted diet plus KAs on BP.[148,154]

Lipid profile. Research indicates that a VLPD supplemented with KAs (0.28-0.40 g protein/kg per day) could improve serum lipid profiles of patients with CKD. In adults with CKD, 1 NRCT[145] and 4 RCTs reported on the effects of a protein-restricted diet (0.3-0.4 g/kg per day) plus KAs on serum lipid profile.[146,147,171,177] Feiten et al[146] and Malvy et al[177] reported no effect of a VLPD plus KAs on serum lipid profile, whereas Bellizzi et al[145] indicated a decrease in TC and TG levels only in the VLPD group. Coggins et al[171] indicated a significant decrease in TC, HDL-C, and LDL-C levels in the VLPD group. Garneata et al[147] showed that cholesterol levels remained stable during the entire duration of the study; however, patients were taking statins/fibrates as standard therapy.

Dietary protein intake and diabetes mellitus. Nutrition plays a significant role in the management of individuals with diabetic kidney disease (DKD) in conjunction with pharmacologic interventions. The goal is to maintain optimal glycemic control and at the same time maintain adequate protein and energy intake to achieve optimal nutritional status. There are some previous guidelines that suggest 0.8 g/kg body weight per day among those with CKD stages 1-4 and also for CKD stage 5.[180] However, the KDIGO (Kidney Disease: Improving Global Outcomes) guideline[181] suggested more liberalization with protein restriction and recommended that 0.8 g/kg body weight per day be maintained, avoiding levels > 1.3 g/kg body weight.

Evidence from controlled trials in this nondialyzed DKD population has been conflicting.[164,170,182-187] Recent meta-analysis shows a small beneficial impact of LPD on eGFR decline; however, the heterogeneity was really high (type of diabetes, stages of CKD, types on interventions, duration, and adherence to recommendations).[188,189]

For patients with DKD receiving dialysis, evidence from observational studies indicated that low dietary protein intake is associated with higher hospitalization rates and higher risk for mortality.[190,191] The KDOQI guideline for dialysis patients suggests dietary protein intake > 1.2 g/kg body weight per day to manage the protein catabolism and losses of protein in dialysate.

Ko et al[192] conducted an extensive review of existing guidelines and original research in patients with DKD and indicated that dietary protein intake of 0.8 g/kg body weight per day was advised for patients with DKD not receiving dialysis and dietary protein intake > 1.2 g/kg body weight per day was advised for patients with DKD receiving dialysis.

Special Discussions

These diets should be progressively installed to allow careful dietary counseling and adequate adherence. Although such diets are not associated with wasting in carefully monitored research studies, on a routine basis, attention should be focused on energy intake, which may decrease over time and induce weight loss and wasting. A potential beneficial effect of reducing protein intake relies on the fact that it also reduced glomerular hyperfiltration and potentially protects them from hyperfiltration, accelerated hyalinosis, and proteinuria. On a nutritional point of view, reducing protein from animal sources and moving toward more vegetable protein sources also reduced acid production and metabolic acidosis. These effects are mostly observed for more reduced protein intakes (0.3-0.5 g/kg protein/kg per day) supplemented with KAs.

Are LPDs/VLPDs plus KAs indicated for patients with CKD with PEW? This question cannot easily be answered because it may depend on the cause of patient wasting. For example, an acute catabolic state may induce PEW despite nutrient intake that is normally considered adequate. Therefore, priority should be given to the correction of the cause of wasting and protein and energy intake should be increased until the wasting state improves. An LPD/VLPD plus KA should not be started during a catabolic state in patients with CKD and should be implemented only in metabolically stable patients without intercurrent illnesses.

Do an LPD and VLPD plus KAs have an impact on nutritional status? In a post hoc analysis of the MDRD

Study,[150] the authors compared the randomly assigned groups (LPD vs VLPD plus KAs) for various outcomes related to nutritional status. Overall, the results demonstrate the safety of dietary protein restriction over 2 to 3 years in patients with moderate to advanced CKD. However, there were small but significant changes from baseline in some nutritional indices and minimal differences between the randomly assigned groups in some of these changes. In both LPD and VLPD plus KAs, both protein and energy intake declined. Serum albumin levels increased, while serum transferrin levels, body weight, percent BF, arm muscle area, and urine creatinine excretion declined. In a longitudinal study looking at body composition, a VLPD plus KA induced a small decline in LBM on the average of 1.2 kg, with concomitant increase in FM, mainly in the first 3 months. These parameters subsequently stabilized and even improved slightly thereafter.[193] Other short-term studies did not show noticeable effects of LPDs and VLPDs plus KAs on nutritional parameters. Nevertheless, the small anthropometric measurement declines observed in some studies are of concern because in routine practice, LPDs and VLPDs plus KAs are used in the long term and because of the adverse effect of PEW in patients with ESKD. This is why physicians who prescribe LPDs must regularly monitor patients' protein and energy intake, body weight, and nutritional status.

Implementation Considerations

Energy Intake.

- Energy intake of patients with CKD should take into account the patients' overall metabolic state and comorbid conditions. Accordingly, the recommended range should be personalized to each patient.
- The RDN should consider a number of factors when determining the energy requirements for adults diagnosed with CKD, and these include the patient's overall health status, CKD diagnosis and associated therapies, level of physical activity, age, sex, weight status, metabolic stressors, and treatment goals.
- Patients should be monitored routinely to assess whether energy requirements are being met satisfactorily. Changes in nutritional status should be treated and the energy prescription modified accordingly.
- Among patients with stage 5 CKD receiving maintenance dialysis (HD or PD), there are several factors that may influence energy expenditure beyond the traditional determinants (age, sex, and FFM), such as hyperparathyroidism, hyperglycemia, chronic inflammation, infections, and other intercurrent illnesses that should be considered into the overall energy prescription.
- Energy needs will be variable depending on the health status of the patient; for example, acutely versus chronically ill versus, overall health goals, and weight maintenance, repletion, or loss.
- Energy needs may be different depending on the stage of CKD and its respective treatment (dialysis vs transplantation).

Protein Restriction.

- Increase the training and number of specialized renal dietitians worldwide who could effectively and safely implement LPDs and VLPDs.
- Promote low-protein products to simplify dietary counseling and help achieve an LPD.
- Be more aggressive with dietary interventions to improve symptoms when maintenance dialysis is not a treatment option or needs to be postponed (vascular access maturation or organizing a preemptive kidney transplant).
- The need for food information is important to obtain good adherence to the restricted protein intake. However, therapeutic education can help patients improve personal motivation and can even become a personal goal to achieve. Getting more interested in food harvesting, preparation, and cooking may improve QoL. In addition, postponing initiation of dialysis undoubtedly maintains a better QoL rather than undergoing maintenance dialysis.[194]
- Certain patient populations such as patients with polycystic kidney disease do not benefit from an LPD or VLPD. Individual dietary plans should be considered for these patients.

Monitoring and Evaluation

Adherence to diets should be monitored frequently during the first year of dietary intervention using dietary interviews (3 is optimal) and 24-hour urine collection for urinary urea nitrogen excretion to assist monitoring dietary adherence. Then twice-yearly follow-up may be recommended until the start of maintenance dialysis.

Future Research

- Determine whether an LPD has an additive or a synergistic effect to that of renin-angiotensin aldosterone system antagonists or newer nephroprotective agents (ie, sodium-glucose transport protein 2 inhibitors) on proteinuria and nephroprotection through RCTs.
- Examine the impact of an LPD and VLPD with or without KAs on gut microbiota in patients with CKD.
- Investigate at which CKD stage it is best to initiate dietary protein intake modification.
- Examine ways and strategies to improve adherence and compliance with LPDs and VLPDs plus KAs.

3.2 Statement on Protein Type

3.2.1 In adults with CKD 1-5D (1B) or post-transplantation (OPINION), there is insufficient evidence to recommend a particular protein type

(plant vs animal) in terms of the effects on nutritional status, calcium or phosphorus levels, or the blood lipid profile.

Rationale/Background

Vegetable protein diets (VPDs) may have beneficial effects on health. A recent population-based study suggested that soy or soy isoflavones intake significantly reduced the risk for postmenopausal breast cancer.[195] Oxidative stress significantly decreased in postmenopausal women when treated with VPDs (soy isoflavones), and in vitro experiments have shown that a VPD protects against inflammation in vascular endothelial cells.[196] These findings lead to the development of preventive strategies for human health and disease. For example, the US Food and Drug Administration suggested that intake of 25 g of soy protein daily may prevent the risk for coronary heart disease due to reduced serum lipid and lipoprotein levels.

In patients with CKD, VPDs may have positive biological actions and possibly clinical benefits through a variety of mechanisms. In vitro studies showed that VPDs reduce the expression of renin-angiotensin.[197] Studies in rodents demonstrated that VPDs retard the development and progression of CKD, versus animal protein diets (APDs),[198] presumably through favorable effects on GFR. In addition, a vegetarian diet was associated with a significant reduction in serum phosphate and FGF-23 levels in CKD patients not receiving dialysis.[199] As a result, it was thought that VPDs may be used in helping to reduce phosphorus load and potentially CKD progression in this group of patients.

Detailed Justification

Three RCTs (CKD 5D) and 2 randomized crossover (stages 3-4 CKD) trials compared the impact of vegetable-based protein (VPD) versus animal-based protein (APD) intake on biomarkers and health outcomes in patients with CKD.

Serum Albumin. Protein type did not affect nutritional status as measured by serum albumin. In Soroka et al,[200] serum albumin levels significantly increased after both VPDs and APDs, compared to the prestudy diet, but there was no significant difference in serum albumin levels between VPDs and APDs. Fanti et al[201] found no significant difference between VPDs and APDs in serum albumin levels. Tabibi et al[202] found a significant ($P < 0.05$) increase in serum albumin levels within both groups, but no significant difference was found between groups. Finally, Chen et al[203] found no significant difference in serum albumin levels between groups. However, the power to discriminate might have been insufficient due to the small number of patients enrolled. In pooled analysis of 4 studies, there was no effect of protein type on serum albumin levels.

Protein Catabolic Rate. VPDs may be associated with a decrease in PCR after 6 months, but evidence was limited. In Soroka et al,[200] PCR was significantly ($P < 0.05$) lower after 6 months of a VPD compared with the prestudy diet, but there were no changes in the APD. In a secondary analysis, there was a mean difference of −0.10 (95% CI, −0.17 to −0.03) g/kg per day in PCRs with the VPD versus the APD. This might have been the consequence of slightly reduced absorption of protein from vegetal source (estimated to be 90% of animal protein).

Prealbumin Levels. A VPD did not affect serum prealbumin levels compared with a control group, but evidence was limited. Fanti et al[201] found no significant difference between a VPD and APD on serum albumin or prealbumin levels after receiving soy protein for 8 weeks, compared with the control group.

Inflammatory Markers (CRP, IL-6, and TNF-α). Protein type did not affect inflammatory marker levels. Fanti et al[201] compared the impact of a soy protein versus a milk protein supplement on inflammation. No significant differences were found within or between groups for CRP, IL-6, or TNF-α levels.

Calcium and Phosphorus Levels. There was no effect of protein type on plasma/serum or urinary calcium levels. A VPD for 7 days to 6 months did not affect plasma/serum phosphate levels, but decreased 24-hour urinary phosphate levels by a mean difference of −126.6 (95% CI, −200.4 to −52.7) mg. Soroka et al[200] found no significant difference between a VPD, APD, or prestudy diet on urinary sodium, potassium, or calcium excretion or serum calcium or phosphate levels. Urinary phosphate excretion was significantly lower after the VPD versus the APD and prestudy diet. In a small randomized crossover trial in CKD patients not receiving dialysis, Moe et al[199] demonstrated that plasma phosphate levels were significantly higher in the APD versus the VPD group at day 7 ($P = 0.02$), but there was no difference in urinary phosphorus excretion. There were no differences in plasma calcium levels or urinary calcium excretion between groups. In pooled analysis of these 2 studies, there was no effect of a VPD, compared with an APD, on serum/plasma phosphate levels. However, a VPD decreased 24-hour urinary phosphate levels by a mean difference of −126.6 (95% CI, −200.4 to −52.7) mg.

TC, LDL-C, HDL-C, and TG Levels. Protein type did not affect lipid profiles in patients with stages 4 and 5D CKD. Three studies examined the effect of a VPD versus an APD on blood lipid panel. Chen et al[203] compared the impact of a soy protein versus a milk protein supplement on plasma lipid levels during 12 weeks in MHD patients with and without hyperlipidemia. In patients without hyperlipidemia, no significant differences were found in TC, LDL-C, HDL-C, and TG levels within or between groups. However, in hyperlipidemic patients, soy protein lead to a significant decrease in TC, LDL-C, and TG levels compared with milk protein, whereas HDL-C levels

significantly increased. Tabibi et al[202] compared the impact of a soy protein supplement versus control in PD patients and found no significant impact on TC, LDL-C, HDL-C, and TG levels in the intervention group. Soroka et al[200] found no significant differences after a VPD, APD, or prestudy diet on TC, LDL-C, and TG levels in patients with stage 4 CKD. HDL-C level was significantly lower after a VPD compared with the prestudy diet.

In pooled analysis of 3 studies, there was no mean difference in TC, LDL-C, HDL-C, or TG levels between groups.

Special Discussions

VPDs have been studied to test metabolic hypotheses in patients with CKD. In particular, phosphorus may be less absorbed during a VPD, which may benefit calcium and phosphate metabolism. This becomes more important because currently processed food contains much added inorganic phosphorus as compared with a VPD. The fat content of a VPD possesses a healthier profile and may benefit patients in long-term studies. Finally, toxic middle molecules such as *p*-cresyl sulfate, indoxyl sulfate, and trimethylamine oxide, almost exclusively produced from animal source protein, could be reduced by VPDs and this hypothesis should be tested in long-term clinical trials in patients with CKD. As demonstrated in other subtopics of this guideline, VPDs have shown reduction in acid load, increase in dietary fiber intake, and reduction of phosphorus and body weight. There is increasing interest in the role of VPDs in CKD due to the benefits of this dietary pattern on CVD risk factors in the general population. However, current evidence from RCTs specifically comparing benefits of a VPD versus an APD in patients with CKD is limited.

Implementation Considerations

- Work with patients to help them meet their individualized dietary protein and energy intake needs.
- Based on the preference of the patient with CKD for animal- or plant-based protein, ensure that they meet their dietary protein and energy needs and their diets provide adequate EAAs.

Monitoring and Evaluation

Adherence to diets should be monitored frequently during the first year of dietary intervention by using dietary interviews (3 is optimal). Then yearly follow-up may be recommended until the start of maintenance dialysis.

Future Research

- Conduct adequately powered randomized clinical trials to study the effect of a VLPD on mortality, CKD progression, proteinuria, markers of mineral and bone metabolism, and urinary phosphorus excretion in patients with CKD.
- Examine the effects of a VLPD on the lipid profile in hyperlipidemic patients with CKD.
- Examine the impact of a VLPD on the generation of toxic middle molecules.

3.3 Statements on Dietary Patterns

Mediterranean Diet

3.3.1 In adults with CKD 1-5 not on dialysis or post-transplantation, with or without dyslipidemia, we suggest that prescribing a Mediterranean Diet may improve lipid profiles (2C).

Fruits and Vegetables

3.3.2 In adults with CKD 1-4, we suggest that prescribing increased fruit and vegetable intake may decrease body weight, blood pressure, and net acid production (NEAP) (2C).

Rationale/Background

Dietary patterns reflect the variety of foods that represent habitual dietary intake.[204] Particular dietary patterns, including the Mediterranean diet, the Dietary Approach to Stop Hypertension (DASH), and plant-based and diets high in fruits and vegetables (including vegetarian diets) are examples of healthy dietary patterns that have been the subject of interest in nutritional epidemiology.[205] A whole-diet approach considers the synergistic effects of nutrients resulting in cumulative effects on health and disease.[205]

CKD presents many challenges for nutrition management, including increased risk for death and appreciable CVD burden among affected persons. Traditionally, nutrition education has focused on individual nutrients, such as protein, phosphorus, potassium, and sodium. Recent evidence has linked healthy dietary patterns with reduced chronic CVD and mortality risk in the healthy population.[206-208] However, these relationships have not been explored conclusively with the CKD population.

Detailed Justification

Although various dietary patterns were investigated (fruits and vegetables, Mediterranean diet, low-fructose diet, hypolipidemic, carbohydrate-restricted low iron polyphenol-enriched diet, and high-protein/low-carbohydrate), there was little evidence examining the efficacy of most of these patterns in controlled trials. Hence, only the Mediterranean and high fruit and vegetable dietary patterns had sufficient evidence to create recommendations.

Mediterranean Dietary Pattern. Estimated GFR. One RCT reported on the effect of the Mediterranean dietary pattern on eGFR.[209] Mekki et al[209] indicated no clear effect of the Mediterranean dietary pattern on eGFR at 90 days postintervention in adults with CKD stage 2. Additional research on the effect of the Mediterranean dietary pattern is needed.

Lipid profile. Limited evidence from 3 studies, 2 of which examined CKD patients not receiving dialysis (stages 2 and 3) and 1 of which examined posttransplant patients, demonstrated that the Mediterranean diet improved lipid panels by decreasing TC, LDL-C, and TG levels compared with control groups.

Two controlled trials reported on the effect of the Mediterranean dietary pattern on lipid profiles in CKD patients not receiving dialysis.[209,210] In the RCT, Mekki et al[209] (stage 2) reported a 35% reduction in TC levels ($P < 0.05$) in the Mediterranean diet group, whereas no change in TC levels was observed in the control group. LDL-C and TG levels were also reduced compared to standard care. In an NRCT, Di Daniele et al[210] reported a significant reduction in TC levels in both the Mediterranean diet group and the organic Mediterranean diet group. However, most reduction was noted in the organic Mediterranean diet group. In posttransplant patients, 1 RCT reported that the Mediterranean diet led to significant reductions in TC, TG, and LDL-C levels compared with a low-fat diet.[209,211]

Other outcomes. Compared with a control group, the Mediterranean diet had no clear effect on BP in posttransplant patients[211] or on CRP levels in stage 2 patients.[209]

However, 1 NRCT reported on the effect of the Mediterranean dietary pattern on albuminuria in adults with stages 2 and 3 CKD, and both Mediterranean diet groups (normal and organic) had significant reductions in albuminuria values compared with the low-protein group.[210]

High Fruit and Vegetable Dietary Pattern.

CKD progression. In adults with stages 3-4 CKD, the fruits and vegetables dietary pattern has mixed effects on eGFR compared with oral bicarbonate supplementation.[212,213]

Body weight. Two RCTs reported on the effect of a fruit and vegetable dietary pattern on body weight in adults with CKD. Goraya et al[213] reported that the group following the fruit and vegetable dietary pattern had greater net body weight loss than both the oral-bicarbonate and standard-care groups ($P < 0.05$). Goraya et al[212] reported lower body weight in adults with CKD stages 3-4 following a fruit and vegetable dietary pattern compared with the oral bicarbonate supplementation group at the 1-year follow-up ($P < 0.01$; mean difference, −5.09; 95% CI, −7.73 to 2.44 kg; $I^2 = 56\%$).

Blood pressure. Three studies (2 RCTs and 1 NRCT) reported on the effect of increased fruit and vegetable intake on BP in adults with CKD. All 3 studies indicated that increased intake of fruit and vegetable had a significant effect on lowering SBP compared with the oral bicarbonate supplement intake group or standard-care group.[212-214] Goraya et al[213] indicated reductions in SBPs in all groups; however, the 3-year value for the fruits and vegetables group was lower than those in bicarbonate and control. Goraya et al[212] showed that compared with the bicarbonate group, the fruit and vegetables group had lower SBPs at the 1-year follow-up ($P < 0.01$). Goraya et al[214] (NRCT) showed that fruit and vegetable intake, but not control or bicarbonate, significantly decreased SBPs in individuals with CKD stages 1 and 2 ($P < 0.001$). Pooled analysis of data from Goraya et al[212] (2013) and Goraya et al[213] (2014) indicated a mean difference of −5.6 (95% CI, −8.3 to −2.8) mm Hg. Increased intake of the fruits and vegetable dietary pattern lowered SBP compared with oral bicarbonate supplement intake or the standard-care group in adults with CKD stages 1-4.

Comparison With Recent Research.

A recent systematic review examined the effect of dietary patterns on CKD outcomes using cohort studies.[215] In agreement with the current analysis of controlled trials, Kelly et al[215] found no effect of dietary pattern on CKD progression in studies with follow-up ranging from 4 to 6.4 years. However, unlike the current systematic review, Kelly et al[215] were able to demonstrate a relationship between a dietary pattern rich in vegetables, fruit, fish, cereals, whole grains, fiber, legumes, and nuts and seeds and lower in red meat, sodium, and refined sugars in studies reporting outcomes from 4 to 13 years of follow-up (RR, 0.73 [95% CI, 0.63-0.83]).

A recent Cochrane review of 6 RCTs evaluated dietary patterns in CKD (1 study [n = 191] of a carbohydrate-restricted low-iron polyphenol enriched diet, 2 studies [n = 355] of a Mediterranean diet, 2 studies [n = 181] of increased fruit and vegetable intake, and 1 study [n = 12] of a high-protein/low-carbohydrate diet). From this review, dietary interventions had uncertain effects on all-cause mortality and cardiovascular events. However, with low-quality evidence, there was reduced SBP and DBP and higher GFRs and albumin levels following dietary interventions.[216]

Although the intervention studies examining dietary patterns in CKD are limited, there is consistent evidence from observational analyses on dietary patterns containing fruits, vegetables, whole grains, lean meats, low-fat dairy, and low added salt and improved clinical outcome (notably mortality) in CKD.[215] A recent study confirmed that intake of nuts, low-fat dairy products, and legumes is protective against the development of CKD.[217] There is therefore a need to undertake future trials to further investigate more holistic dietary interventions over single-nutrient approaches in these patients. Dietary pattern may improve additional outcomes not reported in the systematic review, including constipation.

Implementation Considerations

- The safety and acceptability of various dietary patterns, including the DASH and Mediterranean diets, with high intakes of fruit and vegetables must be determined on an individual basis in advanced stages of kidney disease, especially in regard to serum potassium control and adequacy of protein and energy intake.

- Individualized support and follow-up may be required to support patients in implementing and adhering to complex dietary changes.

Monitoring and Evaluation

Adherence to dietary patterns in clinical trials can be challenging. Engaging a process of self- monitoring against food group targets may assist with supporting adherence.

Future Research

- Establish the optimal method to support dietary change to implement dietary patterns into clinical trials with CKD.
- Conduct large-scale pragmatic clinical trials implementing Mediterranean, DASH, and/or dietary guideline–based dietary patterns in patients with CKD to determine the effect on clinical outcomes, including kidney disease progression, mortality, CVD, and patient-centered outcomes such as QoL measures.
- Evaluate the association of multiple dietary patterns with CKD progression and CVD and patient-centered outcomes in a large cohort with established CKD over a longer duration than currently available (ie, >10 years).

Guideline 4: Nutritional Supplementation

4.1 Statement on Oral, Enteral, and Intradialytic Parenteral Nutrition Supplementation

Oral Protein-Energy Supplementation

4.1.1 In adults with CKD 3-5D (2D) or post-transplantation (OPINION) at risk of or with protein-energy wasting, we suggest a minimum of a 3-month trial of oral nutritional supplements to improve nutritional status if dietary counseling alone does not achieve sufficient energy and protein intake to meet nutritional requirements.

Enteral Nutrition Supplementation

4.1.2 In adults with CKD 1-5D, with chronically inadequate intake and whose protein and energy requirements cannot be attained by dietary counselling and oral nutritional supplements, it is reasonable to consider a trial of enteral tube feeding (OPINION).

Total Parenteral Nutrition (TPN) and Intradialytic Parenteral Nutrition (IDPN) Protein-Energy Supplementation

4.1.3 In adults with CKD with protein-energy wasting, we suggest a trial of TPN for CKD 1-5 patients (2C) and IDPN for CKD 5D on MHD patients (2C), to improve and maintain nutritional status if nutritional requirements cannot be met with existing oral and enteral intake.

