CLINICAL PRACTICE GUIDELINE FOR NUTRITION IN CHRONIC KIDNEY DISEASE: 2019 UPDATE

Public Review DRAFT
October 2019
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.

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

SECTION II: DISCLOSURE

Kidney Disease Outcomes Quality Initiative (KDOQI) and American Academy of Nutrition and Dietetics (AND) 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 will be printed in the final publication and are on file at the National Kidney Foundation (NKF).
### TABLE OF CONTENTS

Table of Tables ........................................................................................................................................... 4
Table of Figures ............................................................................................................................................... 4
Abbreviations and Acronyms ......................................................................................................................... 5
Work Group Membership ............................................................................................................................... 8
Organization Leadership ................................................................................................................................. 9
Abstract ......................................................................................................................................................... NA
Foreword ....................................................................................................................................................... NA
Methods ......................................................................................................................................................... 10
Summary of Guideline Statements .................................................................................................................. 25

**Guideline 1: Assessment** ......................................................................................................................... 36
  1.0 Usual Care Statements .............................................................................................................................. 36
  1.1 Technical Devices & Anthropometric Measurements to Measure Body Composition ...................... 36
  1.2 Laboratory Measures of Body Composition ......................................................................................... 50
  1.3 Handgrip Strength ................................................................................................................................. 57
  1.4 Methods to Assess Energy Requirements ............................................................................................ 59
  1.5 Composite Nutritional Indices to Measure Nutritional Status in CKD Patients ................................. 62
  1.6 Tools/Methods Used to Assess Protein Intake and Calorie Intake ...................................................... 71

**Guideline 2: Medical Nutrition Therapy** .................................................................................................. 74

**Guideline 3: Dietary Protein and Energy Intake** ...................................................................................... 82
  3.0 Energy Intake ......................................................................................................................................... 82
  3.1 Protein Amount ....................................................................................................................................... 82
  3.2 Protein Type ........................................................................................................................................... 94
  3.3 Dietary patterns (Fruits and Vegetables; Mediterranean) ................................................................... 98

**Guideline 4: Nutritional Supplementation** ............................................................................................... 103
  4.1 Nutrition Supplementation - Oral, Enteral, and Parenteral Nutrition ............................................... 103
  4.2 Nutrition Supplementation - Dialysate ............................................................................................... 115
  4.3 Long Chain Omega-3 Polyunsaturated Fatty Acids ......................................................................... 119

**Guideline 5: Micronutrients** ..................................................................................................................... 128
  5.0 General Guidance ................................................................................................................................. 128
  5.1 Folic acid (with and without other B Vitamins) ................................................................................. 132
  5.2 Vitamin C ............................................................................................................................................. 137
  5.3 Vitamin D ............................................................................................................................................. 142
  5.4 Vitamin E and A ................................................................................................................................. 148
  5.5 Vitamin K ............................................................................................................................................. 155
  5.6 Selenium and Zinc ............................................................................................................................... 159

**Guideline 6: Electrolytes** .......................................................................................................................... 164
  6.1 Acid-Base .............................................................................................................................................. 164
  6.2 Calcium ............................................................................................................................................... 171
  6.3 Phosphorus .......................................................................................................................................... 175
  6.4 Potassium ............................................................................................................................................ 184
  6.5 Sodium ............................................................................................................................................... 188

Biographic and Disclosure Information ......................................................................................................... 196
References ................................................................................................................................................... 206
TABLES

Table 1. Key Questions for Evidence Review .......................................................... 16
Table 2. Evidence Review Inclusion and Exclusion Criteria ................................. 18
Table 3. Quality of Evidence Grades ...................................................................... 24
Table 4. Implications of strong and weak recommendations for different users of guidelines .... 25

FIGURES

Figure 1. Flow diagram of identified studies for Assessment questions ....................... 21
Figure 2. Flow diagram of identified studies for Intervention questions ...................... 22
**ABBREVIATIONS AND ACRONYMS**

- **ACE**: Angiotensin converting enzyme inhibitors
- **APD**: Animal-based Protein Diet
- **AND**: Academy of Nutrition and Dietetics
- **ARB**: Angiotensin II receptor blocker
- **BF**: Body fat
- **BIA**: Bio-electrical impedance analysis
- **BMI**: Body mass index
- **BP**: Blood pressure
- **BPI**: Body protein index
- **CAPD**: Continuous ambulatory peritoneal dialysis
- **CIMT**: Constraint induced movement therapy
- **CK**: Creatinine kinase
- **CKD**: Chronic kidney disease
- **CRP**: C-reactive protein
- **CVD**: Cardiovascular disease
- **DBP**: Diastolic blood pressure
- **DEXA**: Dual-energy X-ray absorptiometry
- **eGFR**: Estimated glomerular filtration rate
- **EAAs**: Essential amino acids
- **ESRD**: End-stage renal disease
- **FM**: Fat mass
- **FFM**: Fat free mass
- **FSA**: Four-site skinfold anthropometry
- **GFR**: Glomerular filtration rate
- **GNRI**: Geriatric Nutrition Risk Index
- **GRADE**: Grades of Recommendation Assessment, Development, and Evaluation
- **HD**: Hemodialysis
- **HDL-C**: High-density lipoprotein cholesterol
- **HGS**: Handgrip Strength
- **HOMA-IR**: Homeostatic Model Assessment of Insulin Resistance
- **HR**: Hazard ratio
- **hsCRP**: High sensitivity C-reactive protein
- **IBW**: Ideal body weight
- **IDPN**: Intradialytic parenteral nutrition
- **IL-6**: Interleukin
- **IMT**: Intima media thickening
- **IV**: Intravenous
KA  Ketoacid
KAA  Ketoacid analogue
KDIGO  Kidney Disease: Improving Global Outcomes
KDQOL-SF  Kidney disease quality of life short form
KDOQI  Kidney Disease Outcomes Quality Initiative
KQ  Key question
LBM  Lean body mass
LDL-C  Low-density lipoprotein cholesterol
LPD  Low protein diet
MAMC  Mid-arm muscle circumference
MF-BIA  Multi-frequency-bio-electrical impedance analysis
MGP  Matrix Gla protein
MHD  Maintenance hemodialysis
MHDE  Maintenance Hemodialysis Equation
MIS  Malnutrition Inflammation Score
MNA  Mini-nutrition assessment
MNA-SF  Mini-Nutrition Assessment-Short Form
MST  Malnutrition Screening Tool
MUST  Malnutrition Universal Screening Tool

NEAAs  Non-essential amino acids
NEAP  Net endogenous acid production
NHANES  National Health and Nutrition Examination Survey
NIS  Nutrition Impact Symptoms NKF
      National Kidney Foundation
NRCT  Non-randomized controlled trial
nPCR  Normalized protein catabolic rate
nPNA  Normalized protein nitrogen appearance
NST  Nutrition Screening Tool

ONS  Oral nutritional supplements
PCR  Protein catabolic diet
PD  Peritoneal dialysis
PEW  Protein energy wasting
PNA  Protein nitrogen appearance
PNI  Protein Nutrition Index

RCTs  Randomized controlled trials
RDN  Registered dietitian nutritionist
REE  Resting energy expenditure
R-NST  Renal-Nutrition Screening Tool
RRT  Renal Replacement Therapy
<table>
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<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<td>SGA</td>
<td>Subjective Global Assessment</td>
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<td>SKF</td>
<td>Skinfold thickness</td>
</tr>
<tr>
<td>SR</td>
<td>Systematic review</td>
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<tr>
<td>TBF</td>
<td>Total body fat</td>
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<td>TG</td>
<td>Triglycerides</td>
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<td>TNF-a</td>
<td>Tumor Necrosis Factor alpha</td>
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<td>TSF</td>
<td>Triceps skinfold thickness</td>
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<td>VPD</td>
<td>Vegetable proteindiet</td>
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<td>VLPD</td>
<td>Very low protein diet</td>
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METHODS

The Guideline Development Process

According to the Institute of Medicine (National Academy of Sciences), “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”. This chapter describes the process and methods used to conduct comprehensives systematic reviews and how the findings from these systematic reviews were used to develop clinical practice nutrition guidelines for patients with chronic kidney disease. These guidelines were developed according to the Standards for Developing Trustworthy Clinical Practice Guidelines as stated by Institute of Medicine.