Rationale/Background

PEW is common among patients with CKD, especially those undergoing maintenance dialysis therapy,[218] and is associated with increased morbidity and mortality.[219] The cause of PEW in patients with CKD is complex and multifactorial and includes reduced energy and protein intake resulting from anorexia and dietary restrictions, inflammation, hypercatabolism, protein losses during dialysis, metabolic acidosis, uremic toxicity, and the presence of comorbid conditions.[218,219] As a result, patients with CKD may develop an imbalance between dietary intake and nutritional requirements. Many patients with CKD consume less protein and energy than their recommended intakes even when individualized dietary counseling is provided by a renal dietician.[220]

When dietary counseling alone proves insufficient to bridge the gap between protein-energy intake and target requirements in patients with CKD, provision of ONS is often the next appropriate step to prevent and treat PEW. Therefore, it is important to establish the effectiveness of ONS on nutritional status, clinical outcomes, and QoL in patients with CKD.

Although feeding through the gastrointestinal route should be the preferred choice of nutritional supplementation, feeding through the parenteral route (ie, total parenteral nutrition [TPN]) may be a safe and convenient approach for patients who cannot tolerate oral or enteral administration of nutrients.[218] In MHD patients, use of the HD access for TPN provides a significant advantage by eliminating the need for an additional permanent venous catheter placement. Because HD access is routinely used for the HD procedure, TPN can be conveniently administered during HD through the dialysis tubing. This type of TPN administration is called intradialytic parenteral nutrition (IDPN).

Detailed Justification

This evidence review included 15 clinical trials: 12 RCTs[221-231] and 3 NRCTs.[232-234] Most of the studies examined the effect of ONS in patients receiving MHD. However, Moretti et al[227] included both patients receiving MHD and PD, Gonzalez-Espinoza et al[225] and Teixido-Planas et al[228] studied patients receiving PD only, and Wu et al[231] studied patients with CKD stages 3-4. No studies were performed in patients with CKD with kidney allografts. Most of the studies examined the effect of oral protein-energy or protein-based ONS using commercial products. However, Allman et al[221] used a glucose-polymer ONS and Wu et al[231] used a nonprotein calorie ONS. Four studies used renal-specific protein-energy ONS.[224,226,233,234] A major drawback of the literature was the limited use of a placebo group, though most studies included a comparator group that was defined as participants not receiving ONS or receiving only nutritional counseling. Study durations ranged from 12 weeks to 13.5 months. Seven of the RCTs included participants with

some level of malnutrition at baseline.[221-226,230,235] In contrast, 5 studies did not actively enroll malnourished patients.[226-229,231] Of the NRCTs, Sezer et al[234] enrolled malnourished patients as defined by serum albumin level or weight loss, Cheu et al[232] enrolled patients with hypoalbuminemia, and Scott et al[233] did not actively recruit patients with malnutrition.

Mortality, Hospitalizations, and QoL. One NRCT examined the effect of ONS on mortality in 276 patients receiving MHD who were treated with ONS for a low serum albumin level versus 194 similar patients who refused ONS or for whom treatment was deemed inappropriate.[232] No difference in mortality (HR, 0.70 [95% CI, 0.36-1.35]) was noted over a median duration of 13.5 months.

Two RCTs[227,230] and 1 NRCT[232] evaluated the effect of ONS on hospitalization over a period of 6 to 13.5 months in patients receiving MHD or PD. A pooled analysis of the 2 RCTs[227,232] found no significant difference in the odds of hospitalization by group assignment, but an NRCT[232] reported a 34% reduction in risk of hospitalization (HR, 0.66 [95% CI, 0.50-0.86]) by 12 months in patients receiving ONS compared with controls.

Three studies (2 RCTs[223,224] and 1 NRCT[233]), each of 3 months' duration, examined the effect of ONS on QoL measures in patients receiving MHD. One RCT[223] and 1 NRCT[233] reported that patients receiving general[223] or renal-specific[233] protein-energy ONS had higher QoL scores in the domains of physical functioning[223,233] and bodily pain[223] compared to receiving dietary advice only[223] or no supplementation,[233] but another RCT[224] reported that renal-specific protein-energy ONS did not influence QoL scores in any domain. A pooled analysis of the 2 RCTs[223,233] found that ONS did not significantly influence bodily pain, physical functioning, or general health QoL domain scores.

CKD Progression. An RCT[231] conducted for 24 weeks examined the effect of an energy-based ONS on progression of CKD in 109 patients with CKD 3-4 who were following an LPD. Although no difference in serum creatinine levels or eGFRs was observed between ONS and controls, there was a comparative reduction in proteinuria in the ONS arm ($P < 0.05$).

Composite Nutritional Scores and Biochemical Markers of Nutritional Status. A 3-month RCT in 18 patients receiving MHD examined the effect of a food-based ONS on SGA scores.[223] The authors describe a significantly greater SGA score improvement in patients receiving ONS compared with patients receiving nutritional guidance only. One NRCT found that ONS over a 6-month period did not influence the MIS as compared with dietary advice.[234]

Fifteen studies (12 RCTs[221-225,227-231,236] and 3 NRCTs[232-234]) examined the effect of ONS on serum albumin levels in patients with CKD 3-5D. These included 11 in patients receiving MHD of 3 to 13.5 months' duration, 1 RCT[227] in patients receiving MHD and PD of 6 months' duration, 2 RCTs[225,228] in patients receiving PD of 6 months' duration, and 1[231] in patients with CKD 3-4 of 24 weeks' duration. Overall, the literature suggested that protein-energy ONS modestly improved serum albumin levels, though the results should be interpreted with caution. A pooled analysis of 11 studies[221-228,231,233,234] that included patients with CKD 3-5D found that ONS modestly improved serum albumin levels as compared with controls (mean difference, 0.121 [95% CI, 0.006-0.236] g/dL). However, a subgroup analysis found the effect to be significant only when using protein-energy ONS[223,224,226,228,233,234] (mean difference, 0.16 [95% CI, 0.08-0.24] g/dL) and not energy[221,231] or protein-based[222,225,227] supplements. Heterogeneity of results in the pooled analysis was high ($I^2 = 68.3\%$; $P < 0.001$) so results should be interpreted cautiously.

One RCT in 86 patients receiving MHD reported that ONS did not influence serum prealbumin levels as compared with dietary advice.[224] Two RCTs of 3 to 6 months' duration in patients receiving MHD reported conflicting effects of ONS on total-protein levels, perhaps related to the type of ONS.[2211,222] The first study of 30 patients reported a positive effect on total-protein levels using an amino acid–based ONS,[222] while a second of 21 patients found no effect of a 6-month energy-based ONS intervention.[221] Two studies (an RCT[221] and an NRCT[233]) in patients receiving MHD of 3 to 6 months' duration found no effect of ONS on serum transferrin levels, either individually or in a pooled analysis.

Anthropometric Measurements. The effect of ONS on anthropometric indices varied in large part according to the type of ONS used, with the greatest effects being seen in 1 study[221] that used an energy-based ONS.

Body mass index. Seven studies (6 RCTs[221-226] and 1 NRCT[234]) evaluated the effect of ONS on BMI during a 3- to 6-month period. Six of the studies were conducted in patients receiving MHD[221-224,226,234] and 1 in patients receiving PD.[225] A pooled analysis demonstrated no overall effect of ONS on BMI, though the study using an energy-based ONS noted an increase in BMI.[221] Overall, the heterogeneity was moderate ($I^2 = 49.8\%$; $P = 0.06$).

Body weight. Six studies (5 RCTs and 1 NRCT) investigated the effect of ONS on body weight over 3 to 6 months in patients receiving MHD[221,222,229,233] or PD[228] and patients with CKD 3-4.[231] Overall, ONS was linked to increased body weight but mainly in patients receiving MHD consuming an energy-based supplement. However, 1 RCT in patients receiving PD that used a protein-based ONS reported increased body weight.[228] A pooled analysis of all 6 studies[221,222,228,229,231,233] found higher body weight in the ONS group compared with the control arm (mean, 2.77 [95% CI, 1.19-4.36] kg) in patients with CKD 3-5D. However, the difference was mainly driven by energy-based ONS in patients on MHD.

Dialysis target weight. Four studies (3 RCTs[223,224,235] and 1 NRCT[234]) in patients receiving MHD[223,224,234,235] examined the effect of ONS on dialysis target weight over a 3- to 6-month period. Overall, no effect of ONS on target weight was observed, though 1 NRCT[234] reported an increase in target weight using a renal-specific protein-energy ONS,[234] as did 1 RCT[236] using a protein-based ONS. A pooled analysis of 3 studies[223,224,234] found no overall effect. Hiroshige et al[236] reported results in a figure and could not be included in pooled analysis.

LBM/FFM/muscle mass. Seven trials (6 RCTs[221-223,228,229,236] and 1 NRCT[234]) in patients receiving MHD[221-223,229,234,236] or PD[228] studied the effect of ONS on markers of lean mass over 3 to 6 months. Overall, ONS increased LBM or FFM only in patients receiving MHD who received an energy-based ONS. In patients receiving MHD, the effect of protein-based ONS on LBM was mixed. In a pooled analysis of 6 studies,[221-223,228,229,234] ONS was associated with a significant increase in LBM or FFM (mean difference, 1.18 [95% CI, 0.16-2.20] kg) compared with the control arm, but a subgroup analysis found the effect to be significant only in patients receiving MHD using energy-based ONS.

Body fat. Seven studies (6 RCTs[221-223,226,229,238] and 1 NRCT[234]) in patients receiving MHD evaluated the effect of ONS on BF over a period of 3 to 6 months. A pooled analysis of 6 studies[221-223,226,228,234] reported no overall effect of ONS on body FM, though subgroup analyses demonstrated that energy-[221] and protein-energy–based[223,226,234] ONS significantly increased body FM compared with controls with protein-based ONS having no effect.

Skinfold measurements. Five studies (4 RCTs[221,223,225,228] and 1 NRCT[234]) in patients with CKD receiving MHD[221,223,224] or PD[225,228] examined the effect of ONS on skinfold measurements over a 3- to 6-month period. A pooled analysis of 4 studies[221,225,228,234] reported that ONS significantly increased skinfold measurements (mean difference, 3.91 [95% CI, 0.93-6.90] mm) compared with dietary counseling or no supplementation, but this effect was significant only in patients receiving MHD using energy-based ONS.

Arm or muscle circumference. Four RCTs in patients receiving MHD[221,223] or PD[225,228] evaluated the effect of ONS on arm or muscle circumference over a 3- to 6-month period. None of the studies showed any effect.

Dietary Intake. Protein. Ten studies (9 RCTs[221-225,227,228,231,236] and 1 NRCT[234]) examined the effect of ONS on protein intake as estimated using nPCR/nPNA, 24-hour dietary recall, or multiple-day food records with study durations of 3 to 6 months. Overall, protein-based supplements (amino acids[222] or branched chain amino acids[236]) increased reported protein intake and nPCR in patients receiving MHD and PD, but energy[221,231] or protein-energy supplements did not influence either marker in patients with CKD 3-5D. A pooled analysis of 7 studies[222-225,227,228,234] found that ONS significantly increased nPCR in patients receiving dialysis (SMD, 0.29 [95% CI, 0.04-0.53]), suggesting a potentially clinically relevant effect. However, a subgroup analysis found the effect to be significant only in persons receiving protein-based[222,225,227] but not protein-energy–based ONS.[223,224,228,234] Similar results were noted in a pooled analysis of 3 studies[224,225,228] examining the effects of ONS on reported protein intake in which ONS increased reported protein intake in only 1 study that supplemented egg albumin protein.[225]

Energy. Six RCTs[221,224-226,231,236] with study durations of 3 to 6 months examined the effect of ONS on energy intake in patients receiving MHD,[221,224,226,236] receiving PD,[225] and with CKD stages 3-4.[231] Overall, ONS increased energy intake, though the effect was limited to patients on MHD receiving renal-specific protein-energy ONS. Four of 5 studies in patients receiving dialysis reported that ONS increased energy intake.[221,224-226,236] However, a subgroup analysis found the effect to be significant only for patients on MHD receiving protein-energy ONS,[224,226] but not receiving protein-[225] or energy-based[231] ONS alone. The only study in patients with CKD 3-4 found no improvement in energy intake using a nonprotein calorie ONS.[231]

Phosphorus and calcium. An RCT of 3 months' duration in patients receiving MHD found no effect on phosphorus or calcium intake.[224]

Other biochemical markers (CRP, anemia indices, electrolyte and lipid levels). Seven studies (6 RCTs[222-224,226,229,231] and 1 NRCT[234]) of 3 to 6 months' duration in patients receiving MHD[222-224,226,229,234] and with CKD 3-4[232] found no effect of ONS on CRP levels. Seven studies (5 RCTs[221-223,225,229] and 2 NRCTs[223,234]) in patients receiving MHD[221-223,229,234] or PD[225] examined the effect of ONS on markers of anemia over a 3- to 6-month period. Overall, ONS had no effect on these markers. Five studies (4 RCTs[223,225,229,231] and 1 NRCT[233]) examined the effect of ONS on serum calcium, phosphate, and potassium levels over 3 to 6 months. Three of the trials were in patients receiving MHD,[223,229,233] 1 was in patients receiving PD,[225] and 1 was in patients with CKD 3-4.[231] None of the studies found any effect on ONS on these electrolyte levels. Five studies (4 RCTs[221,225,226,231] and 1 NRCT[234]) examined the effect of ONS on plasma lipid levels over 3 to 6 months. Findings from pooled analyses demonstrated no overall effect of ONS on lipid levels.

Intradialytic parenteral nutrition. This evidence review encompassed 3 studies that examined the effects of IDPN on nutritional status and clinical outcomes in MHD patients, including 1 NRCT[235] and 2 RCTs.[237,238] In all these studies participants were malnourished. In Hiroshige et al,[235] participants in the intervention group received dietary counseling from an RDN and an IDPN infusion of 200 mL of 50% dextrose, 200 mL of 7.1% EAAs, and 200 mL of 20% lipid emulsion, providing

2,400 kcal and 42.3 g of amino acid for 1 year. Results were compared with a group receiving dietary counseling only (control group). In Cano et al,[237] all participants were given ONS providing 25 g of protein per day and 500 kcal per day for 1 year, and the intervention group additionally received IDPN to meet target ranges of 30 to 35 kcal per day and 1.2 g protein/kg per day and included a standard lipid emulsion of 50% glucose, 50% nonprotein energy supply, and a standard amino acid solution.[237] In Toigo et al,[238] participants in the intervention group were given EAAs via intravenous (IV) formula for 6 months. Results were compared with participants in the intervention group, in which they received an isonitrogenous standard formula containing both nonessential amino acids (NEAAs) and EAAs for 6 months. Both groups simultaneously received 500 mL of 10% glucose. Participants were followed up for an additional 6 months.

Mortality and hospitalization. Only 1 study examined and found no effect of IDPN on mortality and hospitalization. In Cano et al,[237] statistical comparisons were not provided but the authors described no significant differences in mortality or hospitalization events between the ONS-only and IDPN-with-ONS groups.

Anthropometric measurements. Three studies examined the effect of IDPN therapy on anthropometric measurements in malnourished MHD patients.[235,237,238] The findings from these studies indicated that IDPN, in combination with dietary counseling[235] or ONS,[237] increased BMI,[235,237] dry body weight,[235] skinfold measurements,[235] and MAMC[235] compared with dietary counseling only. However, similar improvement in BMI was observed when adequate and comparable protein and energy were given to patients receiving ONS only.[237] Compared with a standard IDPN formulation of both EAAs and NEAAs, an IDPN formulation with EAAs did not affect percent of desirable body weight, skinfold measurements, or arm muscle area.

Laboratory markers of nutritional status (albumin, prealbumin, and transferrin. Three studies[235,237,238] examined the effect of IDPN on laboratory markers of nutritional status in malnourished MHD patients. The results from these studies concluded that IDPN in conjunction with dietary counseling[235] or ONS[237] increased albumin,[235,237] prealbumin,[237] or transferrin levels,[235] but similar improvements in albumin and prealbumin levels were observed when adequate and comparable protein and energy were provided to patients receiving ONS only.[237] Compared with a standard IDPN formulation of both EAAs and NEAAs, an IDPN formulation with EAAs only did not affect albumin and transferrin levels.[238]

Other laboratory markers (inflammation [CRP], hemoglobin, lipid profile). One study evaluated and found no effect of IDPN on inflammation in malnourished HD patients. Cano et al[237] reported no change in CRP levels in either the ONS-only or IDPN-plus-ONS groups, although data were not provided.

One study examined and found no effect of IDPN therapy with EAAs only versus standard IDPN formulation with both EAAs and NEAAs on hemoglobin levels in malnourished MHD patients after 6 months.[238]

Two studies examined the effect of IDPN on lipid profile. The results from these studies showed that combining IDPN with dietary counseling[235] or ONS[237] did not affect TC[235] or TG levels.[235,237]

Dietary intake (energy and protein intake). Two studies[235,237] examined the effect of IDPN on dietary intake in malnourished MHD patients. The findings from these studies showed inconclusive effects of IDPN on dietary energy and protein intakes.

Special Discussions

A complete nutritional assessment should be performed before considering ONS and should be repeated at regular intervals during the supplementation period.

IDPN therapy does not alter a patient's eating behavior and it does not encourage healthy eating habits. MHD frequency and duration may not provide sufficient time for IDPN. Because IDPN is usually given for 4 hours during dialysis thrice weekly, it may not provide sufficient calories and protein to meet long-term nutritional requirements. TPN is usually administered on a daily basis. The potential of IDPN to meet target protein and energy requirements in MHD patients mainly depends on the actual difference between these targets and spontaneous dietary intakes through ONS or dietary counseling. If the difference can be met by the IDPN regimen, the work group thought that IDPN should be considered in conjunction with ONS or dietary counseling.

This evidence review finds that IDPN offers no additional benefit over ONS. It was postulated that markers of nutritional status improved irrespective of the route of nutrient administration as long as dietary protein and energy targets are met.[237] However, a direct comparison between IDPN and ONS is lacking; this would only imply that ONS is equally effective as IDPN when oral intake is possible. Because ONS was included in the intervention arm as well, the inferiority of IDPN over ONS cannot be evaluated.

A recently published RCT investigating the effect of IDPN therapy on levels of prealbumin and other biochemical and clinical nutritional markers in malnourished MHD patients[239] demonstrated that IDPN therapy increased prealbumin levels and was superior to nutritional counseling after 16 weeks. This study was not included in this evidence review because the date of publication was beyond the cutoff time for study inclusion. In this study, patients randomly assigned to the intervention group received standardized nutritional counseling plus IDPN 3 times weekly for 16 weeks. There were no within-group changes and between-group differences at week 16 in other clinical and biochemical nutritional markers (BMI, albumin, transferrin, PCR, phase angle alpha, and SGA scores).

Implementation Considerations

- ONS should be prescribed 2 to 3 times daily and patients should be advised to take ONS preferably 1 hour after meals rather than as a meal replacement to maximize benefit.[218]
- Monitored in-center provision of high-protein meals or ONS during MHD may be a useful strategy to increase total protein and energy intake.[240] Many of the perceived negative effects of intradialytic feeding such as postprandial hypotension, aspiration risk, infection control, and hygiene, as well as diabetes and phosphorus control, can be avoided with careful monitoring.
- ONS prescription should take into account patient preference. The acceptability of ONS in terms of appearance, smell, taste, texture, and type of preparation (milkshake type, juice type, pudding type, protein/energy bar, or fortification powder) should be carefully considered. The tolerability of ONS should also be carefully monitored because some patients may develop gastrointestinal symptoms with ONS.
- Energy-dense and low-electrolyte renal-specific ONS may be necessary to increase protein and energy intake and avoid fluid overload and electrolyte derangements.
- Concern about infectious complications (particularly when infused through HD catheters) and the high cost of IDPN are the greatest barriers for regular use of IDPN.
- MHD patients meeting all of the following 3 criteria may benefit from IDPN therapy:

1) evidence of PEW and inadequate dietary protein and/or energy intake; 2) inability to administer or tolerate adequate oral nutrition, including food supplements or enteral feeding; and 3) protein and energy requirements can be met when IDPN is used in conjunction with oral intake or enteral feeding.

- IDPN therapy should not be considered as a long-term approach of nutritional support. It should be discontinued and ONS should be attempted as soon as improvements in nutritional status are observed and patients are capable of using the oral or enteral route. Specific criteria for improvement should be patient specific.
- If IDPN therapy in conjunction with oral intake does not achieve the nutritional requirements of the patient or the gastrointestinal tract is impaired, TPN given on a daily basis should be considered.

Monitoring and Evaluation

Gastrointestinal side effects can influence adherence to ONS,[241] and extended periods of monotonous supplementation can lead to flavor and taste fatigue, as well as nonadherence to the prescribed ONS. Therefore, regular monitoring and evaluation during the supplementation period are crucial and adjustments to the ONS prescription may be necessary to improve adherence and optimize effectiveness. Nutritional status should be monitored regularly throughout the supplementation period to evaluate the effectiveness of ONS.

Ongoing monitoring and evaluation of nutritional status during IDPN therapy is necessary. Serum glucose, BP, and volume status should be closely monitored during and after MHD. In the case of new or additional insulin requirement, the use of insulin analogues should be chosen individually tailored with consultation with an endocrinologist to avoid postdialytic hypoglycemia. Ultrafiltration rate should be adjusted accordingly to remove the extra fluid provided by IDPN.

Future Research

- Adequately powered RCTs are necessary to evaluate the impact of ONS on long-term survival, hospitalization, and QoL in patients throughout the range of CKD. An ongoing study will help address this unmet need (NCT02933151).
- In addition, further research is needed to define the optimal composition and scheduling of ONS, as well as define the patient subgroups most likely to benefit.
- Adequately powered and long-term clinical trials comparing the independent effects of IDPN and ONS on nutritional status, morbidity, mortality, and QoL are required.

4.2 Statement on Nutrition Supplementation – Dialysate

Dialysate Protein-Energy Supplementation

4.2.1 In adults with CKD 5D on PD with protein-energy wasting, we suggest not substituting conventional dextrose dialysate with amino acid dialysate as a general strategy to improve nutritional status, although it is reasonable to consider a trial of amino acid dialysate to improve and maintain nutritional status if nutritional requirements cannot be met with existing oral and enteral intake (*OPINION*).

Rationale/Background

PEW is common among patients receiving maintenance PD and is associated with increased morbidity and mortality.[242] Inflammation, acidosis, insulin resistance, insufficient dietary intakes of protein and energy as a result of anorexia, and peritoneal losses of proteins and amino acids contribute to PEW.[243] Intraperitoneal amino acid (IPAA) supplementation was introduced to compensate for low protein intake and protein losses. Substituting amino acids for glucose in PD solutions should increase the amino acid intake and decrease the net amino acid losses of the patient, thereby increasing the net intake of protein precursors.[244] IPAA supplementation may also reduce the infused carbohydrate load, thereby reducing the risk for hyperglycemia and the tendency for hypertriglyceridemia.[244]

Detailed Justification

This evidence review included 3 studies that examined the effect of IPAA supplementation on nutritional status in malnourished PD patients, including 2 RCTs[245,246] and 1 nonrandomized crossover trial.[247] In the 2 RCTs,[245,246] results were compared between those receiving traditional 1.5% dextrose dialysate versus those who replaced 1 to 2 daily exchanges of 1.5% dextrose dialysate with 1.1% amino acid dialysate. Study durations ranged from 3 months[245] to 3 years.[246] In the nonrandomized crossover trial, Misra et al[247] used the same study design in which the participants were assigned to each exposure (amino acid dialysate for 1 exchange per day or dextrose dialysate only) for 6 months. In all these studies, PD patients demonstrated some level of malnutrition or PEW. In Misra et al,[247] most patients presented with hypoalbuminemia; in Li et al,[246] all patients were malnourished; and in Jones et al,[245] participants were mildly to moderately malnourished.

Anthropometric Measurements and Laboratory Measures of Nutritional Status. Two RCTs examined the effect of IPAA therapy on anthropometric measurements in malnourished PD patients.[245,246] MAMC, TSF measurements, and FM were maintained at 3 months[245,246] and 3 years[246] in both the IPAA and dextrose dialysate groups. The results from these studies indicated that substituting amino acid dialysate for dextrose dialysate had no effect on anthropometric measurements.

Two RCTs[245,246] and 1 nonrandomized crossover trial[247] examined the effect of IPAA supplementation on serum albumin, prealbumin, and transferrin levels in malnourished PD patients. One RCT evaluated the effect of IPAA supplementation on total-protein level.[245] The findings from these studies concluded that substituting amino acid dialysate for dextrose dialysate in malnourished PD patients did not affect serum albumin, prealbumin, transferrin, and total-protein levels compared with those receiving dextrose dialysate only.

Electrolyte Levels (Phosphorus/Phosphate, Bicarbonate, and Potassium Levels). One RCT[245] and 1 nonrandomized crossover trial[247] examined the effect of IPAA supplementation on electrolyte levels in malnourished PD patients. The findings from these studies suggested that substituting amino acid dialysate for dextrose dialysate in malnourished PD patients decreased their phosphate and bicarbonate levels, but the effect on potassium levels was unclear.

Jones et al[245] showed that serum potassium and phosphate levels decreased significantly in the IPAA group and levels were different between groups at 3 months ($P < 0.05$ for each measure). In contrast, Misra et al[247] showed no within-group changes in potassium, phosphate, or bicarbonate levels in either the IPAA or dextrose dialysate groups. However, when averaged across time, patients receiving IPAA therapy had lower mean phosphate ($P = 0.018$) and bicarbonate levels ($P = 0.002$). In a secondary analysis, the IPAA groups in Jones et al[245] and Misra et al[247] demonstrated a mean difference of −0.50 (95% CI, −0.87 to −0.13) mEq/L in potassium and −1.10 (95% CI, −1.43 to −0.77) mmol/L in bicarbonate levels, respectively, when compared with the dextrose dialysate group. In pooled analysis, there was a mean difference of −0.55 (95% CI, −0.70 to −0.41) mg/dL in phosphate levels in the IPAA group compared with the dextrose dialysate group.

Dietary Intake (Protein and Energy Intake). One RCT examined the effect of IPAA supplementation on total and oral protein and energy intakes in malnourished PD patients.[246] Compared with baseline intake levels, total-protein intake increased in the IPAA group beginning at 6 months and continuing until 3 years ($P = 0.002$ for each measure), but there was no significant difference between the IPAA and dextrose dialysate groups. Compared with baseline intake, total energy intake increased in the IPAA group at 6 months ($P < 0.001$) and 3 years ($P = 0.002$), but it decreased in the dextrose dialysate group ($P < 0.001$), though there were no significant differences between groups. Similar results were observed for oral and peritoneal energy intake only. nPNA (nPCR) increased in the IPAA group at 3 years, but decreased in the dextrose dialysate group, and values were significantly different between groups at 3 years ($P < 0.001$).

Special Discussions

The recommendation statement is based on 2 RCTs and 1 nonrandomized crossover trial. The included studies assessed only intermediate nutrition-related outcome measures, including dietary intake (total energy and protein intakes and oral energy intake); laboratory markers of nutritional status (serum albumin, prealbumin, transferrin, and total-protein levels); and anthropometry (MAMC, TSF, and FM). The effects of substituting amino acid dialysate for conventional dextrose dialysate on patient survival, hospitalization, other clinical outcomes, and QoL have not been adequately evaluated. The long-term effect of IPAA therapy remains unclear.

Implementation Considerations

- IPAA supplementation decreased bicarbonate levels[247] and was associated with mild acidosis in some patients,[243,244] though the condition is readily treatable.
- In diabetic patients receiving PD with uncontrolled hyperglycemia, substituting amino acid for glucose in PD solutions may serve as an immediate strategy for glycemic control.
- IPAA should only be used if spontaneous protein and energy intakes in conjunction with IPAA are able to meet the required protein and energy targets. Otherwise, daily TPN or partial parenteral nutrition should be considered.

Future Research

Adequately powered long-term RCTs are required to evaluate the effects of IPAA therapy on nutritional status, patient survival, hospitalization, other clinical outcomes, and QoL in PD patients at risk or with PEW.

4.3 Statements on Long Chain Omega-3 Polyunsaturated Fatty Acids (LC n-3 PUFA)

LC n-3 PUFA Nutritional Supplements for Mortality and Cardiovascular Disease

4.3.1 In adults with CKD 5D on MHD or post-transplantation, we suggest not routinely prescribing LC n-3 PUFA, including those derived from fish or flaxseed and other oils, to lower risk of mortality (2C) or cardiovascular events (2B).

4.3.2 In adults with CKD 5D on PD, it is reasonable not to routinely prescribe LC n-3 PUFA, including those derived from fish or flaxseed and other oils, to lower risk of mortality or cardiovascular events (OPINION).

LC n-3 PUFA Nutritional Supplements for Lipid Profile

4.3.3 In adults with CKD 5D on MHD, we suggest that 1.3-4 g/d LC n-3 PUFA may be prescribed to reduce triglycerides and LDL cholesterol (2C) and raise HDL levels (2D).

4.3.4 In adults with CKD 5D on PD, it is reasonable to consider prescribing 1.3-4 g/d LC n-3 PUFA to improve the lipid profile (OPINION).

4.3.5 In adults with CKD 3-5, we suggest prescribing ~ 2g/d LC n-3 PUFA to lower serum triglyceride levels (2C).

LC n-3 PUFA Nutritional Supplements for Arteriovenous (AV) Graft and Fistula Patency

4.3.6 In adults with CKD 5D on MHD, we suggest not routinely prescribing fish oil to improve primary patency rates in patients with AV grafts (2B) or fistulas (2A).

LC n-3 PUFA Nutritional Supplements for Kidney Allograft Survival

4.3.7 In adults with CKD posttransplantation adults, we suggest not routinely prescribing LC n-3 PUFA to reduce the number of rejection episodes or improve graft survival (2D).

Rationale/Background

Long chain omega-3 polyunsaturated fatty acids (LC n-3 PUFAs) include eicosapentaenoic (EPA),docosapentaenoic and docosohexaenoic acids (DHA), all of which are obtained primarily from dietary sources such as cold-water fish (ie, fish oil) or linoleic acid, which is derived from flaxseed or certain other vegetable oils. In recent decades, LC n-3 PUFA have demonstrated protean biological effects on eicosanoid production, cell membrane physiology, signal transduction, metabolism, apoptosis, oxidation, and inflammation. Accordingly, they have been tested in a variety of medical conditions. Of particular interest has been their putative effects on cardiac membrane stabilization, leading to possible reduction of malignant arrhythmias and sudden cardiac death. Patients with CKD have been documented to have some of the lowest blood levels of LC n-3 PUFAs in the literature,[248] thus making them potentially very suitable candidates for supplementation interventions. LC n-3 PUFA supplementation has also been studied as possible therapy for a number of conditions commonly observed in patients with CKD, including dyslipidemia, HD access failure, CVD, and death, as well as for their immunomodulatory effects in patients with kidney allografts.

Detailed Justification

Thirty-five RCTs studied the impact of LC n-3 PUFA supplementation on a variety of health biomarkers and outcomes in adults with CKD 2-5D and kidney transplant. Twenty-four of these studies included patients receiving MHD as the target population, though 1 study also included patients receiving PD.[249] Nearly all the interventions used fish oil as the main source of LC n-3 PUFAs, but flaxseed oil[249] and ground flaxseed[250] were also studied. Study length (4 weeks to 2 years) and size (12-567 participants) varied widely. The heterogeneity of this literature in terms of the absolute and relative amounts of n-3 PUFAs supplemented, type of placebo used, and study duration makes it more difficult to provide conclusive evidence for or against the use of LC n-3 PUFAs as a treatment option.

All-Cause Mortality and Cardiovascular Events. Despite the putative overall benefits of LC n-3 PUFAs and the elevated risk for death in patients with CKD, 3 RCTs demonstrated no improvement in mortality with supplementation. However, the studies were heterogeneous in terms of study population (1 in patients with MHD,[251] 2 in patients with CKD with kidney allografts[252,253]), the dose of LC n-3 PUFAs (1.44 g/d of EPA + 0.96 g/d of DHA[253]; 1.62 g/d of EPA + 1.08 g/d of DHA[252]; 0.77 g/d of EPA + 0.64 g/d of DHA) [251]; and study duration (1-2 years), with the combined study population being fairly modest in size (n = 264).

Two well-designed but modestly sized (combined n = 351) RCTs in patients receiving MHD reported mixed results on the effect of LC n-3 PUFA supplementation on cardiovascular events.[251,254] Lok et al[254] reported that 4 g/d of fish oil (1.6 g/d of EPA and 0.8 g/d of DHA) for 12 months as compared with corn oil–based placebo significantly lowered the cardiovascular event rate (relative risk, 0.41 [95% CI, 0.20-0.85]; P = 0.02) and improved cardiovascular event–free survival (relative risk, 0.43 [95% CI, 0.19-0.96]; P = 0.04) but did not influence the number of patients with 1 or more event (relative risk, 0.78 [95% CI, 0.55-1.09]; P = 0.15). All were secondary outcomes in a trial designed to study MHD vascular access.

In a secondary prevention trial, Svensson et al[251] reported that 1.7 g/d of fish oil (0.77 g/d of EPA and 0.64 g/d of DHA) for 2 years had no effect on the primary combined end point of cardiovascular events or death as compared with olive oil–based placebo, but improved the secondary end points of myocardial infarctions (MIs; relative risk, 0.30 [95% CI, 0.10-0.92]; P = 0.036) and major coronary events (relative risk, 0.40 [95% CI, 0.17-0.97]; P = 0.043).

HD Access. Previous studies have suggested that LC n-3 PUFAs, in particular those derived from fish oil, have antiproliferative, antioxidant, and vasodilatory effects. This was the impetus for the 4 RCTs that examined whether LC n-3 PUFA supplementation could improve the patency of arteriovenous (AV) grafts or AV fistulas in patients receiving MHD. Of the 3 RCTs[254-256] studying AV graft survival, the 2 smallest (using 0.96-1.76 g/d of EPA and 0.6-0.96 g/d of DHA) had mixed results, with 1 showing no benefit at 6 months (n = 29)[255] and the other (n = 24) reporting higher primary patency rates compared with the placebo group at 1 year (P < 0.03).[256] The third and much larger trial (n = 201) noted a borderline statistically significant improvement in the loss of native patency at 1 year (relative risk, 0.78 [95% CI, 0.60-1.03; P = 0.064) after providing 1.6 g/d of EPA and 0.8 g/d of DHA.[254] Although the overall results are not clearly positive, they suggest a possible beneficial effect. However, by far the largest study in this field (n = 567), which examined patency rates in new AV fistulas at 12 months,[257] reported that fish oil, 4 g/d (1.84 g/d of EPA and 1.52 g/d of DHA), had no benefit.

Rejection Episodes and Graft Survival in Kidney Allografts. Although LC n-3 PUFAs have been reported to mediate the immunologic response, they have not yet demonstrated any benefits on kidney transplants. Two RCTs[253,258] with differing study interventions (2.4 g/d of EPA + DHA for 1 year, 9 vs 18 g/d of EPA for 26 weeks) found no benefit on rejection episodes or a relationship between supplementation dose and rejection episodes.[258] Supplementation using approximately 2.5 g/d of EPA plus DHA also did not influence graft survival.[252,253]

GFR and CKD Progression. Based on 6 RCTs with widely differing study designs and populations (CKD stage 3, MHD, and kidney allografts),[252,253,258-263] fish oil supplementation was not found to influence eGFR or measured GFR. In the study by Guebre Egziabher et al,[260] participants received 1.8 g of n-3 fatty acids, but the authors do not document EPA or DHA amounts. In the study by Bennett et al,[258] participants received "9 or 18g/d EPA capsules." In the remaining studies, EPA dose ranged from 0.46 to 1.62 g/d, and DHA dose ranged from 0.25 to 1.08 g/d.

Similarly, fish oil supplementation for 8 to 12 weeks did not influence serum creatinine levels in 3 studies of CKD patients not receiving dialysis who used placebo or non–placebo-based control groups. In the study by Guebre Egziabher et al,[260] participants received 1.8 g/d of n-3 fatty acids, but authors do not describe EPA or DHA amounts. In the remaining studies, EPA amounts ranged from 0.69 to 1.44 g/d, and DHA amounts ranged from 0.25 to 0.96 g/d.[259,260,263]

Blood Pressure. Five RCTs examined the effect of LC n-3 PUFA supplementation on BP, 2 in CKD patients not receiving dialysis (no stage reported),[261,262] 2 in patients receiving MHD,[254,263] and 1 in patients with CKD with kidney allografts.[258] The results were mixed. In CKD patients not receiving dialysis, Svensson et al[262] reported that fish oil (0.96 g/d of DHA and 1.44 g/d of EPA) for 8 weeks did not affect BP, whereas Mori et al[261] found that fish oil (0.38 g/d of DHA and 0.46 g/d of EPA) for 8 weeks lowered both SBP (mean ± standard error of the mean, −3.3±0.7 mm Hg) and DBP (−2.9±0.5 mm Hg (P < 0.0001 for each change). A pooled analysis of these 2 trials did not find an overall beneficial effect. In patients receiving MHD, Lok et al[254] reported an improvement in SBP in patients receiving MHD with fish oil (0.8 g/d of DHA and 1.6 g/d of EPA) for 1 year (mean difference, −8.10 [95% CI, −15.4 to −0.85]; P = 0.014) and a reduction in the number of BP medications, but no effect on DBP. In contrast, Khajehdehi et al[263] found no effect on BP of 1.5 g/d of fish oil (DHA and EPA content not reported) as compared to placebo for 2 months. Data from these 2 trials could not be pooled. Bennett et al[258] randomly assigned patients with CKD with kidney allografts and reported no benefit of "9 or 18 g EPA capsules" per day versus placebo for 26 weeks on SBP but noted a reduction in DBP in both EPA arms (P < 0.05 for each) only.

Lipid Profiles. Nineteen separate RCTs (though 1 without a true control group[264]) addressed the impact of LC n-3 PUFA supplementation on lipid levels. Thirteen studied patients receiving MHD[249,250,255,265-273] (with 1 study also including patients receiving PD[186]), 4 studied patients with CKD 2-5,[192,193,206,207] and 2 studied patients with CKD with kidney allografts.[257,274] The studies ranged greatly in terms of type of supplement (17 with fish oil and 2 with flaxseed oil or ground flaxseed [2 g/d of oil in Lemos et al[249] and 40 g/d of seed in Khalatbari et al[250]]) and duration (3-6 months). Additionally, amount and reporting of dosing were inconsistent. Studies reporting the amount of LC n-3 PUFA doses to be from 0.42 to 1.8 g/d of EPA and 0.25 to 0.82 g/d of DHA. The specific amounts of EPA and DHA used were not clear in several studies.[258,260,263,266,271,725]

Triglycerides. Eighteen RCTs studied the impact of LC n-3 PUFA on serum TG levels. Seven of the 13 trials studying patients with MHD found no effect[249,255,265,266,269,270,272] and 6 reported a reduction in levels.[249,250,263,268,271,273] In a pooled analysis of 12 of these studies, LC n-3 PUFA supplementation lowered TG levels by an average of −33.78 (95% CI, −63.21 to −4.36) mg/dL as compared with placebo/controls, though heterogeneity was high (I^2 = 92.36%; P < 0.001). Although

outcomes did not appear to be related to study quality or duration, TG lowering tended to be associated with using lower doses of LC n-3 PUFAs (0.42-0.96 g/d of EPA and 0.24-0.6 g/d of DHA), flaxseed oil (2 g/d), or ground flaxseed (40 g/d), a counterintuitive finding. Interestingly, positive results were more consistent in CKD patients not receiving dialysis,[259,261,262,264] in whom fish oil supplementation (1.8 g/d total or 0.46-1.44 g/d of EPA with 0.25-0.96 g/d of DHA) for 8 to 12 weeks consistently lowered TG levels.

Total cholesterol. The literature did not suggest a beneficial effect of LC n-3 PUFA supplementation on TC levels. Eleven of 13 studies in patients receiving MHD reported no effect (0.42-1.8 g of EPA and 0.24-1.14 g of DHA per day for 4 weeks to 6 months),[249,255,263,265,266,268-273] while the 2 studies supplementing with flaxseed oil (2 g/d for 120 days)[249] or ground flaxseed (40 g/d for 8 weeks)[250] noted a significant reduction in TC levels (though 1 study did not compare differences between groups[250]). A pooled analysis of all 13 studies did not find any effect on mean TC level but noted a high level of heterogeneity in the data (I^2 = 95.77%; $P < 0.001$). Three of 4 supplementation studies in CKD patients not receiving dialysis reported no effect on TC levels,[251,261,264] whereas the fourth demonstrated a reduction at 3 months ($P < 0.05$) with no difference between arms.[259] Results could not be pooled for these 4 studies. Although Ramezani et al[274] reported lower cholesterol levels in patients with CKD with kidney allografts compared to placebo after 6 months of supplementation with 1.76 g/d of EPA with 0.96 g/d of DHA in fish oil, Schmitz et al[256] found no such benefit in a similar population.

LDL cholesterol. Eight of 12 studies in patients receiving MHD found no benefit of supplementation,[249,265,266,268,270-273] while 4 reported a reduction in LDL-C levels.[249,250,255,263] Two of the 4 positive studies supplemented with fish oil (1.5 g total in Khajehdehi et al[263] and 0.96 g/d of EPA with 0.6 g/d of DHA in Bowden et al,[255] while the other 2 used flaxseed oil or ground flaxseed[249,250] (with both latter studies observing a decrease in LDL-C levels).[249,250] Study quality or duration or type of comparison group used did not influence the outcome. A pooled analysis of all 12 studies noted an improvement in LDL-C levels only when excluding the flaxseed-based supplement studies (mean difference, −5.26 [95% CI, −9.51 to −1.00] mg/dL) and even then the result was clinically marginal. In CKD patients not receiving dialysis, 4 studies of 8 to 12 weeks length using fish oil found no effect on LDL-C levels (1.8 g/d total in Guebre-Egziabher et al[264] and 0.46-1.44 g/d of EPA with 0.25-0.96 g/d of DHA[251,259,261,264]). In patients with CKD with kidney allografts, 1 study reported that EPA "9g capsules" per day increased LDL-C levels (but a higher dose did not), while another study reported negative results.[256,258]

HDL cholesterol. Seventeen RCTs included HDL-C level as an outcome. Though HDL-C level may be influenced by physical activity, smoking status, and sex, the preponderance of these studies did not control for these factors. Of the 12 studies in patients receiving MHD, 6 reported negative results[249,265,266,268,270,272] and 6 found that HDL-C levels were increased.[249,250,255,263,271,273] Effects were not clearly influenced by study quality or duration. However, the positive studies tended to use lower doses of LC n-3 PUFA (0.72-0.96 g/d of EPA with 0.42-0.6 g/d of DHA), flaxseed oil (2 g/d), or ground flaxseed (40 g/d). In a pooled analysis of all 12 studies, LC n-3 PUFA supplementation was found to increase HDL-C levels by a mean of 7.1 (95% CI, 0.52-13.63) mg/dL. However, heterogeneity was high overall. Results were mixed in the 4 trials of CKD patients not receiving dialysis, with 2 showing a benefit[262,264] and 2 reporting no effect.[259,261] Again, the outcome was not clearly influenced by quality of study, study duration, or dosage, and results could not be pooled. Finally, the only study in patients with CKD with kidney allografts showed no benefit.[258]

Inflammatory markers. The putative anti-inflammatory effects of LC n-3 PUFA were tested on 2 established biomarkers of inflammation.

C-Reactive protein. Fifteen RCTs studied the effect of fish oil supplementation on circulating CRP levels. In CKD patients not receiving dialysis, fish oil either compared to placebo[261,275] or at varying doses[264] had no effect. The pattern in patients receiving MHD was similar. A pooled analysis of 10 studies[249,250,255,265,268-270,276-278] found no effect of LC n-3 PUFA supplementation (9 using fish oil containing 0.42-1.8 g/d of EPA with 0.24-1.14 g/d of DHA, 1 using 2 g/d of flaxseed oil) on circulating CRP levels as compared to placebo (mean difference, −1.73; 95% CI, −3.54 to 0.09 mg/L). Ewers et al[266] found that fat supplementation (which also included fats other than LC-n-3 PUFA and specific n-3 PUFAs were not described) was associated with a reduction in CRP levels ($P = 0.01$) after 12 weeks as compared with nonsupplemented patients.

Interleukin 6. Six RCTs studied the effect of LC n-3 PUFA on circulating IL-6 levels. Neither of the 2 studies in CKD patients not receiving dialysis comparing fish oil supplementation with placebo or at varying doses found a significant effect on IL-6 levels (1 study reported a total of 1.8 g/d of n-3 PUFA and 1 reported 1.4 g/d of EPA with 1.0 g of DHA),[264,279] nor did a pooled analysis of 4 studies in patients receiving MHD (mean difference, 5.32; 95% CI, −5.637 to 16.275 pg/mL) in which participants received 0 to 1.93 g/d of EPA with 0.72 to 0.97 g/d of DHA.[268,276,277,280]

Special Discussions

The clinical impact of LC n-3 PUFA supplementation in patients with CKD was challenging to assess due to short study durations, modest sample sizes, and broad heterogeneity in the composition of the supplements and dosing strategies. Furthermore, baseline LC n-3 PUFA levels

(either in blood or tissues) were not typically used to target populations that would most benefit. This is an important but often overlooked point because the putative benefits of LC n-3 PUFA supplementation may be inversely related to baseline blood or tissue concentrations.[248,281]

Implementation Considerations

- LC n-3 PUFA supplementation considerations will differ depending on whether the intervention is diet based or capsule based.
- For dietary interventions, the goal of supplementation must be clearly defined. If it is to increase blood levels of α-linolenic acid (ALA), supplementation should focus on soybean, flaxseed, and other oils, as well as meat and dairy products. If it is to increase EPA or DHA blood/tissue levels, the primary dietary sources must be sardine, mackerel, salmon, and other high-content marine-based foods.[282] Potential limitations to dietary supplementation include their relatively high cost and difficulty achieving high daily intake. In addition, the source and processing method will influence LC n-3 PUFA foodstuff content. For example, farmed fish typically (but not always) have lower LC n-3 PUFA content compared with wild fish, while frying fish could alter the n-3 to n-6 ratio, which may be of clinical significance.[283]
- Capsule-based supplementation involves a set of different considerations. Although dozens of commercial LC n-3 PUFA supplements are available, quality control is often lacking.[284] This makes precise dosing recommendations difficult. An alternative route is to have the patient obtain supplements through physician prescription (eg, icosapent ethyl and omega-3 ethyl esters). For either option, cost could be an issue. Achieving high-dose supplementation will be easier with capsules than through dietary consumption. Adverse effects of capsule-based supplementation may lead to gastrointestinal side effects such as stomach upset and eructation (though the latter can be masked by different formulations). Theoretical risks such as bleeding have not been borne out in clinical trials. LC n-3 PUFA content is listed on the website of the National Institutes of Health.[285]

Monitoring and Evaluation

There is no need to routinely monitor dietary LC n-3 PUFA intake other than in the context of general dietary counseling. An exception could be if the patient is specifically instructed to consume greater dietary quantities of LC n-3 PUFA.

Future Research

- There are no adequately powered studies into whether LC n-3 PUFAs reduce cardiovascular risk, and in particular sudden cardiac death, in the high-risk CKD population. This is a high-priority topic and there is currently an ongoing RCT looking into these outcomes (ISRCTN00691795).[286]
- The dosage and ratio of LC n-3 PUFA to be supplemented, as well as the quality control and purity of the supplement used, should all be carefully considered and documented in any study design. For example, a recent RCT found that a highly purified form of EPA ethyl ester (with no ALA or DHA included) at a high dose (4 g/d) available only in prescription form was effective in reducing cardiovascular risk.[287] This is in contrast to several negative trials in recent years that used different formulations and doses of LC n-3 PUFA.

Guideline 5: Micronutrients

5.0 Statements for General Guidance

Dietary Micronutrient Intake

5.0.1 In adults with CKD 3-5D or posttransplantation, it is reasonable for the registered dietitian nutritionist (RDN) or international equivalent to encourage eating a diet that meets the recommended dietary allowance (RDA) for adequate intake for all vitamins and minerals (*OPINION*).

Micronutrient Assessment and Supplementation

5.0.2 In adults with CKD 3-5D or posttransplantation, it is reasonable for the registered dietitian nutritionist (RDN) or international equivalent, in close collaboration with a physician or physician assistant, to assess dietary vitamin intake periodically and to consider multivitamin supplementation for individuals with inadequate vitamin intake (*OPINION*).