Development of these guidelines was a collaborative process between National Kidney Foundation (NKF) and the Academy of Nutrition and Dietetics (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® (EAL®) CKD guidelines and the Kidney Disease Outcomes Quality Initiative (KDOQI) Nutrition Guidelines. Hence, the objective of this initiative is to provide medical nutrition therapy (MNT) guidelines for patients with chronic kidney disease (CKD) to assess, prevent and treat protein-energy wasting, mineral and electrolyte disorders, and other metabolic co-morbidities 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 below (some steps were completed concurrently):

1. Select the Work group or expert panel that works with the evidence review team.
2. Orient the work group the 5-step systematic review process of the Academy of Nutrition and Dietetics’ 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 (Study characteristics and findings table). Grade the quality of evidence for
   each outcome and provide 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 of Nutrition and Dietetics led the process of work
   group member recruitment. To assure appropriate expertise and limit bias, the Evidence Based
   Practice Committee Work Group Selection sub-committee 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 chronic kidney disease.
   Interested candidates provided: signed Disclosure and Conflict of Interest From, curriculum
   vitae, and personal statements indicating interest and qualifications that related to the topic.
   The workgroup selection committee then evaluated each candidate based on set criteria.
   Higher scoring candidates were considered for position of workgroup chair/co-chair. A total
   of 15 workgroup 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. The selected
   members, according to their experiences and skill sets, were assigned to corresponding
   subtopics. The work group participated in all steps of systematic review process, which
   included developing research questions, agreeing on inclusion and exclusive criteria,
   developing the search plan, evaluating the evidence, and approving and grading the evidence
   and developing recommendation statements. All workgroup members and the evidence review
   team (ERT) met twice for 2-day face to face meetings as well as a 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 question under these subtopics were proposed. Three workgroups were developed, with five members assigned to each workgroup and a Chair appointed to help lead the workgroup.

**Systematic review process:** Question development, literature search and study selection This guideline followed the Academy of Nutrition and Dietetics 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 workgroup developed a list of questions that were deemed important for clinicians and patients (Table 1). The workgroup developed the *a priori* inclusion and exclusion criteria as listed in Table 2.

A comprehensive search of 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 in order to identify studies that answered more than one question. Inclusion criteria included in the search plan included: human adults with CKD aged 19 years and older published between 1985 and December 2016. hu Search terms included terms to identify relevant nutrition interventions assessment tools in adult CKD patients.

The first literature search focused on assessment questions identified 4,857 potential studies. The PRISMA diagram illustrating the study selection process are 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 additional *a priori* inclusion/exclusion criteria. For intervention questions, only randomized controlled trials that had at least 6 individuals per arm were included. Included studies investigated an intervention of interest (e.g. protein restrictions, phosphorus intake, sodium intake etc.) 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 were independently reviewed and marked for inclusion or exclusion (along with the reason) and any differences were resolved by discussion with a third reviewer. Full texts 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 of Academy of Nutrition and Dietetics Evidence Analysis Center website).

*Data extraction and study quality assessment:* Relevant data was extracted from the included articles using a standardized online data extraction tool. Key information extracted from each study included: Authors information; year of publication; type of study design; details of intervention: type of intervention, duration of the intervention, who delivered the intervention, setting, number of centers; Participants: sample size, mean age, age range, gender, study inclusion and exclusion criteria, comorbidities; Interventions: intervention details, comparison group details, medication use; Outcomes: reported primary and secondary outcomes, time points of reported outcomes; other details such as funding source.

All included studies were critically appraised for risk of bias. Two independent reviewers assessed the quality or studies using the Academy’s online risk of bias tool, the Quality Criteria Checklist (QCC). The questions of the QCC are based on quality constructs and risk of bias domains identified by the Cochrane Collaboration and the Agency for Healthcare Research and Quality (AHRQ). Questions examine sampling bias, performance bias, detection bias, attrition
bias, and reporting bias. Any discrepancies between the two 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 random-effects model. For continuous data, results were summarized as mean difference (MD) between treatment groups (intervention v/s control/placebo) with 95% confidence interval (CI) or standardized mean differences (SMD). Dichotomous outcomes were reported as odds ratio (OR) or risk ratios (RR) with 95% CI. The I² statistic was used to determine the degree of heterogeneity in the calculated effect size, and 25%, 50%, and 75% were considered low, moderate, high, respectively. Sub-group analysis was conducted as appropriate to manage clinical heterogeneity.

After completion of the data extraction and data synthesis, the ERT provided the systematic review results in the following formats for the workgroup 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 table: provided information regarding study characteristics, sample size, population, intervention details and quality of each included study; 3) Quality of evidence (strength of evidence): Each of the conclusion statements were assigned a GRADE (reference) 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 workgroup 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 workgroup and ERT used the GRADE method for development of recommendations. The GRADE method involves two major components: a rating for quality of evidence (described above) and rating the strength of recommendations. The evidence grades are reported at the end of the recommendation statements (e.g. A, B, C, or D) and reflect the confidence in the estimated effects (Table 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 workgroup determined it was important to provide some guidance to patients and practitioners. These recommendations are ungraded, and usually refer to general or routine practice.

Once the full draft of recommendation statements was ready, it was reviewed and edited multiple times by all the workgroup members and the ERT. The workgroup 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: Once 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 National Kidney Foundation Scientific Advisory Board. Feedback from this internal review were 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 was 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 workgroup members for discussion and possible edits. Work group chairs coordinated the final revision of the guideline document based on review comments and the final guideline manuscript will be submitted for publication.

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<th>Table 1. Key Questions for Evidence Review</th>
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<td>Topics</td>
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<td>Assessment: Nutritional status</td>
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<td>Assessment: Macronutrients</td>
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<td>Assessment: Micronutrients</td>
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<td>Assessment: Electrolytes</td>
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<td>Medical Nutrition Therapy</td>
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<td>Macronutrient: Protein restriction and type</td>
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<td>Macronutrient: Dietary patterns</td>
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<td>Macronutrient: Omega-3 supplementation</td>
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<td>Macronutrient: Oral Nutrition supplements</td>
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<td>Macronutrient: Dialysate supplements</td>
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<td>Macronutrient: IDPN supplements</td>
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<td>Micronutrients: intervention questions</td>
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<td>Electolytes: intervention questions</td>
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### Table 2. Evidence Review Inclusion and Exclusion Criteria

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<th>Assessment Research Questions</th>
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<th>Exclusion</th>
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<tr>
<td><strong>Age</strong></td>
<td>Adults (age 18 and older)</td>
<td>Young adults ≤18 years of age, infants, children and adolescents.</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Clinical or outpatient</td>
<td>Other than clinical or outpatient</td>
</tr>
<tr>
<td><strong>Health Status</strong></td>
<td>CKD of any stage, nephrotic syndrome, maintenance hemodialysis chronic peritoneal dialysis, and kidney transplantation with different CKD stages, with or without dyslipidemia and diabetes; kidney transplant recipients</td>
<td>Cancer or any other terminal condition or serious condition</td>
</tr>
<tr>
<td><strong>Nutrition Related Problem/Condition</strong></td>
<td>Chronic kidney disease</td>
<td>None</td>
</tr>
<tr>
<td><strong>Study Design Preferences</strong></td>
<td>• Diagnostic, validity, reliability studies, prediction, and/or correlation studies</td>
<td>• Review article; meta-analysis (Pertinent review articles will be hand searched)</td>
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<tr>
<td></td>
<td>• Studies need to have a comparative tool/method included</td>
<td>• 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.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>• Evaluates validity, agreement and reliability of the screening tool</td>
<td>• No evaluation of validity, agreement or reliability of the screening tool</td>
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<tr>
<td></td>
<td>• Reports one or more of the following outcomes:</td>
<td>• Does not report on at least one of the outcomes of interest.</td>
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<td>• Validity [e.g., construct (convergent, divergent) criterion (concurrent or predictive)]</td>
<td>• Tools evaluated as predictors of morbidity and mortality outcomes.</td>
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<td>• Reliability (e.g., inter- or intra-rater)</td>
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<td>• Sensitivity / Specificity</td>
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<td></td>
<td>• Positive and/or negative predictive value</td>
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### Study Dropout Rate

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<th>Agreement [kappa]</th>
<th>&gt;20% for studies &lt; 1 year and &gt;30% for studies &gt; 1 year</th>
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<tr>
<td>20% for studies &lt; 1 year and</td>
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<td>30% for studies &gt; 1 year.</td>
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### Year Range

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### Authorship

- If an author is included on more than one 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 more than one Review Article or primary research article and the content is different, then both reviews may be accepted.

### 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

#### Inclusion

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<th>Age</th>
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<td>CKD of any stage, nephrotic syndrome, maintenance hemodialysis chronic peritoneal dialysis, and kidney transplantation with different CKD stages, with or without dyslipidemia and diabetes; kidney transplant recipients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nutrition Related Problem/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Design Preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT or Clinical Controlled Studies</td>
</tr>
</tbody>
</table>

#### Exclusion

- Young adults ≤18 years of age, infants, children and adolescents.
- Other than clinical or outpatient
- Cancer or any other terminal condition or serious condition
- 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.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality, renal replacement therapy, quality of life, nutritional status outcomes, dietary intake outcomes, inflammation outcomes, anthropometrics, micronutrient biomarkers, electrolyte biomarkers, CKD progression, comorbidity outcomes (lipid profile, blood pressure)</th>
<th>• Does not report on at least one of the outcomes of interest.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of Study Groups</td>
<td>For controlled trials at least 6 subjects in each arm • &lt;6 individuals for each study group</td>
<td></td>
</tr>
<tr>
<td>Study Dropout rate</td>
<td>20% for studies &lt; 1 year and 30% for studies &gt; 1 year. &gt;20% for studies &lt;1 year and &gt;30% for studies &gt;1 year</td>
<td></td>
</tr>
<tr>
<td>Year Range</td>
<td>1985 to December 2016 Published prior to 1985</td>
<td></td>
</tr>
<tr>
<td>Authorship</td>
<td>• If an author is included on more than one 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 more than one Review Article or primary research article and the content is different, then both reviews may be accepted.</td>
<td>Studies by same author similar in content.</td>
</tr>
<tr>
<td>Language</td>
<td>Limited to articles in English Languages other than English</td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>Humans Animals</td>
<td></td>
</tr>
<tr>
<td>Publication</td>
<td>Published in peer-reviewed journal. Not published in peer-reviewed journal.</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Flow diagram of identified studies for assessment questions

Records identified through database searching (n = 4,784) → Additional records identified through other sources (n = 73) → Records after duplicates removed (n = 3147) → Records screened (n = 3147) → Full-text articles assessed for eligibility (n = 388) → Full-text articles excluded, with reasons (n = 263) → Studies included in qualitative synthesis (n = 125)
Records identified through database searching (n = 10,974)

Additional records identified through other sources (n = 43)

Records after duplicates removed (n = 10,309)

Records screened (n = 10,309)

Records excluded (n = 9508)

Full-text articles assessed for eligibility (n = 801)

Full-text articles excluded, with reasons (n = 247)

Studies included in qualitative synthesis (n = 225)

Studies included in quantitative analysis (n = 126)
Table 3. Quality of Evidence Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (A)</td>
<td>We are very confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>Moderate (B)</td>
<td>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.</td>
</tr>
<tr>
<td>Low (C)</td>
<td>Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Very Low (D)</td>
<td>We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.</td>
</tr>
</tbody>
</table>

Source: Reproduced with permission from the GRADE handbook¹
Table 4. Implications of strong and weak recommendations for different users of guidelines

<table>
<thead>
<tr>
<th></th>
<th>Strong Recommendation (Level 1 = We recommend)</th>
<th>Weak Recommendation (Level 2 = We suggest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients</td>
<td>Most individuals in this situation would want the recommended course of action and only a small proportion would not.</td>
<td>The majority of individuals in this situation would want the suggested course of action, but many would not.</td>
</tr>
<tr>
<td>For clinicians</td>
<td>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.</td>
<td>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 towards a decision.</td>
</tr>
<tr>
<td>For policy makers</td>
<td>The recommendation can be adapted as policy in most situations including for the use as performance indicators.</td>
<td>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.</td>
</tr>
</tbody>
</table>

Source: Reproduced with permission from the GRADE handbook¹
SUMMARY OF GUIDELINE STATEMENTS

GUIDELINE 1: NUTRITION ASSESSMENT

1.0 Usual Care Statements

Routine Nutrition Screening
1.0.1 In adults with CKD 3-5D and post-transplant, 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 and post-transplant, there is limited evidence to suggest the use of one tool over others for identifying those at risk of protein-energy wasting (2D).

Routine Nutrition Assessment
1.0.3 In adults with CKD 3-5D and post-transplant, 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, 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 & Anthropometric Measurements to Assess Body Composition

Bioelectrical Impedance for Patients on Maintenance Hemodialysis (MHD)
1.1.1 In adults with CKD 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 Patients, Non-Dialyzed and on Peritoneal Dialysis (PD)
1.1.2 In adults with CKD who are non-dialyzed or on PD, there is insufficient evidence to suggest using bioelectrical impedance to assess body composition (2D).