Micronutrient Supplementation, Dialysis

5.0.3 In adults with CKD 5D who exhibit inadequate dietary intake for sustained periods of time, it is reasonable to consider supplementation with multivitamins, including all the water-soluble vitamins, and essential trace elements to prevent or treat micronutrient deficiencies (*OPINION*).

Rationale/Background

Micronutrients are essential for metabolic function and hence, maintaining an adequate intake of these micronutrients is important. For healthy individuals, many countries have established dietary reference intakes for individual micronutrients. However, there is a paucity of guidance regarding appropriate intake for people with chronic diseases. There is some evidence to indicate that

patients with CKD are likely to be deficient in certain micronutrients. Some of the common reasons for this include insufficient dietary intake, dietary prescriptions that may limit vitamin-rich foods (particularly water-soluble vitamins), dialysis procedures that may contribute to micronutrient loss, improper absorption of vitamins, use of certain medications, and illness. Due to these concerns, multivitamin supplements are routinely prescribed. Findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS) indicate that >70% of MHD patients in the United States take supplements. However, there is insufficient evidence to indicate whether micronutrients or multivitamin supplementation is beneficial or detrimental in this population.

Detailed Justification

At present there is a paucity of good-quality evidence to either support or oppose routine supplementation on micronutrients, including multivitamins. There is some evidence to state that patients with CKD might be deficient in thiamine,[288-290] riboflavin,[291] vitamin B_6,[292-294] vitamin C,[295,296] vitamin K,[297-299] and/or vitamin D.[300] However, most of the supporting evidence on deficiencies is for the MHD population and not much has been explored in other stages of CKD or those treated by PD or posttransplant.

This systematic review included a comprehensive search of controlled trials evaluating the effects of micronutrient supplementation (both water- and fat-soluble) in patients with CKD. A total of 80 controlled trials were included in the systematic review (folic acid alone, 14 trials; folic acid + B vitamins, 13 trials; vitamin E, 8 trials; vitamin K, 1 trial; vitamin D, 14 trials; vitamin B_{12}, 4 trials; vitamin C, 8 trials; thiamine, 1 trial; zinc, 10 trials; and selenium, 7 trials). Some of the good-quality evidence from these articles led to the development of recommendation statements for specific micronutrients (see specific sections).

However, the current evidence in this field has significant limitations. A majority of the included studies in this systematic review did not report either baseline status of micronutrients examined or dietary intake during the trials. Moreover, the outcomes reported by these studies varied significantly across the studies, making it difficult to integrate evidence. Also, dosage of supplementation and duration of intervention varied across studies. Included studies primarily reported the effect of micronutrient supplementation on the serum level of the micronutrient being supplemented. The quality of evidence from these trials ranged from very low quality to moderate quality for a majority of the micronutrients. Due to these significant limitations, it is very difficult to provide recommendations regarding the exact levels of supplementation or routine supplementation for all patients with CKD. However, there is some evidence to support that care should be taken to avoid excessive doses, and there might be some individuals who are at higher risk for certain micronutrient deficiencies. Taking all these issues into consideration, the expert panel thought that it was important to draft expert opinion–based recommendation statements to guide practitioners and to emphasize the need for individualization of micronutrient use.

In recent years, there have been a few systematic or narrative reviews on the topic of micronutrient supplementation in patients with CKD. The findings from these SRs are in line with findings from the current systematic review. Tucker et al,[301] in a detailed review of micronutrients in patients receiving MHD, state that there is insufficient evidence to support routine supplementation; instead, supplementation should be individualized and based on clinical judgment. Similarly, Jankowska et al[302] and Kosmadakis et al[303] also state that there is insufficient evidence to support or oppose supplementation and more good-quality trials are needed to help clarify evidence in this area.

Special Discussions

Certain CKD populations might be at higher risk for micronutrient deficiencies, and this must be taken into consideration. For example, pregnant women, patients after gastric bypass surgery, patients with anorexia and wasting syndrome with poor intake, patients with malabsorption conditions, patients following vegetarian diets, and patients taking certain medications may have different micronutrient needs.

Nutrition Focused Physical Examination should be conducted with patients to identify whether signs and symptoms of certain vitamin and mineral deficiency are present. These can be used in combination with laboratory measures to get a complete picture of the problem.

If patients with CKD are not meeting their recommended intake as assessed by 24-hour recall and have poor nutritional status, it is likely that they might be at risk for micronutrient deficiencies and appropriate intervention is required.

Implementation Considerations

- Gather patient information on whether they are taking any micronutrient or multivitamin supplements.
- Suggested vitamin intake should be based on recommendations for the general population (eg, Recommended Dietary Allowance [RDA]) unless there are specific considerations requiring modification.
- Assess dietary intake, including consideration of fortified foods.
- Review if patients may be at risk for vitamin and mineral deficiencies.
- Supplementation dose should be individualized based on each patient's needs and risk profile.

Future Research

- Well-designed trials are needed to investigate whether supplementation improves outcomes. These trials should limit inclusion to a certain baseline status (eg, deficiency/insufficiency) or adjust for baseline status in results. Researchers should consider the effect of dietary intake of micronutrients on findings.
- There is a need to determine how dietary interventions targeting micronutrient intake may affect relevant outcomes.

5.1 Statements on Folic Acid

Folic Acid Supplementation for Hyperhomocysteinemia

5.1.1 In adults with CKD 3-5D or posttransplantation who have hyperhomocysteinemia associated with kidney disease, we recommend not to routinely supplement folate with or without B-complex since there is no evidence demonstrating reduction in adverse cardiovascular outcomes (*1A*).

Folic Acid Supplementation for Folic Acid Deficiency and Insufficiency

5.1.2 In adults with CKD 1-5D (*2B*) or post-transplantation (*OPINION*), we suggest prescribing folate, vitamin B12, and/or B-complex supplement to correct for folate or vitamin B12 deficiency/insufficiency based on clinical signs and symptoms (*2B*).

Rationale/Background

Folic acid is involved in the synthesis of several amino acids, including serine, glycine, methionine, and histidine. Folic acid can be provided by dietary sources as well as over-the-counter nutritional supplements. Over-the-counter supplements come in various forms, such as folic acid, methyl folate (also known as L-methyl folate, L-5-methyl folate, or MTHF), and folinic acid, among others. Folic acid's primary mechanism of action is its role as a 1-carbon donor. Folic acid is reduced to methyl folate, which helps transfer single methyl groups in various metabolic reactions in the body. Folic acid also plays a role in the functioning of the nervous system, in DNA synthesis, and in cell division. Food sources rich in folic acid include green leafy vegetables, fruits, yeast, and liver. Although intake of foods naturally rich in folic acid is limited in patients with CKD due to their high potassium content, folic acid deficiency among this patient population seems to be rare. This is especially true since 1996, when folic acid fortification of enriched cereal grain products was mandated in the United States and Canada.[301] Because folate, vitamin B_{12}, and vitamin B_6 assist in the conversion of homocysteine to methionine (and thereby reduce serum homocysteine levels), they have received considerable attention as a putative treatment for CVD in patients with CKD.

Detailed Justification

Mortality, Cardiovascular Outcomes, and Vascular Function. Four RCTs did not show any effect of folic acid when taken with vitamins B_6 and B_{12} on hard outcomes, including all-cause mortality and/or cardiovascular events in patients with stage 5 CKD, receiving MHD or PD, and posttransplant.[304-307] Folic acid and other B-vitamin supplementation ranged from 2.5 to 40 mg/d of folic acid, 1.4 to 100 mg/d of vitamin B_6, and 150 μg/wk to 2 mg/d of vitamin B_{12} for a duration of 2 to 5 years.

Folic acid (alone) intake of 1 to 5 mg/d for 4 to 40 weeks showed no effect on flow-mediated dilation.[308,309] Additionally, folic acid supplementation did not alter the risk for cardiovascular outcomes in 4 RCTs.[310-313] The 4 RCTs included patients with CKD, stage 5 nondialyzed, and treated by PD and MHD. The folic acid supplementation dose ranged from 1 to 15 mg/d and supplementation duration ranged from 1 to 3.6 years in these studies.

Supplementation with folic acid in combination with other B vitamins did not improve TC levels, intima media thickness, or BP in MHD patients. Doses ranged from 5 to 15 mg of folic acid and a B-complex vitamin for 3 to 6 months.[314,315]

CKD Progression. One RCT examined the effect of folic acid supplementation on CKD progression.[316] In a substudy of a larger primary stroke prevention trial 15,104 participants with CKD stage 3 diagnosed with hypertension and taking the angiotensin-converting enzyme (ACE) inhibitor enalapril were randomly assigned to receive 0.8 mg/d of folic acid or placebo for a median of 4.4 years. Compared with the group receiving enalapril and placebo, the enalapril plus folic acid group significantly reduced the adjusted risk for CKD progression (HR, 0.45 [95% CI, 0.27-0.76]; $P = 0.003$), which was the substudy's primary outcome.[316] The limitation of this study was that a placebo-alone group (without enalapril) was not included.

Two other RCTs showed no effect of supplementation with folic acid with vitamins B_6 and B_{12} on the risk for dialysis initiation/ESKD in participants with stages 3-5 CKD and those posttransplantation.[304,306]

Serum Homocysteine Levels. Fourteen studies examined the effect of folic acid supplementation alone on plasma homocysteine levels.[308-313,316-323] Participants included were those with CKD, nondialyzed (4 studies), receiving MHD (10 studies) and PD (4 studies), and posttransplant (1 study). In the 10 RCTs, folic acid supplements ranged from 0.8 to 60 mg/d and duration varied from 4 weeks to 4.4 years in patients with various stages of CKD. All but 1 study concluded that folic acid supplementation significantly decreased homocysteine levels.[309]

Thirteen RCTs examined the effect of supplementation with folate and other B vitamins on homocysteine levels.[304-307,314,315,324-330] Serum homocysteine level was a primary outcome of interest in 8 studies.[314,315,324-326,328-330] Twelve of 13 studies found that folic acid with other B vitamin supplementation decreased

homocysteine levels in participants with CKD stages 3-5, treated by MHD or PD, and posttransplant. Supplementation doses in these studies ranged from 2.5 to 40 mg/d of folic acid (1 study used 3 mg of IV folinic acid per week), 1 μg/d of oral to 1,000 mg/wk of IV vitamin B_{12}, and 1.4 to 100 mg of vitamin B_6 and supplementation duration ranged from 8 weeks to 5 years.

CRP and IL-6 Levels. Daily oral folic acid (5 mg) with a B-complex vitamin for 3 months was associated with a decrease in CRP but not IL-6 levels in an RCT that included 121 patients receiving MHD.[310]

Folic Acid and Vitamin B_{12} Levels. Six RCTs reported that supplementation of folic acid alone increased serum folic acid levels in participants with stages 3-5 CKD and those treated by MHD and PD.[308,313,316,319,320,323] When folic acid with vitamins B_6 and B_{12} was provided, it is worth noting that serum folic acid levels increased with a daily intake of 5 mg for 3 months or a daily intake of 2.5 mg for a longer time frame. In the Mann et al[307] study that included patients receiving MHD, serum folic acid levels significantly increased with an intake of 2.5 mg after 2 years of supplementation as compared with the control group. In Chiu et al,[326] supplementation of 3 mg of folinic acid weekly IV for 3 months did not result in a significant increase in serum folic acid levels in participants with stages 3-5 CKD or who were treated by MHD and PD.

Of the 10 studies that examined the effect of supplementation of folic acid with B complex, 9 found a significant increase in serum folic acid levels.[305-307,314,315,324,325,327,330] Doses ranged from 2.5 to 60 mg of folic acid and study duration ranged from 4 weeks to 5 years.

Special Discussions

Folate status is most often assessed through measurement of folate levels in plasma, serum, or red blood cells (RBCs). Serum or plasma folate levels reflect recent dietary intake, so deficiency must be diagnosed by repeated measurements of serum or plasma folate. In contrast, RBC folate levels are more reflective of folate tissue status than serum folate and represent vitamin status at the time the RBC was synthesized (ie, longer-term folate status). Usually RBC folate concentrations diminish after about 4 months of low folate intake, reflecting the 120-day life span of RBCs in healthy individuals. In patients with CKD, such concentrations often decrease more rapidly, reflecting the shorter RBC life span in CKD. Excessive folate intake inhibits zinc absorption in the gut by forming a complex with zinc in the intestinal lumen.

High intake of folic acid may mask signs of pernicious anemia, leading to undetected progression of neurologic disease. Based on the 2015 US Renal Data System annual report, more than two-thirds (38.9%) of patients who are receiving dialysis are 65 years or older. Older people have a higher risk for impaired gastrointestinal function. Because absorption of vitamin B_{12} is dependent on intrinsic factor and normal gut function and the latter is often at least partially impaired in older individuals, assessment of serum vitamin B_{12} may be necessary if folate supplementation is considered.

Serum homocysteine, vitamin B_{12}, and folate level monitoring may be considered for patients who take certain medications such as methotrexate, nitrous oxide, 6-azaridine, phenytoin, carbamazepine, and oral contraceptives and have excessive alcohol intake that can interfere with folate absorption.

Implementation Considerations

- Vitamin B deficiencies may be identified by clinical signs and symptoms. Assessment of serum vitamin B_{12} should be considered if folate supplementation is administered.
- High folic acid intake may mask signs of pernicious anemia and undetected progression of neurologic disease, and thus folate and vitamin B_{12} levels should be monitored if folate is being supplemented.
- Suggested vitamin intake should be based on recommendations for the general population (eg, RDA) unless there are specific considerations requiring modification.
- Individualization of therapy, including supplementation dosage, is essential to the management of any comorbid condition.
- Individualization should include patient age because adults older than 50 years may have increased needs due to the prevalence of atrophic gastritis in this population.

Monitoring and Evaluation

Serum/plasma/RBC folate and serum vitamin B_{12} levels should be assessed as appropriate.

Future Research

- Conduct dose-response studies for folic acid intake, especially in people undergoing maintenance dialysis and persons who are taking medications that interfere with the intestinal absorption, serum levels, or actions of folate and/or vitamin B_{12}.
- Assess the recommended daily allowance of folic acid and other B vitamins in various stages of CKD and various types of kidney diseases.
- Examine the prevalence of serum folate deficiency in patients with various stages of CKD.
- Given 1 preliminary positive report, conduct more RCTs to confirm whether folic acid intake may slow down CKD progression.

5.2 Statement on Vitamin C

Vitamin C Supplementation

5.2.1 In adults with CKD 1-5D or posttransplantation who are at risk of vitamin C deficiency, it is

reasonable to consider supplementation to meet the recommended intake of at least 90 mg/d for men and 75 mg/d for women (OPINION).

Rationale/Background

There are currently limited studies identifying daily vitamin C requirements for individuals with CKD at all stages of the disease. Amount of daily intake and optimal serum level of vitamin C required to maintain nutritional health, reverse deficiency, and avoid toxicity are unclear. Studies included for this current review evaluated the effect of vitamin C supplementation on nutritional status, inflammation, anthropometrics, micronutrient levels, electrolyte levels, fluid status, serum uric acid levels, lipid levels, morbidity events, QoL, mortality, and hospitalizations. Limited data from a very small number of studies prohibit definitive evidence-based conclusions for all these surrogate and hard outcomes. Therefore, we suggest that individualized decision making is the best clinical approach to determine whether vitamin C supplementation, or termination of supplementation, is required for adults with CKD stages 1-5D and posttransplant.

Detailed Justification

Nine studies examined the effect of vitamin C on nutrition-related outcomes in the CKD population, including 5 RCTs,[331-335] 1 randomized crossover trial,[296] and 3 comparative studies.[336,337] All studies examined MHD patients. Two studies (Canavese et al[338] and Singer[335]) also included PD patients and those with eGFRs < 20 mL/min.

QoL, Mortality, and Hospitalizations. In adults with CKD, 1 RCT (250 mg of oral ascorbic acid 3 times per week for 3 months)[335] and 1 comparative study[337] (500 mg of oral vitamin C per day for 2 years) measured the effect of vitamin C supplementation, compared with either a placebo or control, on hard outcomes, including all-cause mortality, QoL or hospitalization events.

Singer[335] reported no changes in symptom, cognitive, or nausea subscales of the Kidney Disease Quality of Life Short Form (KDQOL-SF) in either the vitamin C–supplemented or placebo groups in MHD/PD participants. QoL was the primary outcome of interest. Approximately 40% of participants were vitamin C deficient at baseline. In a comparative study by Ono,[337] there were no differences in mortality rates or hospitalization events between vitamin C–supplemented and non-supplemented periods in MHD participants. Mortality was a primary outcome measure. Baseline vitamin C status was not reported.

In summary, vitamin C supplementation did not affect QoL, mortality, or hospitalizations in MHD patients, but evidence was extremely limited. Evidence-based recommendations for the use of vitamin C in this patient population for these end points could not be provided.

Nutritional Status Parameters: Serum Albumin, Prealbumin, Transferrin, and PNA. Three studies examined the effect of vitamin C supplementation on nutritional status in MHD participants: 1 RCT,[333] 1 randomized crossover trial,[296] and 1 comparative study.[336] However, nutritional status was not the primary outcome of interest. In Zhang et al,[296] all patients were vitamin C deficient at baseline, while in De Vriese et al,[336] 44% of participants were deficient at baseline. In Fumeron et al,[333] vitamin C deficiency status at baseline was unclear. All outcomes were reported as quantitative values but were not compared to a reference standard. Supplementation dosage and duration ranged from 750 mg/wk for 2 months[333] to 1,500 mg/wk for 3 months.[336]

All 3 studies reported no effect of supplementation on albumin levels, as did pooled analysis of 2 of the RCTs. Zhang et al[296] measured the effect of vitamin C supplementation on prealbumin levels in a randomized crossover trial with MHD participants. Although 1 supplemented group experienced an increase in prealbumin levels after 3 months of supplementation with 200 mg of vitamin C, prealbumin levels did not change in the other group after the same intervention. Therefore, the effect of vitamin C supplementation on prealbumin levels is unclear. Fumeron et al[333] supplemented MHD participants with 750 mg/wk of vitamin C for 2 months. There were no significant changes in transferrin levels in either group. De Vriese et al[336] measured nPNA (nPCR) in an NRCT and found no effect of vitamin C supplementation on nPNA (nPCR) following supplementation with 360 mg/wk or 1,500 mg/wk for 9 months in MHD patients.

CRP Levels. Three studies examined the effect of oral vitamin C supplementation on CRP levels in MHD participants[296,333,336] and found no significant effects compared with the placebo or control groups, but evidence was limited.

Vitamin C Levels/Deficiency. Four RCTs[296,331,333,335] and 2 comparative studies[336,337] examined the effect of vitamin C supplementation in doses ranging from 360 to 3,500 mg/wk and duration ranging from 3 months to 2 years. In summary, oral vitamin C supplementation increased serum vitamin C levels in MHD patients and decreased the proportion of participants who were vitamin C deficient/insufficient (cutoffs were 11.44 and 23.0 μmol/L). However, in pooled analysis of 3 RCTS, the increase in vitamin C levels may not be clinically significant. The quality of evidence in this regard remains low. Other CKD populations such as nondialysis CKD 1-5, PD, and posttransplant participants remain poorly studied.

These studies did not analyze the effects of vitamin C supplementation on optimal dosing or thresholds for toxicity. The potential for toxicity was acknowledged with dosage ranges maintained at 200 to 250 mg daily or 3 times weekly in most studies. The study by Ono[337] that dosed MHD patients with 500 mg of oral vitamin C

daily for 2 years reported an aggravation of hyperoxalemia. De Vriese et al[336] had participants dosed at 360 mg/wk for 0 to 3 months followed by 1,500 mg/wk dosing for 3 to 6 months and then no supplementations for 6 to 9 months in MHD patients. This study reported an increase in plasma malondialdehyde levels.[336] Supplementation with vitamin C increased the low levels, but there is a potential risk for toxicity that requires monitoring.

Lipid Levels: TC, TG, LDL-C, HDL-C, LDL-C:HDL-C Ratio. The results of 3 trials[331,334,336] demonstrated that vitamin C supplementation of 125 to 200 mg/d for 3 months may decrease TC and LDL-C levels, but there was no effect on TG or HDL-C levels. Vitamin C supplementation of 125 to 200 mg/d decreased the LDL-C:HDL-C ratio or prevented the increase seen in the placebo group.

There were several limitations to this evidence, including a small number of studies, small sample sizes, and low evidence quality. It is important to note that the study by Khajehdehi et al[334] included supplementing patients with potentially toxic doses of ergocalciferol, 50,000 IU, daily for 3 months. The impact of this amount of vitamin D on study outcome parameters, if any, cannot be ascertained.

Treatment of anemia with vitamin C supplementation was beyond the scope of this guideline.

Special Discussions

Current nutritional requirements or Recommended Dietary Intake of vitamin C for individuals with CKD stages 1-5D and posttransplant are not known and are based on those from the general population. The prevalence of vitamin C deficiency may vary according to CKD stage and dialysis modality. Toxicity is a possible concern for excessive vitamin C supplementation.

However, these findings do not preclude the importance of assessing for vitamin C supplementation or when to discontinue supplementation. Ongoing monitoring of overall food intake and nutrition status is required to assess for vitamin C deficiency. An individualized approach to evaluation and monitoring of vitamin C status is ideally accomplished by a multidisciplinary care team that includes nephrologist, nurse practitioner, physician assistant, and RDN.

Implementation Considerations

- Initiation and cessation of vitamin C supplementation, as well as supplementation dose, should take into account the individual's nutritional status, dietary intake, comorbid conditions, and dialysis modality.
- Suggested vitamin intake should be based on recommendations for the general population (eg, RDA) unless there are specific considerations requiring modification.

Monitoring and Evaluation

Higher doses of vitamin C supplementation (500 mg daily) have been shown to increase serum oxalate levels. Vitamin C is a potent physiologic antioxidant. Lipid metabolism may be affected by vitamin C supplementation and patients receiving vitamin C supplementation should have lipid fractions monitored. Vitamin C also affects immune function and carnitine metabolism. Patients with any malabsorption or diseases of an inflammatory nature may be more prone to having lower plasma vitamin C levels than the general population. Therefore, supplementation dose should take into consideration medical history, comorbid conditions, and concomitant medications. Measurement of serum oxalate may be considered in patients prescribed high doses of vitamin C and/or who are susceptible to calcium oxalate stone formation.

Future Research

- Identify methods to assess vitamin C status. Current methods use serum levels of vitamin C, but reliability is unclear.
- Ascertain the optimal vitamin C status of the CKD population, including CKD stages 1-5D and those with a kidney transplant.
- Confirm the RDA for vitamin C in various CKD populations and the supplemental vitamin C dose that will prevent vitamin C deficiency without increasing risk for toxicity.
- If feasible, evaluate the effect of vitamin C supplementation on hard outcomes, including survival, hospitalization, cardiovascular events, and QoL measures with RCTs in CKD populations.

5.3 Statements on Vitamin D

Vitamin D Supplementation for Vitamin D Deficiency and Insufficiency

5.3.1 In adults with CKD 1-5D (2C) or posttransplantation (OPINION), we suggest prescribing vitamin D supplementation in the form of cholecalciferol or ergocalciferol to correct 25-hydroxyvitamin D (25(OH)D) deficiency/insufficiency.

Vitamin D Supplementation with Proteinuria

5.3.2 In adults with CKD 1-5 with nephrotic range proteinuria, it is reasonable to consider supplementation of cholecalciferol, ergocalciferol, or other safe and effective 25(OH)D precursors (OPINION).

Rationale/Background

Vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are recognized as prohormones and comprise a group of fat-soluble secosteroids. A unique aspect of vitamin D as a nutrient is that it can be synthesized by the human body through the action of sunlight. These dual

sources of vitamin D (diet and sunlight) make it challenging to develop dietary reference intake values.[339] The classic actions of vitamin D are the regulation of calcium and phosphorus homeostasis contributing to bone health. More recently, there has been growing interest in the potential pleiotropic actions of vitamin D on immune, cardiovascular, and neurologic systems and on antineoplastic activity because extrarenal organs possess the enzymatic capacity to convert 25-hydroxyvitamin D (calcidiol; 25[OH]D) to 1,25-dihydroxyvitamin D (1,25 $[OH]_2D$).[340]

Insufficiency/deficiency of vitamin D, assessed by serum concentration 25(OH)D, has been found to be common in the general population and even more prevalent in patients with CKD stages 3-5D.[300,341,342] For most experts, vitamin D insufficiency is defined as serum 25(OH)D level between 20 and 29 ng/mL, deficiency is considered as 25(OH)D level < 20 ng/mL, and sufficiency as serum 25(OH)D level ≥ 30 ng/mL.[343]

A number of factors or conditions are implicated in suboptimal vitamin D status in patients with CKD, including aging, diabetes mellitus, obesity, reduced sun exposure, loss of urinary/dialysate vitamin D binding protein, impaired tubular 25(OH) reabsorption, and dietary restrictions.[344-347] Considering the high prevalence of vitamin D deficiency/insufficiency in CKD/ESKD and the potential benefits of restoring vitamin D status, the K/DOQI[348] (2003) and KDIGO[349] (2017) clinical practice guidelines for CKD–mineral and bone disorder (CKD-MBD) have proposed ergocalciferol or cholecalciferol supplementation.