DEXA for Body Composition Assessment
1.1.3 In adults with CKD 1-5D and post-transplant, it is reasonable to use dual-energy x-ray absorptiometry (DEXA) 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 and post-transplant, it 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 and post-transplant who are clinically stable, it is reasonable 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 stages 4-5 and post-transplant patients
- At least Every 6 months in stages 1-3 patients

Assessment of Body Weight

1.1.6 In adults with CKD 1-5D and post-transplant, it is reasonable for registered dietitian nutritionist (RDN) or an international equivalent or physicians to use clinical judgement to determine the method for measuring body weight (e.g. 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).

Body Mass Index (BMI) as a Predictor of Mortality

1.1.7 In adults with CKD who are 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 who are on MHD, we suggest that overweight/obese 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 post-transplant, it is reasonable to consider using underweight and overweight/obesity status (based on BMI) as a predictor of higher mortality (OPINION).

BMI and Protein Energy Wasting

1.1.11 In adults with CKD 1-5D and post-transplant, BMI alone is not sufficient to establish a diagnosis of PEW unless the BMI is very low (<18 kg/m2) (OPINION).

Skinfold Thickness

1.1.12 In adults with CKD 1-5D (1B) and post-transplant (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 on MHD, we suggest that the conicity index may be used to assess nutritional status 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 stages 1-5D and post-transplant, biomarkers such as normalized protein catabolic rate (nPCR), serum albumin and/or serum prealbumin 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 on maintenance dialysis, 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 Statement on Methods to Assess Energy Requirements

Assessment of Resting Energy Expenditure
1.4.1 In adults with CKD 1-5D and post-transplant, 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 Statement 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 and post-transplant, Malnutrition Inflammation Score may be used to assess nutritional status (2C).

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

Considerations when Assessing Dietary Intake

1.6.1 In adults with CKD 3-5D and post-transplant, it is reasonable to assess factors beyond dietary intake (e.g. medication use, knowledge, beliefs, attitudes, behavior and access to food, depression, cognitive function etc.) 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 non-dialysis 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) and 5D (2D), 24-hour food recalls, food frequency questionnaires and normalized protein catabolic rate (nPCR)/normalized protein catabolic rate (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, USA or international nutrition credential) in close collaboration with a physician, or other provider (nurse practitioner or physician assistant), provide medical nutrition therapy (MNT). Goals are to optimize nutritional status, and to minimize risks imposed by co-morbidities 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 and post-transplant, it is reasonable to prescribe MNT that is tailored to the individuals’ needs, nutritional status and co-morbid conditions (OPINION).

MNT Monitoring and Evaluation

2.1.3 In adults with CKD 3-5D and post-transplant, it is reasonable for the registered dietitian nutritionist (RDN) or an international equivalent to monitor and evaluate appetite, dietary intake, biochemical data, anthropometric measurements, and nutrition-focused physical findings to assess the effectiveness of medical nutrition therapy (OPINION).
GUIDELINE 3: PROTEIN AND ENERGY INTAKE

3.0 Statement on Energy Intake

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

3.1 Statements on Protein Amount

Protein Restriction, Non-Dialysis
3.1.1 In adults with CKD 3-5 who are metabolically stable, we recommend protein restriction with or without keto acid analogs, to reduce risk for ESRD/death (1A) and improve QoL (1C).

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

Dietary Protein Intake, Maintenance Hemodialysis and Peritoneal Dialysis
3.1.2 In adults with CKD on MHD (1C) and PD (OPINION) who are metabolically stable, we recommend prescribing a dietary protein intake of 1.0 -1.2 g /kg ideal body weight per day to maintain a stable nutritional status.

Dietary Protein Intake, Diabetes Mellitus
3.1.3 In the adult with CKD 3-5 and who have diabetes, it is reasonable to prescribe a dietary protein intake of 0.8 – 0.9 g /kg ideal body weight per day to maintain a stable nutritional status and optimize glycemic control (OPINION).

3.1.4 In adults with CKD on MHD and PD and who have diabetes, it is reasonable to prescribe a dietary protein intake of 1.0 -1.2 g /kg ideal 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).

3.2 Statement on Protein Type

3.2.1 In adults with CKD 1-5D (1B) and post-transplant (OPINION), there is inadequate 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 (non-dialysis) and post-transplant, 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) and post-transplant (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 counselling 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 and Intradialytic Parenteral Nutrition (IDPN) Protein-Energy Supplementation
4.1.3 In adults with CKD on MHD with protein-energy wasting, we suggest a trial of IDPN for MHD patients, TPN for CKD patients and AA dialysate for PD patients to improve and maintain nutritional status if nutrition requirements cannot be met with existing oral and enteral intake (2C).

4.2 Statement on Nutrition Supplementation – Dialysate

Dialysate Protein-Energy Supplementation
4.2.1 In adults with CKD on peritoneal dialysis with protein-energy wasting, we suggest not substituting conventional dextrose dialysate with amino acid dialysate as a general strategy to improve nutritional status (2C), although in selected cases of protein-wasting when energy intake is adequate, 1.1% amino acid dialysate with alkali supplements may ameliorate protein deficits (OPINION).

4.3 Statement on Long Chain Omega-3 Polyunsaturated Fatty Acids

LC n-3 PUFA Nutritional Supplements for Mortality and Cardiovascular disease
4.3.1 In adults with **CKD on MHD or post-transplant**, we suggest not routinely prescribing long-chain 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 on PD**, it is reasonable to not routinely prescribe long-chain 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 on MHD**, we suggest that 1.3-4 g/d long-chain 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 on PD**, it is reasonable to consider prescribing 1.3-4 g/d long-chain n-3 PUFA to improve the lipid profile (OPINION).

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

**LC n-3 PUFA Nutritional Supplements for AV Graft and Fistula Patency**

4.3.6 In adults with **CKD 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 with kidney allograft**, we suggest not routinely prescribing long-chain 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 and post-transplant**, 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 and post-transplant**, 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).

5.1 Statements on Folic Acid

Folic Acid Supplementation for Hyperhomocysteinemia
5.1.1 In adults with CKD 3-5D and post-transplant 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 cardiovascular outcomes (1A).

Folic Acid Supplementation for Folic Acid Deficiency and Insufficiency
5.1.2 In adults with CKD 1-5 D (2B) and post-transplant (OPINION), we suggest prescribing folate, Vit 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 Limit
5.2.1 In adults with CKD 1-5D and post-transplant 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 1-5 D (2C) and post-transplant (OPINION), we suggest prescribing vitamin D supplementation in the form of cholecalciferol or ergocalciferol to correct 25(OH)D deficiency/insufficiency.

Vitamin D Supplementation with Proteinuria
5.3.2 In adults with CKD 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 E and A

Vitamins A and E Supplementation and Toxicity
5.4.1 In adults with CKD on MHD or PD, it is reasonable to not routinely supplement vitamin A or E because of the potential for vitamin toxicity. However, if supplementation is warranted, patients should be monitored for toxicity (OPINION).
5.5 Statements on Vitamin K

Anticoagulant Medication and Vitamin K Supplementation
5.5.1 In adults with CKD 1-5D and post-transplant, it is reasonable that patients receiving anticoagulant medicines known to inhibit vitamin K activity (e.g., 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: 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 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 Statement 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 (OPINION).
6.3 Statements on Phosphorus

Dietary Phosphorus Amount
6.3.1 In adults with **CKD 3-5 and on MHD**, 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 and post-transplant**, it is reasonable when making decisions about phosphorus restriction treatment to consider the bioavailability of phosphorus sources (e.g. animal, vegetable, additives) (OPINION).

Phosphorus Intake with Hypophosphatemia
6.3.3 For adult **kidney transplant recipients 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 and post-transplant**, it is reasonable to adjust dietary potassium intake to maintain serum potassium within the normal range (OPINION).

Dietary Potassium in Hyperkalemia
6.4.2 In adults with **CKD 3-5D and post-transplant who exhibit hyperkalemia**, it is reasonable to consider lowering dietary potassium intake as a therapeutic strategy (OPINION).

Potassium Intake for Hyperkalemia or Hypokalemia
6.4.3 In adults with **CKD 3-5 on MHD (2D) and post-transplant (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 (non-dialyzed) (1B), maintenance dialysis (1C), and post-transplant (1C)**, we recommend limiting sodium intake to less than 100 mmol/day (or <2.3 g/day) to reduce blood pressure and improve volume control.

Sodium Intake and Proteinuria
6.5.2 In adults with **CKD 3-5 (non-dialyzed)**, we suggest that reduced sodium intake (100 mmol/day or <2.3 g/day) be prescribed to reduce proteinuria (2A).

Sodium Intake and Dry Body Weight
6.5.3 In adults with **CKD 3-5D**, we suggest reduced sodium intake as an adjunctive lifestyle modification strategy to achieve better volume control and a more desirable body weight (2B).
GUIDELINE 1: NUTRITIONAL ASSESSMENT

1.0 Usual Care Statements

Routine Nutrition Screening
1.0.1 In adults with CKD 3-5D and post-transplant, 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 and post-transplant, there is limited evidence to suggest the use of one tool over others for identifying those at risk of protein-energy wasting (2D).

Routine Nutrition Assessment
1.0.3 In adults with CKD 3-5D and post-transplant, 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, 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 & Anthropometric Measurements to Assess Body Composition

Bioelectrical Impedance for Patients on Maintenance Hemodialysis (MHD)
1.1.1 In adults with CKD 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 Patients, Non-Dialyzed and on Peritoneal Dialysis (PD)
1.1.2 In adults with CKD who are non-dialyzed or on PD, there is insufficient evidence to suggest using bioelectrical impedance to assess body composition (2D).

DEXA for Body Composition Assessment
1.1.3 In adults with CKD 1-5D and post-transplant, it is reasonable to use dual-energy x-ray absorptiometry (DEXA) 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 and post-transplant, it 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 and post-transplant** 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 **stages 4-5 and post-transplant** patients
- At least every 6 months in **stages 1-3** patients

Assessment of Body Weight

1.1.6 In adults with **CKD 1-5D and post-transplant**, it is reasonable for registered dietitian nutritionist (RDN) or an international equivalent or physicians to use clinical judgement to determine the method for measuring body weight (e.g. 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).

Body Mass Index (BMI) as a Predictor of Mortality

1.1.7 In adults with **CKD who are 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 who are on MHD**, we suggest that overweight/obese 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 post-transplant**, it is reasonable to consider using underweight and overweight/obesity status (based on BMI) as a predictor of higher mortality (OPINION).

BMI and Protein Energy Wasting

1.1.11 In adults with **CKD 1-5D and post-transplant**, BMI alone is not sufficient to establish a diagnosis of PEW unless the BMI is very low (<18 kg/m2) (OPINION).

Skinfold Thickness

1.1.12 In adults with **CKD 1-5D (1B) and post-transplant** (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.
Conicity Index
1.1.14 In adults with CKD on MHD, we suggest that the conicity index may be used to assess nutritional status and as a predictor of mortality (2C).

Creatinine Kinetics
1.1.14 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 non-invasive 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, 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 since assumptions of hydration are required for accurate interpretation of the results, and fluid/electrolyte balance is likely to be altered significantly in CKD patients. For these reasons, in adults undergoing dialysis, assessments are best obtained after treatment when body fluid compartments levels are balanced.2, 3

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.3 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, gender and disease status.
Detailed Justification

Technical Devices to Measure Body Composition

**Multi-frequency bioelectrical impedance analysis (MF-BIA)**

Twelve studies reported on the use of MF-BIA to assess fat mass (FM) and fat free mass (FFM) in MHD, PD and pre-dialysis patients. Four of these studies were validity/reliability studies: two in MHD patients;\(^4,5\) one in PD patients;\(^6\) and one in pre-dialysis patients.\(^7\)

Three were prediction studies: two in MHD patients, and one in MHD and PD patients.\(^8-10\)

Eight were correlation studies; five in MHD patients;\(^4,6,11-14\) one in PD patients; one in MHD and PD patients;\(^15\) and one in pre-dialysis patients.\(^7\)

**MHD patients:** FM and FFM measured by MF-BIA had good agreement with DEXA in two studies,\(^4,5\) had high correlations with several markers of nutritional status in four studies,\(^4,13-15\) and predicted hard outcomes in three studies.\(^8-10\) Furstenburg et al. concluded that MF-BIA was a more robust tool than DEXA for measuring body composition in MHD patients.\(^5\) Donadio et al. found that MF-BIA yielded a smaller prediction error in MHD patients.\(^4\)

Body composition determined by MF-BIA was found to be predictive of hospitalization and survival.\(^8-10\) In Rodriguez et al., BIA underestimated FM and overestimated FFM when compared with air displacement plethysmography in MHD patients,\(^14\) PEW determined by MF-BIA was positively related to BMI and negatively associated with serum albumin level.\(^13\) In Mancini et al., bioimpedance vector analysis was predicted by normalized protein catabolic rate (nPCR) and albumin in MHD patients with normal nutritional status, but the predictive effects were not accurate in undernourished patients.\(^12\) In MHD patients, a body protein index score calculated from MF-BIA protein mass and height significantly correlated with blood protein levels in men on MHD, but there was no relationship in women on MHD.\(^15\)
**PD patients:** FM and FFM measured by MF-BIA showed wide limits of agreement with DEXA in 1 study, which was affected by hydration status,\(^6\) and was an independent risk factor for survival in another study.\(^8\) In CAPD patients, LBM measured by MF-BIA and creatinine kinetic method were highly correlated but there was no difference in LBM using BIA in patients with or without peritoneal dialysate.\(^11\) A body protein index score calculated from MF-BIA protein mass and height significantly correlated with blood protein levels in men on MHD, but there was no relationship in women on MHD or CAPD patients. The findings varied according to sex and dialysis treatment.\(^15\)

**Pre-dialysis patients:** In diabetic patients, % LBM measured by DEXA 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 DEXA measurements.\(^7\)

### Anthropometric and other measurements to measure body composition

#### Skinfold measurements

Ten studies reported on the use of skinfold measurements to assess body composition, including four agreement/validity/reliability studies,\(^16-19\) one prediction study\(^20\) and six correlation studies.\(^17, 21-25\)

**MHD patients:** Bross et al. used DEXA as the reference test and showed that, triceps skinfold thickness (TSF), BIA (Kushner), and near-infrared interactance were most accurate of the index tests in estimating total BF\%, although the BIA (Segal) and BIA (Lukaski) equations overestimated total BF\%.\(^17\) These results were not affected by skin color. In Bross et al., there were significant correlations (all p<0.001) between DEXA measurements and triceps skinfold measures of body fat in MHD participants.\(^17\) Kamimura et al. compared SKF with DEXA and BIA and found that body fat estimates using SKF and BIA were not significantly different from those obtained by DEXA in the total group.\(^18\) There were significant intra-class correlations between DEXA with SKF (r=0.94) and BIA (r=0.91). DEXA showed relatively good agreement with both SKF [0.47±2.8 (-5.0 to 6.0) kg] and BIA [0.39±3.3 (-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 gender-specific variability in the assessment of body fat.