Detailed Justification

Vitamin D Levels and Deficiency. Despite differences in dosing regimens and vitamin D status at baseline, supplementation was effective in increasing 25(OH)D serum concentrations in 14 RCTs, including in the form of ergocalciferol[350,351] and cholecalciferol.[352-363] This effect was demonstrated in HD patients (8 studies), HD and PD patients combined (1 study), patients with stages 1-4 CKD (4 studies), and in 1 study with any participants with CKD. Five studies reported that ergocalciferol using doses of 50,000 IU/wk and dose dependent on status[350,351] and cholecalciferol in doses ranging from 25,000 to 50,000 IU/wk improved vitamin D status.[352,353,356,360] There were significant effects noted after 3 months of supplementation. However, there was no difference in vitamin D deficiency status between nondialyzed groups receiving 2 different dosing regimens.[358]

A meta-analysis was conducted to determine the odds of vitamin D sufficiency according to vitamin D supplementation, which included Bhan et al[350] (each group compared with the placebo group), Delanaye et al,[356] Massart et al,[360] and Alvarez et al.[352] Participants who were supplemented with vitamin D had an OR of 9.31 (95% CI, 3.38-24.7; P < 0.001) of being vitamin D sufficient (defined as either >30 or 32 ng/mL), though there was moderate heterogeneity in the data (I^2 = 51.84; P = 0.08). Additionally, data from 8 studies were pooled to determine the mean difference in vitamin D levels according to vitamin D supplementation. There was a mean increase of 21.06 (95% CI, 17.46-24.66) ng/mL in the vitamin D–supplemented groups compared with the placebo groups, but heterogeneity was moderate (I^2 = 67.3%; P = 0.003), so results should be interpreted with caution.

Calcium and Phosphorus Levels. In adults with CKD, 12 studies examined the effect of vitamin D intake on biomarker levels and/or health outcomes.[267,350-352,354-356,358-362] Moderate-quality evidence demonstrated no effect of vitamin D supplementation on calcium or phosphorus levels.

In predominantly vitamin D–deficient participants, there was no effect of ergocalciferol supplementation on calcium levels in doses of 50,000 IU per week or per month or in individualized doses.[350,351] The effect of cholecalciferol on calcium levels was unclear, with 7 studies finding no effect on calcium levels and 3 studies determining that supplementation increased calcium levels. In Massart et al,[360] a double-blind randomized placebo-controlled trial, weekly treatment of 25,000 IU of cholecalciferol significantly increased the percentage of HD patients reaching target levels of 25(OH)D ≥ 30 ng/mL at 3 months compared to placebo treatment (61.5% vs 7.4%; P < 0.0001). $1,25(OH)_2D$ levels (22.5 [interquartile range, 15-26] vs 11 [interquartile range, 10-15] pg/mL; P < 0.001) were also higher in the treatment group versus placebo. The proportion of patients achieving the target calcium level (76.9% vs 48.2%; P = 0.03) was higher in the treatment group versus placebo. Incidence of hypercalcemia and phosphate and intact PTH levels were similar between groups. In pooled analysis of 4 studies in which data could be combined, there was no effect of vitamin D supplementation on calcium levels (mean difference, 0.07 [95% CI, −0.18 to 0.31] mg/dL).[267,351,356,362]

Vitamin D supplementation had no effect on phosphorus levels with ergocalciferol supplementation (2 studies with doses of 50,000 IU per week or per month or in individualized doses) or cholecalciferol doses ranging from 50,0000 IU/d to 50,000 IU/mo (10 studies). In pooled analysis of 5 RCTs, there was no effect of vitamin D supplementation on phosphorus levels (mean difference, −0.15 [95% CI, −0.44 to 0.15] mg/dL).[267,351,356,361,362]

Special Discussions

Due to the complex nature of vitamin D, the present guideline is focused on the effect of vitamin D supplementation, in the forms of cholecalciferol and ergocalciferol, on vitamin D insufficiency/deficiency in patients with CKD and not on outcomes related to CKD-MBD or other clinical disturbances. Supplementation of prehormone and activated forms of vitamin D, calcidiol, and calcitriol were not included in this guideline.

There are potential benefits of vitamin D supplementation (cholecalciferol or ergocalciferol) in CKD. A systematic review with meta-analysis of observational and randomized studies showed a significant decline in PTH levels with cholecalciferol or ergocalciferol supplementation in patients who are nondialyzed, those treated by HD or PD, and kidney transplant recipients.[364] However, whether such improvements translate into clinically significant outcomes is yet to be determined.

Cross-sectional analysis of NHANES III showed a progressively higher prevalence of albuminuria with decreasing 25(OH)D levels.[365] In a prospective cohort study, vitamin D deficiency was associated with a higher incidence of albuminuria.[366] There are limited randomized clinical trials investigating the effect of cholecalciferol or calcifediol on proteinuria in CKD and the results are inconclusive.[367,368]

Implementation Considerations

- The optimal serum 25(OH)D concentration for patients with CKD and the concentration at which patients with CKD are considered deficient/insufficient are not well defined but are generally considered to be the same as in the general population, although there is no absolute consensus about the definition of vitamin D sufficiency. For most experts, vitamin D insufficiency is defined as serum 25(OH)D level between 20 and 29 ng/mL, deficiency is considered as 25(OH)D level < 20 ng/mL, and sufficiency as serum 25(OH)D level ≥ 30 ng/mL.[343]
- Both the KDOQI and KDIGO experts recommend checking and supplementing low serum 25(OH)D levels in patients with CKD and dialysis patients.[349,369] In the most recent update of the KDIGO guideline on MBD, it is suggested based on low-quality evidence that patients with CKD stages 1-5D have 25(OH)D levels measured, and repeated testing should be individualized according to baseline values and interventions. However, there was no clear suggestion on how frequently 25(OH)D levels should be reviewed.[349]
- With respect to vitamin D supplementation, current guidelines suggest that patients with CKD stages 1-5D and vitamin D insufficiency/deficiency should receive supplementation using the same strategies recommended for the general population. However, even for the general population, the optimal dosage of supplementation varies among the main guidelines. It has been recommended for 1,000 to 2,000 IU/d of cholecalciferol for vitamin D repletion for the general population. However, KDOQI acknowledges that patients with CKD may require a more aggressive therapeutic plan.[369]
- There is also a debate regarding which form of vitamin D should be used, ergocalciferol or cholecalciferol. In the general population, there appears to be some advantage of using cholecalciferol over ergocalciferol.[370] Because in CKD there is no clear evidence about the superiority of cholecalciferol, clinicians should use the form commercially available in the context of their clinical practice.
- The tolerable upper intake level proposed by the IOM for the general population is 4,000 IU/d.[371] There is no recommendation of a safe dose of cholecalciferol or ergocalciferol supplementation to prevent toxicity or adverse effects such as hypercalcemia or hyperphosphatemia in CKD. However, periodic measurement of serum calcium and phosphorus should be considered, especially for patients who are using calcium-containing phosphate binders and/or vitamin D active analogues.

Future Research

There is a need of well-designed trials to determine:

- Definition of vitamin D adequacy or insufficiency/deficiency
- 25(OH)D thresholds to initiate 25(OH)D supplementation
- Dosing, timing of administration, and type of vitamin D supplements in the CKD population
- Risks and benefits of vitamin D supplementation in the CKD population
- Long-term goals of vitamin D supplementation in the CKD population.

5.4 Statement on Vitamins A and E

Vitamins A and E Supplementation and Toxicity

5.4.1 In adults with CKD 5D on MHD or CKD 5D on PD, it is reasonable to not routinely supplement vitamin A or E because of the potential for vitamin toxicity. However, if supplementation is warranted, care should be taken to avoid excessive doses, and patients should be monitored for toxicity (OPINION).

Rationale/Background

Vitamin E is a fat-soluble nutrient recognized for antioxidant properties. There are 8 known naturally occurring forms of vitamin E,[339] but alpha-tocopherol is the only known form of vitamin E that meets human requirements and is the form found in plasma. Therefore, Dietary Reference Intake for vitamin E is only available for alpha-tocopherol. The RDA for vitamin E was determined by identifying serum vitamin E levels that provided protection to erythrocyte survival when exposed to hydrogen peroxide.

Although vitamin E supplements are typically provided as alpha-tocopherol, products containing other tocopherols and tocotrienols have been reported.[339] The potency of synthetic alpha-tocopherol (*RRR-alpha-tocopherol*, labeled as *D* or *d*) is not identical to the natural form. This is because synthetic alpha-tocopherol contains 8 stereoisomers, of which only 4 are found in tissues and serum. Synthetic alpha-tocopherol: *all rac-alpha-tocopherol*, labeled as

dl or DL, is therefore only half as active as the natural form, therefore requiring 50% more international units to receive a dose equivalent to the natural source.[339] Most supplements provide vitamin E as alpha-tocopherol in a 100- to 400-mg dose.

Vitamin E is a fat-soluble vitamin. The potential risk for vitamin E toxicity is primarily related to the use of supplements.[339,372] High doses of vitamin E supplements in the form of alpha-tocopherol have been reported to cause bleeding and/or disrupt blood coagulation in vivo, and there are some in vivo data that suggest that alpha-tocopherol inhibits platelet aggregation.[372] The RDA for vitamin E for healthy adult men and woman is 15 mg per day (22.4 IU). The Food and Nutrition Board has defined an upper level of intake for vitamin E in the form of alpha-tocopherol and the stereoisomer forms in synthetic vitamin E supplements as 1,500 IU and 1,100 IU/d, respectively. Although not definitive, these levels of intake appear to be the safety limit with regard to the potential of vitamin E to confer bleeding risk.

Several studies evaluated the effects of vitamin E–coated dialyzer membranes on biocompatibility, BP during dialysis, and oxidative stress.[373,374] However, results were inconclusive. Data regarding the effect of vitamin E–coated dialyzers on hemoglobin level, lipid profile, and nutritional status were inconclusive, and study designs for these trials and the meta-analyses were of low quality.[375]

Studies examining daily vitamin A requirements for individuals with various stages of CKD are lacking. Optimal serum vitamin E levels are not defined for this population. Daily vitamin E required to maintain nutritional health, reverse deficiency, and avoid toxicity in CKD populations are unclear. Vitamin A was initially investigated in the systematic review, but there were no dietary trials available, only trials in which vitamin A was delivered IV, which was considered beyond the scope of this guideline.

Detailed Justification

The 8 studies included for this review examined the effect of oral vitamin E supplementation in adults with CKD on serum indices and health outcomes.[334,376-382] In 3 of these studies, vitamin E supplementation was combined with ALA supplementation.[376,379,382] All studies examined MHD patients as the target population except for Ramos et al,[382] who examined individuals with stages 3-5 CKD. Participants in Hodkova et al[380] were vitamin E repleted, but baseline vitamin E status was not reported for any of the other studies.

All- Cause Mortality and CVD Outcomes. Participants with CKD (serum creatinine ≥ 1.4 to 2.3 mg/dL) and high risk for cardiovascular events were given 400 IU daily of oral vitamin E for a median of 4.5 years.[381] Compared with the placebo group, there was no difference in total mortality between groups. Additionally, there was no difference in the relative risk for MI, stroke, death from cardiovascular causes, unstable angina, heart failure hospitalizations, heart failure, transient ischemic attack, or composite of MI, stroke, or death from cardiovascular causes between groups.

Boaz et al[377] examined the effect of vitamin E supplementation on CVD end points (primary outcome) and all-cause mortality. MHD participants with pre-existing CVD were supplemented with daily oral 800 IU of oral vitamin E for a median of 519 days. Risk for all-cause mortality was not significantly different between groups. The vitamin E group had a significantly decreased risk for experiencing a CVD end point compared with the control group, but the RRs for fatal and nonfatal MIs, ischemic stroke, and peripheral vascular disease were not significantly different between groups.

Based on these limited data, vitamin E supplementation did not affect all-cause mortality. Results regarding the effects of vitamin E supplementation on CVD outcomes were mixed. Differences may be due to the population studied or vitamin E dosage. In pooled analysis conducted in the current systematic review, there was no effect of vitamin E supplementation on CVD outcomes, though heterogeneity of results was high.

Anthropometric Measures. Two RCTs examined the effect of vitamin E supplementation on nutritional status in MHD participants.[376,378] Participants received either tocotrienols (90 mg) and tocopherols (20 mg) for16 weeks or 400 IU of oral vitamin E per day, 600 mg of ALA per day, or both for 2 months. Although there were no changes in albumin levels between groups in the former study (Daud et al[378]), in Ahmadi et al,[376] SGA score was improved in the vitamin E, ALA, and combined supplementation groups compared with placebo. SGA score was the primary outcome of interest in this study. Vitamin E deficiency status at baseline was not described in either study.

Three RCTs examined the effect of oral vitamin E supplementation on anthropometric measures.[376,378,382] All studies reported no effect of vitamin E supplementation on BMI or body weight. Anthropometric measurements were not the primary outcomes of interest in any of these studies.

Inflammatory Markers: CRP and IL-6. Five studies examined the effect of vitamin E supplementation on inflammatory biomarkers, particularly CRP and IL-6 levels.[376,378-380,382] In 3 of the studies, these inflammatory markers were the primary outcomes of interest.[368,372,374] Himmelfarb et al[379] and Ramos et al[382] gave vitamin E supplementation in combination with ALA, and Ahmadi et al[376] examined vitamin E supplements alone and in combination with ALA. All studies assessed the effect of oral vitamin E supplementation on the CRP inflammatory marker levels in patients with CKD stages 3-5 and MHD participants. None of them found any effect of vitamin E supplementation ranging from 400 to 800 IU of oral vitamin E per day

(with or without 600 mg of ALA) for durations ranging from 5 weeks to 6 months on CRP levels.

Three of the studies also measured IL-6 and found no relationship between vitamin E supplementation and IL-6 levels.[378,379,382] Ramos et al[382] (stages 3-5 CKD) and Himmelfarb et al[379] (MHD patients) both supplemented with daily oral 666 IU of mixed tocopherols (vitamin E) plus ALA, 600 mg, for 8 weeks and 6 months, respectively. Neither found an effect of supplementation on serum IL-6 levels. However, Ahmadi et al[376] found that oral vitamin E alone (400 IU/d) or in combination with 600 mg of ALA per day reduced IL-6 cytokine levels in MHD participants. In pooled analysis of 2 RCTs that used vitamin E alone or with ALA, there were no effects on IL-6 levels compared with the placebo groups.

Serum Vitamin E Levels. Two RCTs examined the effect of daily oral vitamin E supplementation on vitamin E levels.[377,380] Both studies included MHD patients. Hodkova et al[380] found that serum vitamin E levels increased in the vitamin E–supplemented group (α-tocopherol, 400 mg/888 IU) after 5 weeks, but no change in the control. Between-group differences were not reported. Boaz et al[377] found that the vitamin E–supplemented group had significantly higher vitamin E levels compared with the placebo group when MHD participants with pre-existing CVD were supplemented with 800 IU of oral vitamin E per day for a median of 519 days, but between-group differences were not reported. In pooled analysis of the 2 RCTs that examined vitamin E supplementation alone, there was no significant effect of supplementation compared with the placebo/control group. Therefore, available evidence indicates that vitamin E supplementation alone does not affect vitamin E levels.

Lipid Levels. Daily oral vitamin E supplementation of 110 mg for 4 months[378] and 200 mg for 3 months (Khajehdehi et al[267]) did not change serum TG, TC, or LDL-C levels but demonstrated the efficacy of increasing HDL-C levels.

Special Discussions

As a result of the limited number of high-quality studies (see study selection criteria) and the variability in the outcomes reported in these trials, there is insufficient evidence to make recommendations on vitamin E intake for patients with CKD. The nutritional requirements or Recommended Dietary Intake of vitamin E for individuals with CKD stages 1-5, those undergoing maintenance dialysis, and those posttransplant are unknown. Dose-response studies identifying the relation between vitamin E intake and serum vitamin E levels are not available. The prevalence of vitamin E deficiency in the CKD population is unclear. The potential of vitamin E toxicity with supplementation is a concern for this fat-soluble vitamin.

There is a potential for toxicity in patients who are being supplemented. High doses of vitamin E supplementation have the potential to increase the risk for hemorrhagic stroke and impair platelet aggregation. Vitamin E interacts with anticoagulant and antiplatelet medications and therefore caution is advised on vitamin E supplementation for patients with CKD already receiving these medications.

Vitamin A was investigated in this systematic review. However, there were no trials examining dietary intake of vitamin A, and supplementation trials included IV vitamin A, which the work group determined qualified as a medication versus a nutritional supplement. However, the same concerns regarding toxicity of vitamin E supplementation apply to vitamin A supplementation.

Recommendations cannot be made with regard to vitamin A or E supplementation in the CKD population. An individualized approach is required in considering the need to supplement vitamins A or E or terminate supplementation in the adult CKD population and there is also a need to monitor for toxicity with supplementation.

Implementation Considerations

- Implementation of vitamin E supplementation should consider the individual patient's nutritional status, dietary intake, concomitant medications, comorbid conditions particularly with regard to baseline CVD, and lipid levels.
- Oral doses ≥ 400 IU of vitamin E are not recommended without at least intermittent monitoring of serum vitamin E levels.

Monitoring and Evaluation

Platelet count should be monitored, as should any changes in medical status, medications, and nutritional status.

Future Research

- Identify methods to assess vitamin E status. Current methods use serum levels of vitamin E, but the sensitivity and reliability of this approach are unclear.
- Ascertain the optimal vitamin E status of the CKD population, including CKD stages 1-5, those receiving dialysis, and those who have received a kidney transplant.
- The potential role of vitamin E–treated dialyzer membranes on preventing intradialytic hypotension, improving nutritional status, decreasing/preventing intradialytic inflammation, and anemia resistance is not yet defined. Ongoing studies in this area are indicated to further define the role of vitamin E–treated dialyzer membranes.
- Investigate the recommended dietary vitamin E intake that will prevent vitamin E deficiency and the recommended supplemental dose of vitamin E that will correct vitamin E deficiency without increasing the risk for

toxicity, including investigation of the effects of larger doses of oral vitamin E (ie, 800 IU/d).
- Examine the effects of vitamin E supplementation on hard outcomes, including CVD, morbidity, and mortality, using RCTs.

5.5 Statement on Vitamin K

Anticoagulant Medication and Vitamin K Supplementation

5.5.1 In adults with CKD 1-5D or posttransplantation, it is reasonable that patients receiving anticoagulant medicines known to inhibit vitamin K activity (eg, warfarin compounds) do not receive vitamin K supplements (OPINION).

Background

Vitamin K is a fat-soluble vitamin that acts as a cofactor for gamma-glutamyl carboxylase, which enables the carboxylation of vitamin K–dependent proteins producing coagulation factors. Coagulation factors II, VII, IX, and X are the most well-known vitamin K–dependent proteins, and deficiency in these factors can lead to impairment in blood clotting. Vitamin K also enables normal calcification processes to proceed in bone and soft tissues. Matrix Gla protein (MGP) is a vitamin K–dependent protein produced by vascular smooth muscle cells that is a powerful inhibitor of vascular calcification in culture media and of intimal atherosclerotic plaque calcification. After carboxylation, MGP binds to calcium crystals, inhibiting further crystal growth. MGP binds to bone morphogenetic protein 2, thereby blocking the differentiation of vascular smooth muscle cells toward osteochondrogenic type cells.

Vitamin K participates in the enzymatic carboxylation of proteins controlling bone calcium deposition (eg, osteocalcin) and plays an important role in normal bone formation and structure.

Hence vitamin K, by facilitating carboxylation of certain proteins, has major effects on blood clotting, preventing soft tissue calcification including vascular calcification, and controlling bone calcium crystal formation.

Two classes of vitamin K compounds are primarily responsible for vitamin K activity: phylloquinone (vitamin K_1) and menaquinones (vitamin K_2).[383] Phylloquinone is found primarily in foods, especially green and leafy vegetables (eg, spinach, kale, cabbage, and broccoli), plant-based oils found in many food products, and cow's milk. There are more than 10 menaquinones that differ in the number of isoprenoid units in its side chain. Most menaquinones are produced by bacteria. Menaquinone 4 is different and appears to be produced in vivo from phylloquinone.[383,384] Menaquinones are found in dairy products (yogurt), meats, and fermented foods and also synthesized in the intestine by colonic bacteria. The intestinal absorption of vitamin K requires biliary and pancreatic secretions and occurs in the small intestine, where vitamin K is incorporated into chylomicrons. The role of the menaquinones in vitamin K function and nutritional needs is still not completely understood. Large doses of vitamin E may induce vitamin K deficiency.[384]

Detailed Justification and Special Discussion

The US IOM states that the adequate intake of vitamin K is 120 and 90 μg/d for adult men and women, respectively.[385,386] These values are based on median vitamin K intakes reported in the NHANES III data. Globally, dietary recommendations for vitamin K usually vary from 50 to 120 μg/d.[387] These recommendations do not differentiate phylloquinone from menaquinone intake. At the time the US IOM recommendations were set, the food composition databases on which these recommendations were made contained only the phylloquinone content of foods. Hence, these current recommendations are based on phylloquinone, which is the major form of vitamin K in Western diets.

Increasing age, platelet count, and serum urea and creatinine levels and lower serum albumin concentrations were associated with more severe elevation in prothrombin time in patients taking antibiotics.[388,389] Vitamin K supplements may return prothrombin time to normal in such patients.[389] Patients receiving antibiotics who have poor intake and are at higher risk for bleeding (eg, surgical patients) may be considered for vitamin K supplements, particularly if they have acute kidney injury or CKD.[388] However, the foregoing conclusions were essentially based on observational studies of small numbers of patients.

A study of the NHANES data indicated that 72.1% of adults with mild to moderate CKD (eGFR by the CKD Epidemiology Collaboration [CKD-EPI] equation: 58 mL/min/1.73 m^2) had vitamin K intake below the recommended adequate intake level (mean, 97.5; 95% CI, 89.7-105.3 μg/d).[390] Studies in Italy confirmed that daily intake of vitamin K_1 in MHD patients is commonly below recommended levels.[387] Several observational studies in advanced CKD (stages 3-5) or MHD patients indicated that serum vitamin K_1 (phylloquinone) and vitamin K_2 (menaquinone) concentrations were frequently low and that serum levels of other uncarboxylated compounds, which when elevated indicated vitamin K deficiency, were increased.[391,392]

The recommended dietary vitamin K intake for patients with CKD 1-5, including those with nephrotic syndrome, those who are undergoing MHD or PD, or those who are posttransplant, were not defined and were based on that derived for the general population. In MHD patients, vitamin K intake and serum vitamin K levels are often low or undetectable, and serum uncarboxylated osteocalcin and PIVKA-II (protein induced by vitamin K absence/antagonist-II) levels are commonly elevated.[310,311]

Vitamin K Levels. Only 1 short-term randomized controlled study has been published that examined the effects of vitamin K supplements on vitamin K status in MHD patients.[392] No such studies have been carried out in other stages of CKD or in PD patients or those post-transplant. The study involved a small number of patients who received, by random assignment, supplements of 45, 135, or 360 μg/d of vitamin K_2 (menaquinone-7) for only 6 weeks. In general, there was a dose-dependent increase in serum vitamin K_2 and decrease in serum uncarboxylated desphosphorylated form of-uncarboxylated dpucMGP (MGP), undercarboxylated osteocalcin, and PIVKD-II levels. Mean serum vitamin K_2 level increased to previously reported normal values with the 45-μg/d dose and to modestly above normal values with the 135- and 360-μg/d doses. Serum uncarboxylated desphosphorylated form of MGP, ucosteocalcin, and PIVKD-II levels decreased most with the 360-μg/d dose, but concentrations still tended to be above normal with this dose.

There are currently several clinical trials of vitamin K supplements in MHD patients, and more information regarding vitamin K supplementation should be available within the near future[297,393,394] (Clinical Trials Identifier: NCT01528800; NCT01742273; NCT2610933; NCT02870829; UMIN000011490; UMIN000017119). In a 2019 study published since the systematic review supporting this guideline, when patients receiving HD received 10 mg daily of rivaroxaban, those who received 2,000 mg of menaquinone-7 three times each week after dialysis had no difference in calcification outcomes at 18 months. Though they were secondary outcomes, authors also found no difference in all-cause death, stroke, cardiovascular event rates, or adverse events between groups.[395] There is a paucity of data on the long-term safety of different vitamin K intakes and especially of vitamin K supplements and of the value, if any, of taking different vitamin K compounds. Individuals receiving vitamin supplements should not receive anticoagulant medicines that inhibit vitamin K activity (eg, warfarin compounds).

Implementation Considerations

- Patients receiving antibiotics who have poor intake and are at higher risk for bleeding (eg, surgical patients) may be considered for vitamin K supplements, particularly if they have acute kidney injury or CKD.[388] However, the foregoing conclusions were essentially based on observational studies of small numbers of patients.
- The RDN may provide dietary assessment/counseling related to excess dietary intake of vitamin K or irregular excess intake of foods containing high vitamin K and providing education regarding dietary sources of vitamin K.

Future Research

- Considering the high prevalence of bone disorders and severe atherosclerotic and coronary artery vascular disease in patients with CKD and the relationship of these disorders to calcium deposition in these tissues, there is a great need to more precisely define the dietary vitamin K requirements and the role, if any, for routine vitamin K supplementation or increased vitamin K intake through food sources in patients with different types and stages of CKD and with vascular calcification.
- Examine the confounding effects of different comorbid conditions on the dietary requirements for vitamin K intake and the need for vitamin K supplements and the dose of such supplements in patients with kidney disease.
- Examine the physiology and metabolism of vitamin K in people with CKD, with particular regard to evaluate why vitamin K deficiency appears to be more common in people with advanced CKD, including those undergoing maintenance dialysis.
- Evaluate the long-term clinical effects including the safety and potential risks, if any, of vitamin K supplements.
- Examine whether there are interactions between vitamin K supplements and anticoagulants that are not warfarin-type compounds.
- Examine whether dietary intake of vitamin K_1 and vitamin K_2 have any different clinically important effects in kidney diseases.

5.6 Statement on Trace Minerals – Selenium and Zinc

Selenium and Zinc Supplementation

5.6.1 In adults with CKD 1-5D, we suggest to not routinely supplement selenium or zinc since there is little evidence that it improves nutritional, inflammatory, or micronutrient status (2C).

Rationale/Background

Selenium is a trace element that has known antioxidant properties and plays a role in enzymatic activities inside the body. It acts as a cofactor for the reduction in important antioxidant enzymes such as glutathione peroxidase and thus protects against oxidation. Several studies have suggested that MHD patients have low levels of selenium compared with healthy controls, and deficiency of this trace element may contribute to increased oxidative stress and inflammation.[396-399] There is also some preliminary suggestion that low selenium levels may be associated with increased death risk in MHD patients, especially death due to infections.[398]

Zinc is an essential micronutrient and forms a component of biomembranes. It functions not only as an

antioxidant but also has anti-inflammatory effects and prevents free radical–induced injury during inflammation. There is some suggestion that marginal zinc intake may be associated with an increased risk for CVD in the general population[400] and zinc has been shown to protect against atherosclerosis by inhibiting the oxidation of LDL-C in animal studies.[81] Zinc deficiency has been shown to increase oxidative stress and nuclear factor-κB (NF-κB) DNA-binding activity and induce inflammation in experimental models.[401-403]

Zinc is also essential for insulin synthesis and release and glucose homeostasis,[404] and zinc deficiency has been suggested to impair insulin secretion and decrease leptin levels.[405] Studies have reported a high prevalence of zinc deficiency in HD patients.[406-408]

The current RDA for zinc is 8 mg/d for women and 11 mg/d for men in the general population, and for selenium is 55 μg/d for women and men. Whether a similar amount of intake is recommended in various CKD stages and the maintenance dialysis population is currently not known.

Detailed Justification

Selenium. In adults with CKD, 7 studies have examined the effect of selenium intake on biomarker levels and other surrogate health outcomes. Most of the studies used oral selenium supplementation and all studies were performed in MHD patients. Koenig et al[409] examined the effect of IV selenium supplementation and Stockler-Pinto et al[410] examined the effect of selenium supplementation in the form of a Brazil nut. Selenium dosages generally ranged from 175 to 1,400 μg per week. The selenium dosage in Stockler-Pinto et al[410] was not described (1 Brazil nut per day), and in Koenig et al,[409] the parenteral dose of selenium used was much higher (400 mg 3 times a week) compared with other studies. Study duration ranged from 14 days to 6 months. In Temple et al,[411] participants' selenium status at baseline was normal. In a study by Tonelli et al,[412] 28% of the treatment group versus 15% of the placebo group had low selenium levels after supplementation. Around 20% of participants were selenium deficient in Stockler-Pinto et al,[410] and the remaining studies did not report selenium status at baseline.

Nutritional status. Only 1 very short-term (12 weeks) randomized placebo-controlled study examined the effect of oral selenium supplementation of 200 μg per day on nutritional status in 80 MHD patients.[413] The study reported a significantly greater reduction in SGA score and MIS in the selenium group compared with the placebo group. However, no significant difference was observed in serum albumin concentrations between the 2 groups.[413] The same study by Salehi et al[413] did not observe any difference in median changes in CRP levels between the selenium and placebo groups. Although a smaller increase in IL-6 levels was observed in the selenium group compared with the placebo group,[413] this is the only study that examined inflammation as an outcome. Thus, there is not enough evidence to make recommendation of selenium supplementation for malnutrition-inflammation syndrome in MHD patients.

Selenium levels. Although 2 short-term small randomized controlled studies provided some evidence that selenium supplementation may be useful in increasing plasma and erythrocyte selenium levels,[411,414] it is not known if selenium supplementation may affect any patient health-related or hard clinical outcomes. Only 1 short-term randomized study by Salehi et al[413] examined the effects of oral selenium supplementation on lipid levels. The results showed no difference between the selenium group and control group in any of the lipid parameters, including TG, TC, LDL-C, and HDL-C levels.[413]

Zinc. Nutritional status. Three small short-term RCTs examined the effects of zinc supplementation on nutrition status in MHD patients. The study duration ranged from 8 weeks to 90 days. The dose of zinc supplementation ranged from a daily dose of 11 mg, 50 mg, to 100 mg of elemental zinc.[415-417] In the study by Argani et al,[415] serum albumin levels increased in the zinc-supplemented group but there was no change in the placebo group. Guo et al[416] examined zinc supplementation of 11 mg daily for 8 weeks in a cohort of 65 MHD patients with low baseline zinc levels (<80 mg/dL). Descriptive quantitative data were not provided, but the authors concluded that PNA and albumin levels significantly increased in the zinc-supplemented group but not in control group.[416] Jern et al[417] showed that PCR increased with 50 mg of zinc supplementation for 90 days but no change in the placebo group. Between-group differences were not provided in these studies. The data from these 3 small low-quality trials were regarded as inconclusive and not enough to make recommendation.

Lipid profile. Four short-term RCTs examined the effect of oral zinc supplementation on lipid levels.[415,418-420] The studies by Argani et al[415] and Rahimi-Ardabili et al[419] administered 100 mg of oral zinc daily to MHD patients for 2 months. Argani et al[415] showed no changes in cholesterol and TG levels with zinc supplementation. Rahimi-Ardabili et al[419] showed that cholesterol levels increased significantly in the placebo group but no change in the treatment group, and TC levels were not different between the 2 groups after 2 months' study. In the other 2 studies, Roozbeh et al[420] and Chevalier et al[418] both supplemented MHD patients with 50 mg of zinc daily for 6 weeks and 90 days, respectively. All patients in these 2 studies were zinc deficient at baseline (<80 μg/dL). Both studies showed that TC, LDL-C, HDL-C, and serum TG levels increased in the zinc-supplemented group but no change in the control group. The conclusions by the authors in these studies suggested that this increase in lipid parameters was desirable.[418,420] Pakfetrat et al[421] examined the effect of 50 mg of oral zinc per day for 6 weeks in MHD patients and found that significantly decreased homocysteine levels decreased in the zinc-supplemented

group compared with the placebo group. Two studies examined the effects of zinc supplementation on inflammatory parameters, but results were inconclusive.[422] Data for the effects of zinc supplementation on body weight and BMI were mixed and limited.[415,423]

Zinc levels. Six RCTs examined zinc supplementation in relation to serum zinc levels in MHD patients.[412,415,416,418,420,424] All except the Tonelli et al[412] study described zinc deficiency at baseline. The dosages of zinc supplementation used ranged from 11 to 110 mg. Study durations ranged from 5 weeks up to 6 months. In the study by Tonelli et al,[412] zinc levels in the medium-dose (50 mg/d) but not the low-dose (25 mg/d) group were significantly higher than in the nonsupplemented group at 90 and 180 days after supplementation. A pooled analysis of these 6 studies showed a mean increase of 30.97 (95% CI, 17.45-44.59) μg/dL in serum zinc levels after supplementation compared with the control group. However, heterogeneity was high. Furthermore, it is not known whether zinc supplementation in deficient patients may affect any health-related outcomes or clinical hard outcomes in patients with CKD and dialysis patients. The long-term effects or any toxicity of zinc supplementation are also unclear at this stage.

There were no identified studies examining the effect of zinc supplementation on dysgeusia in patients with CKD, though this topic has been explored in other populations.[425]

Implementation Considerations

- Suggested intake should be based on recommendations for the general population (eg, RDA) unless there are specific considerations requiring modification.

Monitoring and Evaluation

There are no specific guidelines for monitoring selenium and zinc deficiency or supplementation. However, although unlikely, practitioners should be aware of signs and symptoms of severe selenium and zinc deficiency in patients with stages 3-5D CKD.

Future Research Recommendations

- Evaluate biochemical testing and thresholds to define zinc and selenium deficiency and whether the same thresholds in the general population are applicable to patients with kidney diseases.
- Conduct population-based cohort studies to determine the prevalence and importance of selenium and zinc deficiency across different stages of patients with CKD and kidney transplant recipients, as well as dialysis modality, and examine whether selenium or zinc deficiency may be related to various surrogate and hard clinical outcomes.
- Conduct adequately powered clinical trials of long enough duration to evaluate whether selenium or zinc supplementation in deficient patients with CKD and maintenance dialysis patients may improve various surrogate markers of inflammation and PEW, lipid parameters, wound healing, dysgeusia, and other health outcomes in a dose-dependent manner. Limited data suggest that further randomized trials should recruit specifically selenium-deficient patients.
- The safety of prescribing zinc in nondeficient dialysis patients also needs to be determined.

Guideline 6: Electrolytes

6.1 Statements on Acid Load

Dietary Management of Net Acid Production (NEAP)

6.1.1 In adults with CKD 1-4, we suggest reducing net acid production (NEAP) through increased dietary intake of fruits and vegetables (2C) in order to reduce the rate of decline of residual kidney function.

Bicarbonate Maintenance

6.1.2 In adults with CKD 3-5D, we recommend reducing net acid production (NEAP) through increased bicarbonate or a citric acid/sodium citrate solution supplementation (1C) in order to reduce the rate of decline of residual kidney function.

6.1.3 In adults with CKD 3-5D, it is reasonable to maintain serum bicarbonate levels at 24-26 mmol/L (OPINION).

Rationale/Background

Acid-base homeostasis is maintained by urinary acidification using titratable anions, such as phosphate, to trap protons, and trapping ammonium in an acid urine. As kidney function declines, the net acidification requirement by residual nephrons increases. This leads to increased ammonia production per residual nephron and requires delivery of glutamine to the residual nephrons as a source of the delivered ammonia.. The increased per-nephron need for increased acidification and ammonia genesis is in part endothelin controlled and may increase injury to residual nephrons. Acid retention also would have the potential to promote muscle wasting as part of the homeostatic processes of normalizing acid-base status. Metabolic acidosis increases skeletal muscle proteolysis by a ubiquitin proteasome pathway that degrades actin, potentially having an adverse nutritional impact on the patient accompanied by an increase in PCR.

Detailed Justification

Eleven studies examined the association between dietary acid load/oral bicarbonate supplements on health outcomes in the CKD population. Of the included studies,

there were 4 RCTs,[212,213,426,427] 1 NRCT,[214] 3 noncontrolled studies,[428-430] 2 prospective cohort studies,[431,432] and 1 retrospective cohort study.[433]

CKD Progression; Effect of Reducing Net Endogenous Acid Production. Studies aimed at evaluating the effect of reduction in net endogenous acid production (NEAP) have been 2-fold; either directly reducing NEAP by administration of sodium bicarbonate or by dietary alteration using fruits and vegetables, which both decrease NEAP and alter the composition and quantity of dietary protein, partially confounding the effect of reduction of NEAP alone.

In adults with CKD, 4 RCTs,[212,213,426,427] 1 NRCT,[214] 2 noncontrolled studies,[429,430] 2 prospective cohort studies,[431,432] and 1 retrospective cohort study[433] examined the effects of dietary fruit and vegetable or oral bicarbonate supplements on CKD progression. In patients with CKD stages 2-4 (20-65 mL/min/1.73 m^2 in available studies), higher quartiles of NEAP were associated with greater ^{I125}iothalamate GFR decline (P-trend = 0.02).[432] In CKD stages 3-5 not receiving dialysis (≤60 mL/min/1.73 m^2), higher NEAP is associated with CKD progression ($P < 0.05$ for all quartile groups).[433] In CKD stages 3-4 (≥15 or <60 mL/min/1.73 m^2) compared with the lowest dietary acid load tertile, the highest dietary acid load had greater relative hazard of ESKD ($P = 0.05$).[431]

Studies reducing NEAP by the administration of oral sodium bicarbonate are not confounded by alteration in dietary protein composition and are easier to study in a randomized controlled prospective manner. In studies involving patients with CKD stages 4-5, the oral sodium bicarbonate group had significantly greater creatinine clearance after 18 and 24 months ($P < 0.05$). Rapid CKD progression (creatine clearance loss > 3 mL/min/1.73 m^2 per year) was lower in the oral sodium bicarbonate group (RR, 0.15; 95% CI, 0.06-0.40). The development of ESKD was lower in the oral sodium bicarbonate group (RR, 0.13; 95% CI, 0.04-0.40).[426] In another study of CKD stages 4-5, not receiving dialysis, there was no significant difference in creatinine clearance between before and after the intervention ($P > 0.05$).[430] A recent study not included in the systematic review had similar findings in that participants receiving sodium bicarbonate (0.4 mEq/kg IBW per day) for 24 months had no difference in change in eGFR compared with the placebo group.[434] In patients with less impaired kidney function at baseline (CKD stage 3), there was a reduction in eGFR in all groups. However, at 3 years, a lesser reduction in eGFR was observed with the bicarbonate group or fruits and vegetables than the usual-care group.[213]

In a study by Goraya et al[212] in patients with CKD stage 4 using either fruits and vegetables or sodium bicarbonate as the intervention, plasma creatinine levels were comparable between patients treated with either bicarbonate or fruits and vegetables at baseline and the 1-year follow-up ($P = 0.99$ and $P = 0.49$, respectively), eGFRs were comparable between the 2 groups at baseline and the 1-year follow-up ($P = 0.84$ and $P = 0.32$, respectively). This study does not isolate the effects of alteration in dietary composition and NEAP sufficiently to establish which intervention is associated with any biological change observed.

The outcome of studies in patients with CKD stages 1-2 are less clear and the outcomes are not as definitive. This may be in part because the per-nephron stress of maintaining acid-base balance is reduced, either decreasing the renal risk of acidification below a critical threshold or by reducing the power necessary to measure an effect. Additionally, studies that alter NEAP by changing dietary composition are confounded by other variables, such as amino acid load and quality. One of the outcome variables measured was urinary albumin excretion.

Net urine albumin excretion was not different among the 3 groups in patients with CKD stage 1 ($P > 0.05$). However, in patients with CKD stage 2, fruits and vegetables had a greater decrease in net urine albumin excretion than both bicarbonate and control ($P < 0.05$), and the bicarbonate group had a greater decrease in net urine albumin excretion than control ($P < 0.05$).[214] It should be noted that a change in diet toward higher intake of fruit and vegetables is a different and more complex intervention than change in NEAP because the amino acid load and composition are changed. This may affect urinary protein loss and have an effect on progression that is independent of NEAP if the patient population has significant proteinuria.

Hospitalization. The effects of oral bicarbonate supplements on hospitalization in patients with CKD were mixed, though evidence is limited. In adults with CKD, 2 RCTs[426,427] examined the effects of oral bicarbonate supplements on hospitalization. Among patients treated by PD, compared with the placebo group, the intervention group had lower hospital admission (trend) and hospital length of stay ($P = 0.07$ and $P = 0.02$, respectively).[427] In CKD stages 4-5; predialysis, there was no significance difference in hospitalization for heart failure between the 2 groups (P = NS).[426]

Nutritional Status. In patients with CKD stages 3-5 including those receiving maintenance dialysis, oral bicarbonate supplements improved nutritional status (eg, SGA scores, nPCR, and albumin and prealbumin levels) in most studies. Oral bicarbonate supplements increased overall SGA scores (2.7 g/d)[427] and lowered nPNA (nPCR) (de Brito-Ashurst et al,[426] ~1,800 mg/d). Except for Kooman et al,[428] (dialysate bicarbonate and oral sodium bicarbonate, 1,500-3,000 mg, if predialytic bicarbonate did not reach desired level), the other 3 studies observed positive effects of oral bicarbonate supplements on serum albumin or prealbumin levels (de Brito-Ashurst et al,[426] ~1,800 mg/d; Movilli et al,[429] mean dose, 2.7 ± 0.94 g/d; 1-4 g/d; Verove et al,[430] mean dose, 4.5 ± 1.5 g/d.

Oral bicarbonate supplements also had no effects on TSF measurements.[428] de Brito-Ashurst et al[426] (~1,800 mg/d) noted significant increases in MAMC measurements with oral sodium bicarbonate, whereas Kooman et al[428] did not.

Two RCTs[426,427] and 3 noncontrolled studies[428-430] examined the effects of oral bicarbonate supplements on nutritional status in adults with CKD. In PD, the oral bicarbonate group had higher overall SGA scores starting at 24 weeks ($P < 0.0003$).[427] In CKD stages 4-5 (not 5D) the oral sodium bicarbonate group had significant lower nPNA (nPCR) at 12 and 24 months ($P < 0.05$) and the oral sodium bicarbonate group had significant higher serum albumin levels at 12 and 24 months ($P < 0.05$).[426]

In contrast, in a group of patients receiving MHD, there was no significant difference in serum albumin levels among time points ($P > 0.05$).[428] In MHD, oral sodium bicarbonate increased serum albumin levels ($P = 0.01$).[429]

Among patients with CKD stages 4-5 (not 5D), oral sodium bicarbonate increased both serum albumin and prealbumin levels between before and after intervention ($P < 0.05$).[430] Among CKD stages 1-2 compared with control and bicarbonate, the fruit and vegetable group had a significantly greater decrease in body weight at the end of the intervention for both individuals with CKD stage 1 and stage 2 ($P < 0.05$ for both), with no difference between bicarbonate and control.[214] Thus there does not appear to be a significant effect of reduction in NEAP on nutritional status in patients with CKD 1-2. In CKD stage 4 compared with the bicarbonate group, the fruits and vegetables group had lower weight at the 1-year follow up ($P < 0.01$); baseline weight did not differ between the 2 groups ($P = 0.24$).[212] In CKD stage 3, fruits and vegetables had greater net body weight loss than both bicarbonate and control ($P < 0.05$) and the control group had greater net body weight loss than the bicarbonate group ($P < 0.05$).[213]

Special Discussions

In stage 5 MHD patients, higher bicarbonate concentration in the dialysate bath is associated with increased mortality in epidemiologic studies.[435] In an analysis of DOPPS data, it was reported that MHD patients with either very low bicarbonate (≤17 mmol/L) or very high predialysis bicarbonate (>27 mmol/L) concentrations are at the greatest mortality risk.[436] Paradigms that may apply to patients with residual renal function or those undergoing continuous therapy, such as PD, do not directly apply to HD patients who are experiencing large changes in acid-base equilibrium rapidly and/or discontinuously. Higher bicarbonate concentrations in HD patients may also be reflective of lower protein intake.

Research on this topic is complicated because the effect of acidosis differs with the level of residual kidney function. With advanced CKD, net acid load has a higher potential to contribute to loss of kidney function.

Dietary intervention is more complex because the effects of specific amino acids or other dietary constituents on both renal outcomes and vascular and bone pathophysiology (calcium/phosphorus) may play a role that is independent from their effect on acid-base physiology.

Implementation Considerations

- Acid load is a consequence of protein load and is inversely associated with potassium intake. The estimation of net acid intake is (NEAP [mEq/d] = −10.2 + 54.5 (protein [g/d]/potassium [mEq/d]). NEAP can be reduced by administration of sodium bicarbonate or sodium or potassium citrate or by reduction in dietary acid content by changing the dietary pattern to increase fruit and vegetable intake. The latter can be accomplished by reduction in dietary protein intake and changing dietary composition and pattern. Low protein intake may have the added benefit of slowing the rate of progression of kidney disease through other mechanisms (see Section 3.1). In the MDRD Study, patients randomly assigned to low protein intake exhibited a significant increase in serum bicarbonate levels,[437] so that there is an interaction between intake of protein and net acid. Separating the effect of reduction in acid load and the effect of change in dietary protein amount and dietary pattern on outcomes is challenging.
- When increasing fruits and vegetables intake to correct acid load, use caution and monitor potassium levels and make sure that energy and protein intake meet the nutritional needs.

Monitoring and Evaluation

Clinical trials have demonstrated adherence with expected changes in acid-base status as evaluated by measurement of serum bicarbonate.

Consuming fruits and vegetables in the amount that could reduce dietary acid by 50% generally had positive effects on acid-base biomarkers.[212-214] Fruits and vegetables increased plasma total CO_2 (though not significant in 1 study)[214] and decreased potential renal acid load and 8-hour net acid excretion. Except for Goraya et al[214] (0.5 mEq/kg per day), oral bicarbonate supplements also had positive effects on acid-base biomarkers by increasing plasma total CO_2 or bicarbonate levels and decreasing potential renal acid load and 8-hour net acid excretion in 6 studies with different supplement combinations and dosages.

No hyperkalemia events were noted in the studies of Goraya et al,[212] who provided a diet rich in fruits and vegetables to patients with advanced CKD. However, we note that inclusion criteria in those studies considered

patients at low hyperkalemia risk not consuming renin-angiotensin system inhibitors. Although no studies have formally evaluated the contribution of dietary potassium to hyperkalemia risk in these patients, we recommend caution if a fruit and vegetable–rich diet is to be recommended to control metabolic acidosis. Close monitoring of serum/plasma potassium levels is encouraged, and fruit/vegetable consumption should be temporarily limited if the patient is considered at risk for hyperkalemia. Monitoring of circulating potassium level is specially recommended in patients with CKD stage 4 or higher, including those receiving dialysis, because this is the kidney function range in which inabilities to compensate for dietary potassium occur.

Future Research

- Research is needed to identify the contribution of NEAP to that of protein intake to progression of kidney disease, as well as to increase urinary protein excretion. It is unknown what if any of the injurious effects of protein is contributed by acid load.
- Increased dietary acid intake is believed to contribute to loss of kidney function and sarcopenia. Further understanding of the optimal threshold for translation of these benefits to morbidity and mortality is necessary.
- With regard to the effects of fruits and vegetables, it is important to separate the effect of other aspects of differences in dietary composition, amino acid content, and carbohydrate composition from the control diet from the effects of acid load.
- Increasing pH during intermittent HD has not been shown to improve clinical outcomes, albeit most studies are based on epidemiologic data. It is important to establish the optimal intradialytic bicarbonate concentration and dialytic bicarbonate delivery to patients receiving MHD, as well as to understand the contribution of reduced protein intake to higher serum bicarbonate levels in HD patients.