A prediction study by Araujo et al. showed that TSF <90% was not associated with higher odds of mortality.\textsuperscript{20} Oe et al. in MHD patients found a significant correlation in LBM (r=0.69, p<0.025) between four skinfold anthropometry and BIA. BF-FSA was positively correlated with BF-BIA (r=0.65, p<0.005).\textsuperscript{24} Both techniques are comparable for LBM and BF measurements; however, four site skinfold anthropometry (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.\textsuperscript{22} Aatif et al. showed that fat tissue index and TSF had a positive significant correlation (r=0.61, p<0.001).\textsuperscript{21} Kamimura et al. found a strong correlation between BIA and SKF (r=0.87) and near-infrared interactance and SKF (r=0.78).\textsuperscript{18} This study confirmed that the most simple, long-established, and inexpensive method of SFT is very useful for assessing body fat in patients on long-term MHD therapy.

\textit{PD patients:} Stall et al. examined five different tools to assess BF%. BF% measurements were different between all methods (p<0.001), although there were differences according to sex.\textsuperscript{25} For men, all techniques were significantly different from each other (p<0.05) except BIA and DEXA, as well as the Steinkamp method (SKF) and total body potassium. For women, all techniques were significantly different from each other (p<0.05) except DEXA and the two methods for measuring SKF (Durnin & Womersley and Steinkamp). 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).

\textit{HD and PD patients:} Woodrow et al. compared SKF with DEXA and BIA.\textsuperscript{19} Bland & Altman analysis demonstrated no observed differences in 95\% levels of agreement for percent total body fat (TFB) and FFM from SF-BIA or skinfold anthropometry (SFA) compared with DEXA (%TFB BIA-DEXA -13.7 to +8.3; %TFB SFA-DEXA -13.0 to +9.4\%; FFM BIA-DEXA -5.1 to +9.6 kg; FFM SFA-DEXA -5.6 to +9.1 kg). There were considerable variations in agreement between the measures.

\textit{Pre-dialysis patients:} Avesani et al. used a Bland-Altman plot analysis for body fat\% and showed that the best agreement was between SKF and DEXA compared to other
measures.\textsuperscript{16} SKF also had significant intraclass correlations with body fat\% and it significantly correlated with FFM as measured by DEXA (r=0.74, r=0.85) indicating moderate and good reproducibility, respectively. This study indicated that SKF may be a good method to determine body fat\% in pre-dialysis, and mild to advanced CKD patients.

**Serum Creatinine/Creatinine Kinetics**

Seven studies examined the relationship between serum creatinine or creatinine kinetics and comparative measures of muscle mass in MHD, PD and pre-dialysis patients.

**MHD patients:** One study in MHD patients showed that creatinine kinetics correlated with creatinine levels, and other traditional measures of muscle mass (e.g. CT scan, anthropometric measurements).\textsuperscript{26} Another three studies in MHD patients showed that pre-dialysis, inter- dialytic change, and weekly creatinine clearance levels predicted mortality.\textsuperscript{26-28}

**PD patients:** In PD patients, creatinine kinetics was correlated with other body composition measurements in one study;\textsuperscript{29} however, significant differences existed between creatinine and anthropometric measures for LBM/FFM in another.\textsuperscript{30} A study in PD examined creatinine clearance and relative risk of mortality.\textsuperscript{31} Evidence was limited in pre-dialysis patients to one study.\textsuperscript{16} CK was significantly correlated with BF\% and FFM from DEXA (r=0.47 and r=0.57, respectively, indicating moderate reproducibility, though there were significant differences in adjusted means of BF\% and FFM between CK and DEXA (p<0.05).\textsuperscript{16}

**Waist circumference**

Two studies reported on the use of waist circumference to assess nutritional status in dialysis patients.\textsuperscript{32,33}

**MHD patients:** Cordeiro et al. examined risk of 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 by SGA) and inflammation (assessed by IL-6). In the fully adjusted model, there was no increased risk of mortality according to waist circumference tertile.\textsuperscript{33}
**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 ($r=0.86$, $p<0.001$). There was a 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 was also correlated with changes in trunk fat ($r=0.49$, $p<0.001$) and kappa of 0.48 indicated a moderate agreement between the tools. The authors concluded that waist circumference is a reliable marker of abdominal adiposity in PD patients.

**BMI**

Twenty-four studies reported on the use of BMI to assess nutritional status, including 17 prediction studies and nine correlation studies. There were no studies examining 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 three studies, the authors examined mortality risk according to traditional weight categories (underweight, normal weight, overweight and obese), although in a study with Taiwanese participants, these categories were defined differently. In five additional studies, the authors examined risk according to 5 to 11 BMI categories.

In one study that only compared two groups ($<25$ kg/m$^2$), the authors found no association between BMI and mortality at 10 years. 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 of mortality for participants who were underweight, and lower risk for participants who were overweight or obese. 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 three studies, but Harell’s C statistic was not significant in de Roij van Zuijdewijn et al.

Findings from correlation studies indicated that BMI was positively associated with albumin levels, fat and lean body mass (LBM) measured by a variety of methods in HD.
patients. Beberashvili et al. showed that serum albumin was significantly and positively correlated with BMI and FM in MHD patients. The higher BMI group had greater LBM (p=0.001) and FM (p=0.0001), and higher phase angle and Extracellular Mass/Body Cell Mass (p<0.05). MHD patients with elevated BMI demonstrate better nutritional status compared to 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 total body fat percentage measured by near infrared radiation and BIA (Segal) (r ≥ 0.85) in MHD patient. Fat tissue index, as estimated by BIA, was significantly correlated with BMI in the study by Aatif et al. In another study, Kadiri et al. showed that BMI was positively correlated with FM (r=0.493, p=0.002), serum albumin (r=0.340, p=0.04), and anemia in MHD patients. BMI was negatively correlated with CRP (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 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).

Steiber et al. found that mean BMI was significantly different across the 5 categories of SGA (p<0.05) in MHD patients. Visser et al. demonstrated that there was a strong correlation between the 7-point SGA scale and BMI in MHD patients (r=0.79, p<0.001), % 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. reported results for MHD and PD patients separately). In Mathew et al., participants who survived had higher baseline BMIs compared to the group that did not survive, but BMI category was not a significant predictor. Hoogeveen et al. demonstrated that underweight and obesity were risk factors in a combination of MHD/PD patients less than 65 years of age, but for those who were at least 65, there was no relationship between BMI and mortality. Lievens et al. demonstrated that PD patients had lower mortality risk compared to MHD patients. Leinig et al. showed that there was a positive correlation between BMI and FM in predialysis (r=0.67, p=0.0002), in MHD (r= 0.67, p=0.0002), and peritoneal dialysis (r=0.79, p<0.0001) patients. Nakao et al. indicated that BMI was significantly correlated with BPI in MHD patients.
and PD patients (r values ranging from 0.778 to 0.886, p<0.0001). Hoogeveen et al. followed dialysis patients < or ≥65 years of age for seven years. In the multivariable adjusted model, compared to those with “normal” weight status, those who were categorized as underweight (2.00 (1.30-3.07) and obese (1.57 (1.08-2.28) had a significantly higher hazard of mortality for those who were <65 years, but there was no significant relationship between weight status and mortality for those ≥65 years of age. 37

**PD patients:** Four studies reported on the relationship between BMI and mortality in PD patients. Badve et al. found that underweight increased mortality risk at 2.3 years, but results regarding higher BMI categories were not consistent. 34 Leinig et al. found no difference in mortality risk according to whether PD patients had a BMI < or >23 kg/m² at 2 years. 41 McDonald et al. found that, in adjusted analysis, PD patients who were obese had higher risk of mortality (up to 10 years) compared to patients with normal weight status. 45 In the study by Kim et al., the group with the lowest quartile of BMI had the highest mortality risk at 2 years, but there were no other significant associations. 39 In a systematic review performed by Ahmadi et al., authors confirmed an increased risk of 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. found that overweight/obesity status decreased mortality risk at 1, but not 2, 3 or 5 years. 56

**Non-dialyzed patients:** Finally, two studies examined the relationship between BMI and mortality in non-dialyzed CKD patients. Madero, et al. examined risk according to BMI quartile and found no relationship. 43, 57 Hanks et al. took a different approach and examined risk not only according to traditional BMI categories, but also according to whether participants were metabolically healthy. 36 Of those who were metabolically healthy, there was decreased risk for overweight/obese participants compared to those with a 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. 57

**Post-transplant patients:** A systematic review by Ahmadi et al. examined the relationship between BMI and mortality in 150,000+ adults with CKD with kidney transplant. Authors conclude that, compared to participants with “normal” weight status at baseline, those who were underweight [HR (95% CI): 1.09 (1.02, 1.20)] or overweight/obese [1.20 (1.14, 1.23)]
were at increased hazard of mortality.58

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

Special discussions
The guidelines for MF-BIA, DEXA and skinfold measurements require specialized equipment. Good quality calipers are needed to obtain an accurate measurement of SKF. However, the measurer must be trained in order to obtain accurate results. To obtain waist circumference, only a measuring tape is required. Once again, the measurer must be trained on how to obtain this measure. 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.

Implementation considerations

MF-BIA
- The guideline for MF-BIA applies to all adult patients receiving MHD. The measure must be obtained post-dialysis on a non-conducting surface for an accurate assessment.
- When bioimpedance is performed in patients on PD, measurements should be done with an empty abdominal cavity (following PD fluid drainage) and bladder. For individuals on MHD with residual kidney function, 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.

BMI
- BMI is not an ideal marker of obesity, since it cannot differentiate between higher weights due to increased adiposity vs. musculature and it cannot identify visceral adiposity, which has negative metabolic effects.
- To ensure 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 WHO according to BMI ranges for adults should be used in the CKD population; these include <18.5 kg/m² for underweight; 18.5 to 24.9 kg/m² for normal weight; 25.0 to 29.9 kg/m² for overweight; and ≥30 kg/m² for obese. Population-specific BMI cut-offs to define weight status may be lower for Asian populations.

- Limited evidence suggested that obesity (BMI ≥30 kg/m²) may be a risk factor for higher mortality in individuals who are on dialysis and under the age of 65. Therefore, practitioners should consider patient age when determining mortality risk according to BMI.

- In patients on dialysis, weight to calculate BMI should be measured following dialysis treatment to improve accuracy.

**Skinfold measurements**

- The guideline for skinfold measurements apply to all adult CKD patients, including post-transplant. However, for the measurements to be useful to the practitioner, longitudinal assessments must be done to provide meaningful information about changes in percent body fat for that patient.

- There are no potential risks or harms associated with the application of the guideline for skinfold measurements in all adult CKD patients.

- Skinfold measurements may not be accurate for obese patients, since 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 CKD patients. However, the procedure requires the patient to collect his/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 urine creatinine excretion and this must be considered when calculating creatinine kinetics. In MHD patients, creatinine kinetics is more useful for patients who are anuric.

- There are no potential risks or harms associated with the application of the guideline
for creatinine kinetics in adult CKD patients.

*Dual energy x-ray absorptiometry*

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

*Measuring body weight*

When using published weight norms in the anthropometric assessment of adult CKD patients, caution must be use as each norm has significant drawbacks.

- 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.*]
- Hamwi method can be used to estimate LBM. [*Caution: A quick and easy method for determining optimal body weight but has no scientific data to support its use.*]
- Standard Body Weight, NHANES II (SBW as per KDOQI Nutrition Practice Guidelines) describes the median body weight of average Americans from 1976 to 1980 for height, age, sex and frame size. [*Caution: Although data is validated and standardized and uses a large database of ethnically diverse groups, data is provided only on what individuals weigh, not what they should weigh in order to reduce morbidity and mortality.*]
- BMI often defines generalized obesity and CKD research, specific to dialysis patients, has identified that patients at higher BMIs have a lower mortality risk. [*Caution: The researchers may not have statistically adjusted for all confounders related to comorbid conditions occurring in CKD on dialysis (diabetes, malignancy, etc.) and it is unclear how it may relate to CKD patients not on 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 overestimate or underestimate energy and protein requirements.]

**Monitoring and Evaluation**

- Anthropometric measurements for assessment of body composition should be done routinely in CKD patients; these include skinfold measurements, waist circumference and creatinine kinetics.
- BMI should be used routinely to assess weight status in CKD patients since 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/m²).
- However, because of the cost associated with some of these measures (e.g., MF-BIA, DEXA), there is insufficient evidence for the workgroup to suggest the use of these measurements on a routine basis in clinical practice.

**Future research**

**MF-BIA**

- Determine the frequency with which MF-BIA measurements should be performed in CKD patients, particularly in individuals who are non-dialyzed, on PD or post-transplant.
- Determine the validity and reliability of these measurements compared to DEXA and anthropometric markers of nutritional status in PD, post-transplant and pre-dialysis patients.

**BMI**

- 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 measured and monitored in the CKD population.
- Obtain a reference data set for maintenance dialysis patients of the same age, race and gender.

**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 gender.
1.2 Statements on Assessment with Laboratory Measurements

Single Biomarker Measurements
1.2.1 In adults with CKD stages 1-5D and post-transplant, biomarkers such as normalized protein catabolic rate (nPCR), normalized protein catabolic rate (nPCR), serum albumin and/or serum prealbumin 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 on maintenance dialysis, 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 upon biochemical or other related calculated indices such as serum albumin, prealbumin, and normalized protein catabolic rate (nPCR) as diagnostic tools. Albumin is a major circulating protein that plays a number of biologic 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 rise in the blood urea nitrogen in MHD patients and from urinary urea from 24-hour urine collection in on-dialyzed CKD patients. 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). In fact, serum albumin is one of the best predictors of illness or death in patients with ESRD. 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 to other methods used to assess nutritional status, including twelve studies with MHD patients, two studies with PD patients, and two studies with both MHD and PD patients were included in this review.