6.2 Statements on Calcium

Total Calcium Intake

6.2.1 In adults with CKD 3-4 not taking active vitamin D analogs, we suggest that a total elemental calcium intake of 800-1,000 mg/d (including dietary calcium, calcium supplementation and calcium-based phosphate binders) be prescribed to maintain a neutral calcium balance (2B).

6.2.2 In adults with CKD 5D, it is reasonable to adjust calcium intake (dietary calcium, calcium supplements, or calcium-based binders) with consideration of concurrent use of vitamin D analogs and calcimimetics in order to avoid hypercalcemia or calcium overload (OPINION).

Rationale/Background

Calcium is a multivalent cation important for many biological and cellular functions. Approximately 99% of total-body calcium is found in the skeleton and the rest is present in the extracellular and intracellular spaces. In addition to its role in maintenance of bone health, calcium serves a vital role in nerve impulse transmission, muscular contraction, blood coagulation, hormone secretion, and intercellular adhesion.

Calcium balance is tightly regulated by the concerted action of calcium absorption in the intestine, reabsorption in the kidney, and exchange from bone, which are all under the control of calciotropic hormones triggered by demand for calcium.

Serum calcium concentration is maintained in the normal range until very late in CKD, when it decreases slightly.[438] However, calcium balance in CKD is poorly understood. Calcium deficiency due to decreased intestinal calcium absorption is a stimulus for the development of secondary hyperparathyroidism and resultant bone disorders. However, calcium excess may promote extraosseous calcification contributing to the increased risk for CVD and mortality of these patients.[439] In kidney transplant, calcium balance is even more complex and depends on several factors, such as posttransplant kidney function, persistence of hyperparathyroidism, previous bone disease, and immunosuppressive therapy.[440]

Detailed Justification

Serum calcium levels do not reflect overall body calcium balance and may not be very informative except at extremes. Maintenance of serum calcium level in the normal range in CKD depends on several factors, such as bone turnover, mineral-regulating hormones, degree of kidney function, use of vitamin D analogues, dialysate calcium concentration, and calcium intake, especially from supplements. A careful medical and nutritional history may provide some insight into the adequacy of calcium intake. However, due to the multifactorial causes of altered calcium metabolism in CKD, the establishment of adequate amounts of dietary calcium is challenging and depends on the investigation of calcium balance.

The evidence review included 3 small short-term clinical trials in CKD patients not receiving dialysis that investigated the effect of calcium intake in food or supplements on mineral bone biomarkers and calcium balance. No other outcomes were investigated in these studies.

Calcium Balance and Other Laboratory Measures. In an NRCT, 51 patients in the early stage of CKD (creatinine clearance, 66-82 mL/min) were placed on a low-protein (40 g/d) and low-phosphorus (600 mg/d) diet supplemented with or without 0.5 g/d of elemental calcium for 10 days.[441] A decrease in intact PTH level was observed only in the group receiving calcium supplementation and no changes in serum calcium, phosphorus, and calcitriol levels were found in the other groups.

In a crossover study, 6 patients with CKD stages 3 and 4 consumed controlled high- (2,000 mg/d) and low-calcium diets (800 mg/d) for 9 days.[442] Calcium balance was slightly negative to neutral in both patients and healthy controls on the low-calcium diet (−91 ± 113 and −144 ± 174 mg/d, respectively; $P > 0.05$) and more positive in patients than in controls on the high-calcium diet (759 ± 120 and 464 ± 225 mg/d, respectively; $P < 0.05$). Serum calcium and phosphate concentrations were unchanged and intact PTH and $1,25(OH)_2D$ levels decreased in the high-calcium diet.

In a 3-week randomized crossover balance study, 8 patients with CKD stages 3 and 4 were randomly assigned to a controlled calcium intake of 2,457 mg/d (1,500 mg of elemental calcium from calcium carbonate used as phosphate binder + 957 mg/d of dietary calcium) versus placebo (957 mg/d of dietary calcium).[443] Calcium balance was neutral in the placebo group and positive in the calcium carbonate group (508 vs 61 mg/d, respectively; $P = 0.002$). Serum calcium, phosphate, and intact PTH concentrations were unchanged in both groups.

Despite the small number of patients investigated, these well-performed balance studies showed that dietary calcium intake of approximately 800 to 1,000 mg/d may be adequate to maintain calcium balance in patients with CKD stages 3 and 4 who are not receiving active vitamin D analogues, at least at short term. These values are close to the current estimated average requirement (800-1,000 mg/d) and the RDA (1,000-1,200 mg/d) for healthy individuals proposed by the IOM.[371]

Special Discussions

In maintenance dialysis patients, calcium balance is more complex. In addition to dietary calcium load and use of vitamin D analogues, calcium concentration in the dialysate and mode of dialysis also determine the mass balance of calcium. Studies using mathematical modeling have shown a positive calcium balance mass in patients receiving MHD.[444,445] According to estimates and assumptions made, extracellular fluid calcium levels increased with an elemental daily calcium intake > 1.5 g and were numerically more positive when patients are given active vitamin D analogues.[444] The excess of extracellular calcium is deposited in either osseous or extraosseous sites. The extensive soft tissue calcification highly prevalent in MHD patients suggests that extraosseous sites seem to be the repository for this calcium.[446]

Although calcium balance studies are demanding, they are essential to provide data to make conclusive recommendation for calcium intake from diet or supplements for patients receiving maintenance dialysis. Notably in KDIGO (CKD-MBD) 2009 and 2017, there are no recommendations for calcium intake for patients receiving maintenance dialysis or with a kidney transplant.[349,447]

Implementation Considerations

Hypercalcemia is relatively common in patients receiving maintenance dialysis. Evidence has been accumulated linking higher serum calcium concentrations to increased nonfatal cardiovascular events[448] and mortality.[449-452] In the event of hypercalcemia, the following adjustments are recommended[348]:

- In patients taking calcium-based phosphate binders, the dose should be reduced or therapy switched to a non-calcium phosphate binder.
- In patients taking active vitamin D analogues, the dose should be reduced or therapy discontinued until serum concentrations of calcium return to normal.
- If hypercalcemia persists, consider using a low dialysate calcium concentration (1.5-2.0 mEq/L). This should be done with caution because observational studies have linked this approach with increased risk for arrhythmia and heart failure.[453,454]

Future Research

- Adequate dietary management of calcium can contribute in the control of mineral and bone–related complications in CKD. However, there is an urgent need for additional research to cover the existing gap in this area.
- Calcium balance studies are needed to provide data for recommendation of a safe calcium intake threshold for patients with CKD in the different stages of the disease, including maintenance dialysis (MHD and PD) and kidney transplant.
- The effect of different sources of calcium (dairy foods, fortified foods, and calcium supplements) on serum calcium concentrations should be studied.
- Define acceptable serum calcium thresholds for different CKD stages.

6.3 Statements on Phosphorus

Dietary Phosphorus Amount

6.3.1 In adults with CKD 3-5D, we recommend adjusting dietary phosphorus intake to maintain serum phosphate levels in the normal range (*1B*).

Dietary Phosphorus Source

6.3.2 In adults with CKD 1-5D or posttransplantation, it is reasonable when making decisions about phosphorus restriction treatment to consider the bioavailability of phosphorus sources (eg, animal, vegetable, additives) (*OPINION*).

Phosphorus Intake With Hypophosphatemia

6.3.3 For adults with CKD posttransplantation with hypophosphatemia, it is reasonable to consider prescribing high-phosphorus intake (diet or supplements) in order to replete serum phosphate (*OPINION*).

Rationale/Background

Phosphorus intake is necessary for bone growth and mineralization, as well as for regulation of acid-base homeostasis. Phosphorus is an essential nutrient, occurring in most foods both as a natural component and an approved ingredient added during food processing. Because of difficulties of persons with CKD to clear excess phosphorus, additional means of serum phosphate control are necessary to avoid hyperphosphatemia, which could lead to bone and mineral metabolism disorders of CKD.

There are physiologic adaptations in the early stages of CKD that prevent excessive phosphorus retention, so the inability to increase phosphorus excretion to avoid phosphorus accumulation and hyperphosphatemia is generally seen when eGFR decreases to <45 mL/min,[455] being less common in earlier CKD stages. In the setting of anuria in patients receiving maintenance dialysis, hyperphosphatemia risks are particularly heightened,[456] with a prevalence as high as 50%.[457]

Detailed Justification

How much dietary phosphorus/phosphate should be restricted in adult patients with CKD is not well established. Traditionally, CKD-specific recommendations suggest maintaining phosphorus intake between 800 and 1,000 mg/d in patients with CKD stages 3-5 and those receiving maintenance dialysis to maintain serum phosphate levels in the normal range.[67,160,348,349,458,459] However, the work group notes that the efficacy of this recommendation has not been established. Further, such a dietary phosphorus intake range is higher than the current recommended dietary allowance for phosphorus in the adult general population (700 mg/d).[460]

Although dietary intake influences serum phosphate levels in patients with CKD, factors other than intestinal phosphorus/phosphate absorption (namely exchange with bone and excretion by the kidneys in patients with residual renal function) may be major determinants of serum phosphate levels. Thus, the work group prefers not suggesting specific dietary phosphate ranges, but to instead emphasize the need to individualize treatments based on patient needs and clinical judgment, taking into consideration natural sources of organic phosphorus (animal vs vegetal protein-based dietary phosphorus) and the use of phosphorus additives in processed foods.[461-463]

With the goal of better understanding the effect of dietary phosphate control, the work group decided in this evidence analysis to focus on reports that addressed dietary phosphorus intake/output/balance. This resulted in the exclusion of studies reporting solely on serum phosphate levels.

Phosphorus Control. Limiting dietary phosphorus intake (per se or in combination with restriction of dietary protein, the major source of dietary phosphorus) may be recommended to prevent/treat complications related to high phosphate load in patients with CKD stages 3-5 and maintenance dialysis. This can be achieved by intensified patient educational strategies or individualized dietary plans.[464] This evidence review included 5 short-term clinical trials that evaluated the effect of reduced dietary phosphorus on phosphorus intake, phosphate levels, and urinary phosphorus excretion, as discussed in the following.

Phosphate restriction regimens in nondialysis CKD. Two RCTs[157,441] examined the effects of reduced dietary phosphorus in patients with CKD not undergoing dialysis. These studies evaluated the effect of a low-phosphorus diet alone or in combination with an LPD and observed significant reductions in serum phosphate levels and urinary phosphorus excretion postintervention.

Reducing phosphorus by limiting protein intake in nondialysis CKD. Five RCTs in patients with CKD not undergoing dialysis stages 4-5[146,147,154,167,177] evaluated the effect of an LPD or VLPD supplemented with KAs on serum phosphate levels. All 5 studies reported statistically significant[147,154,167,177] or borderline-significant[146] reductions in serum phosphate levels at the end of intervention. The interested reader can find more information on this topic in the evidence analysis of dietary protein restriction in these guidelines.

Phosphate restriction regimens in maintenance dialysis. Two RCTs[136,465] examined the effects of limiting dietary phosphorus in patients with CKD undergoing MHD. Lou et al[136] tested the effect of a 3-month intensified dietary counseling to achieve 800 to 900 mg/d of dietary phosphorus and observed a greater decrease in serum phosphate concentrations compared with standard care. Sullivan et al[465] tested the effect of patient education on identifying foods with phosphorus additives and observed, compared with standard care, a significant reduction in serum phosphate levels after 3 months. No studies were identified that included PD patients.

Although dietary phosphorus restriction may be a valid stand-alone strategy in patients with CKD stages 3-4, the working group notes that collectively, the serum phosphate reductions achieved solely by limiting dietary intake are modest (especially for dialysis patients) and recommend this strategy as only one in the armamentarium of interventions to maintain serum phosphate levels in the normal range. For other nondietary phosphate management strategies, the interested reader can consult recent guidelines on the management of the MBD of CKD.[67,160,348,349,458,459] Aligning with those guidelines, we recommend that decisions to restrict dietary phosphorus be based on the presence of progressively or persistently elevated serum phosphate levels (ie, trends rather than a single laboratory value) and after consideration of concomitant calcium and PTH levels.

Clinical Consequences of Dietary Phosphorus Control. Whereas many studies have explored the outcome associations with serum phosphate levels throughout the spectrum of CKD, the clinical consequences of restricting dietary phosphorus are not well studied.

CKD progression. Three observational studies evaluated the effects of dietary phosphate restriction on CKD progression. Results were mixed and evidence was limited. Williams et al[157] studied the impact of a dietary phosphorus restriction (alone or in combination with protein restriction) on creatinine clearance among 90 patients with CKD of unreported cause or CKD stage over a median intervention time of 19 months. Compared with routine care, dietary protein and phosphate restriction or phosphate restriction only did not show any significant difference in the mean rate of decrease in creatinine clearance. In an observational analysis from the MDRD Study, greater 24-hour urinary phosphate excretion (taken in this study as an estimate of dietary phosphorus intake) was not associated with future risk for ESKD.[466] We note that in this study, baseline phosphate levels were well controlled and normal on average, which may not be the case of real-world settings. A small retrospective observational analysis from Japan including patients with CKD stages 2-5 observed that higher phosphorus excretion per creatinine clearance was associated with higher 3-year risk for CKD progression (defined as the composite of ESKD or 50% reduction in eGFR).[467]

It has been proposed that hyperphosphatemia in nondialysis patients stages 2-5 may reduce the antiproteinuric effect of ACE inhibition[468] or of VLPDs.[469] In a post hoc observational analysis from the Ramipril Efficacy in Nephropathy (REIN) trial, Zoccali et al[468] evaluated the relationships between serum phosphate concentration at baseline, disease progression, and response to ACE inhibition among 331 patients with proteinuric nephropathies. Independent of treatment, patients with higher phosphate levels progressed significantly faster either to ESKD or a composite end point of doubling of serum creatinine level or ESKD compared with patients with phosphate levels below the median, and the renoprotective effect of ramipril decreased as serum phosphate level increased ($P \leq 0.008$ for interaction). In another post hoc study from a nonrandomized study in which 99 proteinuric patients with CKD who sequentially underwent an LPD (0.6 g/kg per day) and a VLPD (0.3 g/kg per day) supplemented with KAs, each for periods longer than 1 year, Di Iorio et al[469] observed that 24-hour proteinuria was reduced modestly in patients who maintained relatively higher serum phosphate levels or relatively higher phosphaturia to be maximal in those who achieved the lowest level of serum and urine phosphate.

Mortality. In observational studies involving patients with CKD, the associations of dietary phosphorus intake on mortality are mixed, affected by residual confounding and probably pointing to a null association. Three studies evaluated the cross-sectional association between measures of dietary phosphorus and mortality in individuals with nondialysis CKD.[466,470,471] Murtaugh et al[470] evaluated the association between 24-hour dietary recall estimation of phosphorus intake in participants with eGFRs < 60 mL/min/1.73 m^2 from the community-based US NHANES III and observed no association between dietary phosphorus intake and mortality. Palomino et al[471] examined patients with MI from the Heart and Soul Study, the majority of whom had normal kidney function, and observed no association between higher urinary phosphorus excretion and mortality but noted an association with CVD-related mortality (*P*-trend across tertiles = 0.02). Selamet et al[466] involved nephrology-referred patients with CKD from the MDRD Study and failed to observe an association between 24-hour urinary phosphorus excretion and mortality.

One study in MHD patients examined the association between dietary phosphate (as estimated from 3-day food recalls) and mortality.[472] Patients with higher dietary phosphorus intake were associated with greater 5-year mortality risk (*P*-trend across tertiles = 0.04). Lynch et al[473] explored the association between prescribed dietary phosphorus restriction and mortality in a post hoc analysis of the Hemodialysis (HEMO) Study, which included 1,751 MHD patients. The study exposure was ascertained by the serum phosphate targets that the dietitians from the clinical dialysis centers settled annually to prescribe their dietary recommendations. A more restrictive prescribed dietary phosphate intake was associated with poorer indices of nutritional status on baseline analyses and a persistently greater need for nutritional supplementation, but not longitudinal changes in caloric or protein intake. There was a stepwise trend toward greater survival with more liberal phosphate prescription, which reached statistical significance among participants prescribed 1,001 to 2,000 mg/d and those with no specified phosphate restriction: HRs of 0.73 (95% CI, 0.54-0.97) and 0.71 (95% CI, 0.55-0.92), respectively.

Special Discussions

Hypophosphatemia in kidney transplant patients: Hypophosphatemia is a relatively common complication after kidney transplantation, especially during the first months, and possibly leading to osteomalacia and osteodystrophy. Its pathogenesis has been attributed to increased renal phosphate excretion due to elevated levels of phosphaturic hormones, the effect of glucocorticoid, persistent elevated PTH levels, suboptimal recovery of vitamin D activation, and imbalance in FGF-23.[474-476]

It has been proposed that dietary intensification of phosphorus can solve this complication; 1 small RCT examined the effects of a 12-week dietary phosphorus supplementation by means of a neutral phosphate salt

(disodium phosphate) in patients with early post-transplantation hypophosphatemia.[477] The authors observed that compared with sodium chloride, supplementation of phosphorus improved hypophosphatemia, as well as adenosine triphosphate in the muscles and the acid excretion capacity of the kidney. No adverse effects on serum calcium and PTH concentrations were noted during the intervention.

However, the serum phosphate level at which supplementation should be considered in these patients or the dose of replacement to be given is not well studied and should be decided based on patient needs and clinical judgment.

Implementation Considerations

Recommendations to lower dietary phosphorus intake in patients with CKD have been met with concerns, often relating to the risk for limiting the intake of other nutrients, particularly protein, which is the main source of phosphate in the diet.[473,478,479] These concerns are particularly relevant to patients treated with dialysis because of protein losses in dialysate and greater protein catabolism from metabolic stress.[219] Dietary counseling that includes information on not only the amount of phosphate but also the source of protein from which the phosphate derives and suggestion on methods of cooking phosphate-rich foods can achieve phosphorus intake without compromising dietary quality or protein status.[480]

- Advise choosing natural foods that are lower in bioavailable phosphorus. Animal- and plant-based foods contain the organic form of phosphate. Although animal-based phosphate is absorbed in the gastrointestinal tract by 40% to 60%, the absorption of plant-based phosphorus is lower (20%-50%).[481] In line with this, a small crossover trial including patients with CKD stage 4 found that a 7-day vegetarian diet led to lower serum phosphate levels and decreased FGF-23 levels than a 7-day meat-based diet.[199] Furthermore, foods with only organic phosphorus typically are more nutrient dense and have higher nutritional value compared with processed foods containing phosphate additives, which tend to have lower nutritional value and are often paired with sodium and potassium additives.[482]
- Advise choosing commercial food items prepared without phosphorus-containing food additives. Phosphorus additives are increasingly being added to processed and fast foods to preserve moisture or color, emulsify ingredients and enhance flavor, and stabilize foods. However, phosphorus additives contain inorganic phosphorus with close to 100% intestinal absorption.[480,481] Meat and poultry products that report the use of additives have an average phosphate to protein ratio much higher than additive-free products.[462,463] The most commonly used phosphorus additives in the food industry can be found, for instance, in bakery products, enhanced meats, and processed cheeses.[483]
- Advise choosing natural foods that have a low amount of organic phosphorus versus high amount of protein. The content of organic phosphorus per 1 g of protein varies widely among foods. Nutrient composition tables reporting on phosphorus to protein ratio content can be used to recommend food substitutions that can considerably reduce the daily intake of organic phosphorus while ensuring adequate dietary protein intake.[481,484-486]
- Advise preparing foods at home, using wet cooking methods such as boiling (and discard the water). These methods are able to remove about 50% of phosphorus content from foods.[487,488] Slicing the meat before boiling and use of a pressure cooker have been shown to be more effective in terms of achieved protein to phosphorus content.[487] At the same time, these methods may remove other minerals (eg, potassium) of concern for patients with CKD.[489] However, such practices result in reduced palatability and texture of the food.

The work group emphasizes to individualize recommendations after appropriate evaluation of the patient's daily intake. It requires nutrition expertise (preferably consultation with a renal dietitian) and should take into consideration culturally appropriate food substitutions. Nutritional counseling sessions should evolve from the simple concept of phosphate restriction to opportunities of educating the patient on differentiation between organic and inorganic sources of phosphate and avoidance of phosphate additives.[137] Simple educational programs on how to read food labels and look for phosphate additives proved to be successful in helping dialysis patients reduce their serum phosphate levels.[464,465] A meta-analysis suggested that nutritional counseling based on structured behavioral change are in general successful in controlling hyperphosphatemia in these patients.[137] However, in this meta-analysis, only about half the studies were randomized controlled interventions with a short duration ranging from 1 to 6 months, which calls for a need of more dedicated long-term interventional studies on this topic.

Future Research

Dietary management of phosphorus is an important strategy for serum phosphate control in CKD. However, as compared with the many studies exploring pharmacologic management of this electrolyte disorder (eg, use of phosphate binders), the amount of evidence on the effectiveness of dietary control is low. The work group recommends future studies to better define the effect of this simple and cost-effective strategy. Examples of still unanswered questions are:

- Study whether dietary phosphorus restriction is able to normalize serum phosphate levels in PD patients.

- Research whether a higher dietary phosphorus intake level is associated with worse clinical outcomes such as cardiovascular events, progression of kidney disease, or mortality and patient-centered outcomes.
- Study the benefits and potential adverse nutritional and metabolic effects of restricting dietary phosphorus and/or limiting the intake of phosphate additives in patients with nondialysis CKD stages 3-5 and maintenance dialysis.
- Study the effects of nutritional counseling with a focus on organic versus inorganic phosphorus sources on the diet quality and metabolic balance of maintenance dialysis patients beyond serum phosphate control.

6.4 Statements on Potassium

Dietary Potassium Amount

6.4.1 In adults with CKD 3-5D or posttransplantation, it is reasonable to adjust dietary potassium intake to maintain serum potassium within the normal range (*OPINION*).

Dietary and Supplemental Potassium Intake for Hyperkalemia or Hypokalemia

6.4.2 In adults with CKD 3-5D (*2D*) or post-transplantation (*OPINION*) with either hyperkalemia or hypokalemia, we suggest that dietary or supplemental potassium intake be based on a patient's individual needs and clinician judgment.

Rationale/Background

As the main intracellular cation, potassium plays a major role mediating cellular electrophysiology, vascular function, BP, and neuromuscular function. High or low serum potassium levels have been associated with muscular weakness, hypertension, ventricular arrhythmias, and death. The influence of dietary potassium consumption on serum potassium content is therefore of great clinical relevance. Because the mechanisms involved in potassium homeostasis and excretion (ie, adrenergic system, insulin, aldosterone, and urinary clearance) are commonly impaired in patients with CKD and ESKD, hyperkalemia is an especially salient concern. Dietary potassium is the focus of these recommendations (potassium binders were outside the scope of the current guideline).

Detailed Justification

There is a scarcity of studies on this topic and we found no clinical trials on how modifying diet can influence serum potassium levels in patients with CKD. The work group emphasizes that factors other than dietary intake influence serum potassium levels. These include medications, kidney function, hydration status, acid-base status, glycemic control, adrenal function, a catabolic state, or gastrointestinal problems such as vomiting, diarrhea, constipation, and bleeding. All these factors should be considered when formulating a strategy to keep serum potassium levels within the normal range.

The consequences of dietary potassium intake in patients with CKD are not known. No clinical trials were identified that directly examined the relationship between dietary potassium consumption and either serum levels or clinical outcomes. However, several studies used urinary potassium excretion or other surrogates for dietary intake to assess the following outcomes. Although we acknowledge that urinary potassium excretion may not necessarily represent dietary potassium in these patients, the studies showed the following results.

Mortality. Data on the association between dietary and urinary potassium excretion and mortality in adults with CKD were mixed. A study in patients receiving MHD found that compared with the lowest quartile of dietary potassium intake (879 mg or 22.5 mEq/24 h) as measured using the Block Food Frequency Questionnaire, higher quartiles of intake were associated with a stepwise increase in 5-year mortality risk (P-trend = 0.03).[490] Another study in patients with CKD stages 2-4 found no significant association between quartiles of urinary potassium excretion and all-cause mortality.[491] Compared to the highest quartile of urinary potassium excretion (mean, 3,600 mg or 92.1 mEq/24 h), persons in the 3 lowest quartiles had higher all-cause mortality (HRs of 1.53 [95% CI, 1.15-2.02], 1.7 [95% CI, 1.25-2.31], and 1.71 [95% CI, 1.23-2.38] for quartiles 3, 2, and 1, respectively). Results remained similar even after using time-updated average urinary potassium excretion.[492]

CKD Progression. Data for the association between urinary potassium excretion and CKD progression in adults with CKD were mixed. In patients with CKD stages 2-4, urinary potassium excretion in the highest quartile (≥67.1 mmol or 2,617 mg/24 h) was significantly associated with CKD progression (defined as incident ESKD or halving of eGFR from baseline; HR, 1.59 [95% CI, 1.25-2.03]) compared with levels in the lowest quartile (<39.4 mmol or 1,541 mg/24 h).[491] In another study in patients with stages 2-4, baseline urinary potassium excretion was not significantly associated with kidney failure (defined as dialysis therapy or transplantation) even when using time-updated average urinary potassium excretion.[492]

Nerve Function. One randomized study examined the effects of dietary potassium restriction on progression of peripheral neuropathy. In 42 patients with stages 3-4 CKD randomly assigned to either dietary potassium restriction versus usual diet (change in dietary potassium, −854 mg vs −343 mg; $P = 0.35$), potassium restriction was associated with stabilization of a neuropathy score (difference, 0.4 ± 2.2; $P < 0.01$) and several other nerve-related or general health scores over 24 months.[493]

Special Discussions

Research on this topic is complicated because potassium handling by the kidney will vary by disease state and CKD stage. In patients with predialysis CKD, the acute and long-

term effects of dietary potassium loading are not consistently reflected in serum potassium levels due to compensatory mechanisms that are triggered to maintain homeostasis.[494-496] Research and evidence in this area are also limited because of difficulties obtaining reliable data for dietary potassium intake and absorption.

Potassium binders bind potassium in the gut and prevent hyperkalemia. In theory, these medications could lead to a more liberalized potassium-rich diet (ie, fruits and vegetables). However, none of the pivotal trials examining potassium binders evaluated dietary potassium intake, and no study investigated how potassium intake should be modified in the presence of potassium binder use. Because the focus of this guideline was dietary intake rather than pharmacologic therapy, potassium binders were outside the scope of this guideline.

Implementation Considerations

- Potassium is widely distributed in foods, ranging from fruits, vegetables, legumes, and nuts, as well as dairy and meat products. Notably, potassium content is available on food labels in many countries and consumers and practitioners could have a better idea of its content, especially foods that are processed. Because these foods are rich sources of vitamins and minerals and some provide additional dietary fiber, it is essential that dietary restrictions of potassium also consider the overall diet and health goals for the individual patient.
- When treating hyperkalemia, clinicians are advised to first try to identify contributing factors that can be corrected, such as a hypoinsulinemic state or certain medications. This is true in light of the physiologic benefits that high potassium intake may confer, such as putative antihypertensive effects.[497] If hyperkalemia cannot be reversed, the next step is to identify the most important dietary sources of potassium by interviewing the patient and using dietary recalls. Clinicians preferably assisted by a renal dietitian should recommend fruits, vegetables, and other foods with low potassium content that still contain higher levels of fiber and other micronutrients. Published food composition tables can be helpful in this regard.[498] In addition, boiling vegetables can reduce potassium content in vegetables. Any reductions in food taste and palatability associated with this strategy can be partially improved with the use of aromatic herbs.[499,500]

Future Research

It will be necessary to approach predialysis and dialysis populations separately in light of the large differences in potassium handling.

- There is a need to study what constitutes an optimal dietary potassium intake according to different stages of CKD and how dietary potassium intake influences blood potassium content and clinical outcomes.
- There is a need to investigate how potassium binders can be integrated with a diet to optimize potassium and overall nutritional intake.
- In patients receiving MHD, the effect of the potassium bath concentration on cardiovascular risk, mortality, and other outcomes needs further elucidation.

6.5 Statements on Sodium

Sodium Intake and Blood Pressure

6.5.1 In adults with CKD 3-5 (1B), CKD 5D (1C), or posttransplantation (1C), we recommend limiting sodium intake to less than 100 mmol/d (or <2.3 g/d) to reduce blood pressure and improve volume control.

Sodium Intake and Proteinuria

6.5.2 In adults with CKD 3-5 we suggest limiting dietary sodium intake to less than 100 mmol/d (or <2.3 g/d) to reduce proteinuria synergistically with available pharmacologic interventions (2A).

Sodium Intake and Dry Body Weight

6.5.3 In adults with CKD 3-5D, we suggest reduced dietary sodium intake as an adjunctive lifestyle modification strategy to achieve better volume control and a more desirable body weight (2B).

Rationale/Background

Sodium is an extracellular cation responsible for fluid homeostasis in the body.[501] Normovolemia is maintained through the action of the renin-angiotensin-aldosterone system. This system acts to adjust the quantity of sodium excreted by the body and thereby extracellular fluid volume and arterial BP. Excess sodium intake is excreted in the urine and serum levels are tightly controlled, requiring normal kidney and blood vessel function.[502] However, this system may be compromised with excessive sodium intake and/or inadequate excretion, which may occur with CKD.

Long-term high sodium intake may affect a number of physiologic functions relating to the vasculature, heart, kidneys, and sympathetic nervous system.[503] Excessive sodium intake is thought to exert toxic effects on blood vessels through mediating factors such as oxidative stress, inflammation, and endothelial dysfunction.[504] Of particular interest in CKD is the role of sodium reduction in improving the pharmacologic effect of antihypertensive medication, thereby controlling hypertension.

In the general population, short-term intervention studies show significant reductions in BP (hypertensive subgroup, reductions of 5.8 mm Hg SBP and 2.82 mm Hg DBP) with a 100-mmol/d reduction in sodium intake.[505] Indications from a small number of long-term studies (>6 months) suggest a benefit for cardiovascular morbidity and

mortality, although the studies were underpowered to adequately examine these outcomes.[506] The following will explore the evidence within CKD.

Detailed Justification

Overall, the evidence for reducing sodium intake comes from RCTs of short duration and typically small sample size. As a result, there is a focus on clinical markers such as BP, inflammation, body weight, fluid, and proteinuria. There is limited evaluation of hard outcomes, which thereby rely on observational evidence. In addition, the certainty of evidence for sodium reduction is limited by imprecision and risk of bias, particularly selection, attribution, and performance bias.

Five RCTs, 1 parallel,[507] and 4 crossover studies[508-511] examined the effects of reduced dietary sodium intake in CKD (stages 2-5, nondialysis). The crossover studies used supplemental sodium[509-511] or provided meals[508] on the background of a low-sodium diet to generate consistent intake in the high- (180 mmol to 200 mmol/d, with about 100-120 mmol/d supplemented) versus low-sodium intake group (placebo, total 50 to 0 mmol of sodium per day). The parallel RCT was the longest study duration (6 months) conducted in a sample of Bangladeshi immigrants in the United Kingdom (n = 48).[507] Participants were randomly assigned to a tailored intervention including cooking classes modifying traditional cultural recipes together with regular telephone calls with a dietitian. From a baseline sodium intake of approximately 260 mmol, the intervention group achieved 138 mmol/d (a reduction of >120 mmol), whereas usual care stayed largely stable (to 247 mmol/d).

Two more recent studies build on this evidence base and include a parallel[512] and a crossover trial.[513] Meuleman et al[512] conducted a 3-month open-label RCT, n = 138 adults with CKD, hypertension, and high urinary sodium excretion (≥120 mmol/d). The intervention focused on self-management advice to reduce sodium (goal, <100 mmol/d) and BP monitoring or usual care. In the most recent crossover trial, Saran et al[513] evaluated the effect of sodium restriction of <2 g/d versus usual diet for 4 weeks (with a 2-week washout in between) in stages 3 and 4 CKD. This study improved on previous crossover trials because it used dietary counseling, rather than sodium supplementation, to achieve the difference between usual and sodium-restricted intakes.

Four trials were conducted in the maintenance dialysis population: 1 RCT in PD,[514] 2 RCTs in MHD,[515,516] and 1 nonrandomized trial in both PD and MHD.[517] In the MHD study, there was no significant reduction in BP.[516] The difference with this study, compared with all others in dialysis, is that dietary prescription (rather than supplemental sodium) was used to achieve a modest reduction of intake (goal, 34 mmol/d lower than usual intake). This compares to the other interventions in maintenance dialysis using sodium supplementation, which achieved a much larger gradient of difference in sodium intake between the low- and high-intake groups (100 mmol/d or 2.3 g sodium difference).

One RCT was undertaken in patients post–kidney transplantation.[518] This was a parallel RCT of a 12-week intervention that included counseling by a dietitian for a target intake of 80 to 100 mmol/d compared with usual care. This trial demonstrated a significant reduction in sodium intake in the intervention group (from 190 ± 75 to 106 ± 48 mmol/d) through dietary counseling, with no significant change in the usual-care group (191 ± 117 to 237 ± 113 mmol/d).

In the vast majority of trials, the target sodium restriction was 80 to 100 mmol/d (or 2-2.3 g/d). However, there was a lack of consensus as to what constitutes a high sodium intake, which was either based on usual intake or providing supplemental sodium to ensure a consistently high sodium intake, around 200 mmol or 4 g of sodium per day.

Mortality, CKD Progression, and Cardiovascular Events. There is insufficient evidence to make a statement on reduced sodium intake and kidney disease progression, mortality, and cardiovascular events. The evidence for clinical end points is derived from observational studies because there were no RCTs in sodium reduction in CKD that reported CKD progression, cardiovascular event, and mortality outcomes. This is attributable to the small sample sizes and the longest trial duration of only 6 months.[507]

The post hoc analysis of 2 observational cohort studies showed mixed results investigating the association between sodium intake (measured using dietary recall) and subsequent mortality in MHD[511] and PD patients.[520] The retrospective cohort study in 303 PD patients in Japan indicated that low sodium intake was significantly associated with higher overall and cardiovascular mortality. However, this study was open to indication bias because sodium intake was also associated with higher LBM, younger age, and higher BMI. In contrast, in a post hoc analysis of a prospective cohort of 1,770 MHD patients, Mc Causland et al[519] found higher dietary sodium intake associated with increased mortality.

More consistent results were demonstrated from a large high-quality prospective cohort (Chronic Renal Insufficiency Cohort [CRIC] Study) of CKD patients not receiving dialysis with stages 2-4, using urinary sodium excretion. In He et al,[491] 24-hour urinary sodium excretion was associated with greater all-cause mortality and CKD progression (defined as incident ESKD or halving of eGFR from baseline). Sodium excretion was also associated with composite CVD (heart failure, MI, or stroke).[521]

Blood Pressure. Overall, sodium reduction probably reduces BP in kidney disease (moderate certainty evidence). This evidence review included 9 small (n = 20 to n = 52) randomized clinical trials (6 were crossover trials) of short duration (1 week to 6 months) evaluating the effect of reducing sodium intake (typically to a level of <2 g or

90 mmol/d) on BP. Lower sodium intake significantly decreased SBP in all except 1 study,[516] which reduced intake by only 34 mmol/d compared with >90 mmol/d from the other trials. However, the certainty of evidence was limited by risk of bias, particularly risk of selection, attribution, and performance bias. When evaluating the evidence across stages of CKD, the vast amount of evidence exists in predialysis CKD; however, the BP benefits were also apparent in trials in dialysis[514,516,517,522] and transplant populations.[518]

Although this review was unable to derive a summary estimate, a Cochrane review on this topic published in 2015 showed that dietary sodium reduction (mean difference, −105.9 [95% CI, −119.2 to −92.5] mmol/d) resulted in significant reduction in SBP (mean difference, −8.76 [95% CI, −11.35 to −3.80] mm Hg). These short-term studies showed clinically meaningful BP reductions ranging from 2 to 12 mm Hg SBP and 1 to 8 mm Hg DBP in trials 1 week to 6 months in duration.[523]

Inflammatory Markers. Sodium reduction may make little to no difference to inflammation (low certainty evidence). Two RCTs, a parallel RCT in MHD[516] and a crossover in stages 3 and 4,[509] investigated the impact of sodium restriction on inflammation, measured by CRP, IL-6, and TNF-α levels. In the Rodrigues Telini et al[516] study, there was a significant reduction in levels of all inflammatory markers within the intervention group; however, not reported were between-group differences (and no difference within control group). The single crossover study in stages 3-4 showed no difference in inflammation comparing high- and low-sodium intake.[509]

Body Weight and Fluid. Sodium restriction may slightly reduce body weight and total-body fluid in nondialysis CKD (low certainty evidence). However, it is uncertain whether sodium restriction reduces body weight and body water in dialysis. The evidence from nondialysis CKD comes from 2 randomized crossover trials, 1 using sodium supplementation to compare intake of 60 to 80 mmol/d with 180 to 200 mmol/d for 2 weeks[509] together with a more recent investigation by Saran et al[513] evaluating the effect of sodium restriction < 2 g/d versus usual diet for 4 weeks (with a 2-week washout in between). Both trials demonstrated a reduction in extracellular volume. Furthermore, in maintenance dialysis, 2 RCTS demonstrated no significant difference in body weight with salt restriction in PD[515] or both HD and PD.[524] In 1 nonrandomized study in HD, the group advised to restrict sodium (<3 g/d) and fluid (<1 L/d) intake demonstrated a within-group decrease in interdialytic fluid gain, but there was no change in the control group, and between-group difference was not significant.[515]

Kidney Function (Including Proteinuria). Restriction of sodium intake may slightly reduce kidney function markers of creatinine clearance[508,510,511,522] and eGFR[525] demonstrated in short-term crossover trials in the stage 1-5 nondialysis population (low-certainty evidence). In the single parallel RCT over 6 months of sodium restriction, de Brito-Ashurst et al[507] found no difference in eGFR. The inconsistency in results may be due to the short-term crossover trials demonstrating acute hyperfiltration response to low-sodium intake compared with the longer-term parallel trial reflecting a more clinically stable circumstance.

Restriction of sodium intake may reduce proteinuria, as demonstrated in 3 randomized crossover trials.[509-511,525] This evidence is supported by further parallel RCTs and observational studies. Meuleman et al[512] demonstrated a reduction in proteinuria over 3 months of self-management intervention using sodium intake < 100 mmol/d that reversed to baseline proteinuria after cessation of the dietary sodium restriction. In addition, post hoc analyses of clinical trials (REIN I and II) in proteinuric patients with established CKD have demonstrated that consuming a higher sodium diet was associated with increased risk for progressing to ESKD compared with a lower sodium diet < 100 mmol/d.[526]

Implementation Considerations

- Achieving a reduced sodium intake in CKD is recommended but can be particularly challenging to achieve.[527] This is a result of the need to navigate a complex interplay between individual food choice and food supply, together with a range of other dietary recommendations that come with CKD. Because sodium is consumed largely from processed foods, the WHO has initiatives for reducing sodium content in manufactured foods among the top priorities to combat noncommunicable diseases.[528] Consuming a low-sodium diet generally requires education and skill development (cooking and label reading) and explicit choice to consume a low-sodium diet. Therefore, a concerted and multifaceted intervention strategy is required to support achieving this intake in clinical practice. This includes targeting individual behavior change for dietary choices, together with a wider public health strategy to reduce the availability of sodium in the food supply.[528]
- The interventions undertaken in clinical trials of sodium reduction have limited applicability when translating into practice. Many trials to date have used sodium supplementation or provided foods to enhance adherence in short-term effectiveness studies.[528] Investigations of efficacy and behavioral interventions to adopt low-sodium intakes in real-life settings are limited in the literature. Of those that exist, the evidence is either short term (<6 months) or demonstrates that achieving reduced sodium intake is only apparent while receiving active intervention.[512] The challenge for the future is to develop an evidence base to inform successful strategies to support long-term adherence to dietary sodium reduction.

- Issues with sodium intake assessment include that measuring sodium intake and thereby accurately evaluating adherence to recommendations is extremely challenging in practice. Sodium intake can be measured in objective (urine collection over 24 hours or spot sample) and self-report (dietary recall) or a combination of methods. Urinary sodium excretion as a surrogate measure of intake assumes: 1) a stable intake reflected in a single 24-hour collection, and 2) sodium excretion is a direct reflection of intake. It is this latter assumption that has been recently challenged by Titze,[529] who identified a sodium storage pool in the skin and wide disparity between sodium intake and excretion day to day. Increasing the number of 24-hour urinary collections may improve the accuracy to partially overcome these concerns; however, it is not practical in clinical practice. Self-reported dietary assessment methods are prone to reporting bias, can be time consuming to collect, and require technical expertise in the analysis. A panel of methods is therefore recommended because no one method is ideal to adequately assess adherence.[528]
- For sodium relative to potassium intake, recent observational evidence suggests that the ratio of sodium to potassium intake may be as important, if not more important, than lower sodium intake alone in CKD.[491] This is the premise of the DASH-Sodium trial and has demonstrated benefits in the general population, with sodium reduction providing additive benefit in BP reduction to the DASH diet.[530] In hypertensive adults, post hoc analysis of clinical trials indicates that sodium to potassium ratio may be more effective in lowering BP than lowering sodium or increasing potassium as single interventions.[531] However, there are unknown safety aspects in CKD, particularly with the risk for hyperkalemia. Investigating the relative benefit of sodium reduction compared with potassium intake is beyond the scope of the current guidelines but warrants further research. Evidence for potassium recommendations is addressed within these guidelines.
- Currently there is too much uncertainty in the evidence to advise on the effectiveness of sodium restriction based on specific thresholds of proteinuria. However, this intervention appears to be effective over a large range of proteinuria.

Future Research

- Clinical trials to investigate behavioral interventions using approaches that are patient centered and support the adoption of long-term strategies for reducing sodium intake. In the design of behavioral interventions incorporating less processed foods, including cooking skills, label reading, avoiding eating out, and provision of interventions that tailor to a range of literacy levels.
- Clinical trials investigating the safety and effectiveness of low sodium relative to increased potassium intake on CVD and CKD outcomes.
- Clinical trials to evaluate the long-term effectiveness of reduced sodium intake on hard outcomes.
- Enhance objective markers of intake and/or improve self-report options with technology advancement.

BIOGRAPHIC AND DISCLOSURE INFORMATION

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Dr Burrowes is Professor of Nutrition in the Department of Biomedical, Health and Nutritional Sciences at Long Island University Post in Brookville, NY. Dr Burrowes has numerous publications in refereed journals and she has been an invited speaker at several professional meetings and conferences on nutrition in kidney disease. She is a co-editor for the 1st and 2nd editions of the textbook entitled *Nutrition in Kidney Disease*, and she is currently the senior editor for the 3rd edition, which will be published by Springer in early 2020. Dr Burrowes has held many leadership and advisory roles in professional organizations and societies, and she has served on numerous association committees. She is currently Council Member of the International Society of Renal Nutrition and Metabolism (ISRNM) for the 2018-2020 term. For the past 8 years, Dr Burrowes served as the Editor-in-Chief for the *Journal of Renal Nutrition*. She was also a member of the work group that developed the initial Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. Dr Burrowes received the Recognized Renal Dietitian Award and the Joel D. Kopple Award from the National Kidney Foundation (NKF) Council on Renal Nutrition, and the Outstanding Service Award from the Renal Practice Group of the Academy of Nutrition and Dietetics. Dr Burrowes earned her Bachelor's degree in biology/pre-medicine from Fisk University in Nashville, TN; her MS degree in foods, nutrition, and dietetics from New York University; and her PhD in nutrition from New York University.

Financial Disclosure: Dr Burrowes reports no relevant financial relationships.

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Financial Disclosure: Dr Byham-Gray has no relevant financial interests to disclose.

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Dr Campbell is an Associate Professor at Griffith University, Brisbane, Australia, and leads a Health Services Research portfolio in the largest health service in Australia (Metro North Hospital and Health Service). As a dietitian with a career spanning clinical practice, teaching, and research, Dr Campbell has been dedicated to advancing the evidence base for the nutrition management in kidney disease. Her recent research includes roles as a clinical trialist with the Australasian Kidney Trials Network Scientific Committee, Associate Investigator on a large research program "BEAT-CKD," and the sole dietitian on the landmark DIET-HD study, recruiting more than 10,000 participants worldwide. Her work includes lifestyle interventions in chronic kidney disease (CKD), investigating the role of dietary patterns in the trajectory of CKD, and nutrition status assessment and workforce issues, published in more than 120 peer-reviewed papers. To translate evidence to practice, Dr Campbell has led capacity-building workforce initiatives, authored numerous clinical guidelines and systematic reviews, and evaluated the impact of research translation changing models of care, including co-design and evaluation for the delivery of lifestyle interventions using technology.

Financial Disclosure: Dr Campbell reports no relevant financial relationships.

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Disclosures: Dr Carrero reports funding to the Karolinska Institutet for research from AstraZeneca, Viforpharma, Novartis Astellas, and MSD for topics unrelated to this guideline. He has performed consultation for Fresenius, Rubió laboratories, Astellas, and Baxter and participated as speaker for events organized by Abbott, Nutricia, and Dr Schär.

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Dr Chan is a Post-Doctoral Research Fellow at University of Birmingham. She has more than 10 years of experience as a clinical dietitian specializing in renal nutrition. She was appointed as a Dietetic Research and Postgraduate Education Lead, and a Dietitian Representative of Non-Medical Clinical Academic Research Group at Queen Elizabeth Hospital Birmingham. Dr Chan received her Bachelor's Degree in Nutrition and Postgraduate Diploma in Dietetics from King's College, University of London. She obtained her PhD from the University of Birmingham, co-funded by a National Health Service West Midlands Strategic Health Authority PhD Research Training Fellowship and a British Renal Society research grant. She has fostered keen research and clinical interests in kidney transplantation. Her research work focuses on investigating the role of nutrition, body composition, and physical strength on clinical outcomes and quality of life in kidney transplant recipients. She is a multi–award-winning researcher, having delivered numerous presentations and invited lectures in her areas of academic and clinical expertise at national and international conferences. In addition to consistent publications in well-respected journals, Dr Chan has authored book chapters and Practice-based Evidence in Nutrition Knowledge Pathway in the field of renal nutrition. She serves on the editorial board of *Journal of Renal Nutrition*. She is an active research grant review panel member for Kidney Research UK and the British Renal Society. To date, she continues her pivotal role as an Expert Adviser for the National Institute for Health and Care Excellence (NICE) Centre for Guidelines in Renal Disease.

Financial Disclosure: Dr Chan reports no relevant financial relationships.

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Financial Disclosure: Dr Cuppari reports no relevant financial relationships.

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Financial Disclosure: Dr Fouque received honoraria, travel support, and lecture fees from Sanofi, Lilly, Vifor, and Fresenius Kabi.

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Financial Disclosure: Dr Friedman is a member of the scientific advisory board for GI Dynamics.

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Financial Disclosure: Dr Ghaddar reports no relevant financial relationships.

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Financial Disclosure: Dr Goldstein-Fuchs reports no relevant financial relationships.

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Financial Disclosure: Dr Kaysen has no relevant conflicts of interest and nothing to disclose.

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Disclosures: Dr Teta reports no relevant financial disclosures.

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Financial Disclosure: Dr Handu reports no relevant financial relationships.

SUPPLEMENTARY MATERIAL

Supplementary File 1 (PDF)

Evidence Summary Tables

Guideline 1: Assessment

Table S1. Technical Devices & Anthropometric Measurements to Measure Body Composition
Table S2. Laboratory Measurements of Body Composition
Table S3. Handgrip Strength
Table S4. Methods to Assess Energy Requirements
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Table S6. Tools/Methods Used to Assess Protein Intake and Calorie Intake

Guideline 2: Medical Nutrition Therapy

Table S7. Medical Nutrition Therapy

Guideline 3: Dietary Protein and Energy Intake

Table S8. Protein Restriction (Protein Restriction + KAA; Protein Restriction only)
Table S9. Protein Type in CKD
Table S10. Dietary Patterns (Fruits and Vegetables; Mediterranean Diet)

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Table S11. Nutritional Supplementation – Oral, Enteral, and Parental Nutrition
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Guideline 4: Micronutrients

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Guideline 5: Electrolytes

Table S23. Acid-Base
Table S24. Calcium
Table S25. Magnesium
Table S26. Phosphorus
Table S27. Potassium
Table S28. Sodium

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