*MHD patients:* Among the MHD studies, one was a prospective cohort study,27 two were retrospective cohort studies,20,59 seven were cross-sectional studies,21,49,50,60-63 Two studies were diagnostic validity or reliability studies.12,64

Gurreebun et al. determined that serum albumin concentration was a sensitive method for identifying patients at risk of PEW defined by the 7-point SGA score.64 In a study by Mancini, et al., albumin independently predicted bioimpedance vector analysis in patients with normal values of other nutritional indexes, but the association was not significant in with patients with worse nutritional values.12 Araujo et al. demonstrated that serum albumin concentration <3.5 g/dL were associated with higher odds of mortality over 10 years [OR (95%CI) = 2.34 (1.33-4.10); p=0.002].20 Campbell et al. found that low albumin concentration (<38 g/L) were significantly associated with higher mortality and morbidity (length of hospital stay), but there was no adjustment for comorbidities.20,59 De Roij van Zuijdewijn et al. determined that albumin concentration predicted all-cause mortality and was the most predictive of 8 other nutrition measures.27

In Yelken et al., serum albumin concentration were significantly correlated with high sensitivity C-reactive protein (hsCRP), triceps skinfold, mid-arm circumference, and mid-arm muscle circumference (MAMC).63 Serum albumin concentration were associated with nPCR and inflammatory markers,60,62 BMI;50 7-point SGA score,61 and lean tissue index, but not fat tissue index from bioimpedance spectroscopy21 BMI and FM.49

*PD patients:* Of the two studies in PD, one was a prospective cohort study31 and the other was a retrospective cohort study.65 Leinig et al. demonstrated that hypoalbuminemia was a significant independent predictor of mortality [HR (95% CI): 2.3 (1.1-5.0) ] after 24 months of
follow-up.\textsuperscript{65} Churchill et al. described that for every g/L increase in serum albumin, there was a 2-year relative mortality risk (95% CI) of 0.94 (0.90, 0.97).\textsuperscript{31}

**MHD and PD patients:** Both MHD and PD patients were evaluated in two prospective cohort studies.\textsuperscript{44,66} Mathew et al. found that serum albumin concentration did not predict mortality and was not correlated with lean tissue index.\textsuperscript{44} De Mutsert et al demonstrated a 1g/dL decrease in serum albumin was associated with an increased mortality risk of 47% in MHD patients and 38% in PD patients.\textsuperscript{66} After adjusting for systemic inflammation, or for SGA and nPCR, these mortality risk ratios were not statistically significant indicating potential confounding effects of systemic inflammation.

In summary, one 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 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 utilizing inflammatory markers to measure nutritional status. Thirteen studies examined correlations between inflammatory markers and other nutrition indices, including seven studies in MHD patients, one study in PD patients, two studies in both MHD and PD patients, one study in patients with kidney transplant, and two studies in pre-dialysis patients.

**MHD patients:** Among the MHD studies, all seven were cross-sectional studies.\textsuperscript{49-51, 60, 62, 63, 67} hsCRP levels were positively associated with FM,\textsuperscript{67} and negatively associated with LBM,\textsuperscript{67} serum albumin \textsuperscript{60, 62, 63, 68} and serum prealbumin\textsuperscript{62} concentrations. hsCRP was not associated with SGA score, nPCR, anthropometric indices, or BIA measurements.\textsuperscript{67} While CRP was not associated with BMI in Vannini et al.,\textsuperscript{67} there was a negative correlation in Kadir\textsuperscript{50} et al.\textsuperscript{67} Kahraman et al. found that CRP levels were highest in obese and underweight participants compared to their counterparts.\textsuperscript{51} Beberashvili et al. found no relationship between proinflammatory cytokine level and BMI.\textsuperscript{49}
PD patients: de Araujo Antunes et al. conducted a cross-sectional study in PD patients. Compared to patients with CRP level <1 mg/dL, those with CRP level ≥1 mg/dL had higher BMI (29.4 ± 6.1 vs. 24.4 ± 4.5 kg/m²; p=0.009), % standard body weight (124.5 ± 25.4 vs. 106.8 ± 17.9 %; p=0.012), and % BF measured by SF-BIA (38.9 ± 6.3 vs. 26.2 ± 12.6 %; p<0.001).69

MHD and PD patients: Isoyama et al. demonstrated that low handgrip strength, rather than low muscle mass measured with DEXA, was associated inflammatory markers including hsCRP, IL-6 and TNF-α.70 In addition, CRP levels were negatively associated with BIA phase angle.8

Post-Transplant patients: Only one cross-sectional study was identified for kidney transplant recipients. In this study, malnutrition inflammation score (MIS) was positively correlated with IL-6 (p=0.231; p<0.001), TNF-α (p=0.102; p<0.001), and CRP levels (p=0.094; p=0.003).71

Non-dialyzed patients: Both studies in pre-dialysis patients were cross-sectional in nature.72,73 In a study by Wing et al., hsCRP levels were higher in the highest BMI quartile, but results with other cytokines were mixed. In Stages 2-4 CKD men, CRP levels were negatively associated with testosterone distribution.73

In summary, many studies found correlations between higher inflammatory markers 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 inflammatory in kidney transplant patients.

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

MHD patients: Of the three studies with MHD patients, one was a prospective cohort study27 and the other two were cross-sectional studies.60,62 In the study by de Roij van Zuijdewijn et al., nPNA (nPCR) was a significant predictor of all-cause mortality (Harrell's C statistic=0.56,
p<0.01), but the authors reported that MIS and serum albumin had the best predictive value.\textsuperscript{27} Jones et al. and Molfino et al. found that nPCR was a significant predictor of serum albumin and prealbumin.\textsuperscript{60,62}

**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.\textsuperscript{74} The latter study demonstrated that PCR was not correlated with LBM measured by creatinine kinetic method or MF-BIA.\textsuperscript{11}

**MHD and PD patients:** A cross-sectional study demonstrated that SGA was associated with nPCR (r=-0.29 p=0.027) in a group of MHD and PD patients.\textsuperscript{75}

**Pre-dialysis patients:** 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.\textsuperscript{72}

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 four studies that examined relationships between prealbumin concentration and comparative measures in CKD patients.

**MHD patients:** Of the three studies in MHD, one was a prospective cohort study\textsuperscript{9} and the other two were cross-sectional studies.\textsuperscript{21,62} In the study by Molfino et al., pre-albumin concentrations were associated with nPCR and IL-6 levels.\textsuperscript{62} Prealbumin increased by 20.8 mg/dL for each g/kg increase in nPCR (p<0.001), and there was a decrease in pre-albumin concentration of 0.94 mg/dL for each increase in IL-6 concentration of 1 pg/mL. In the multiple regression model, pre-albumin concentration increased by 1.8 mg/dL for each kg increase in VAT (p=0.015). Fiedler et al. determined that pre-albumin concentration was predictive of 3-year
mortality and hospitalizations. CRP was correlated with prealbumin (r=- 0.45, p<0.001) concentration. Additionally, Aatif et al. demonstrated that lean and fat tissue index derived by bioimpedance spectroscopy were significantly correlated with pre-albumin concentration.

**PD patients:** In a cross-sectional study, Cigarran et al. found that pre-albumin concentration was progressively reduced across decreasing tertiles of testosterone in men with stages 2-4 CKD (p<0.05).

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

**Special Discussions**
The biochemical markers must be obtained pre-dialysis for maintenance dialysis patients.

**Implementation considerations**

- The guideline for serum albumin applies to all adult patients with CKD on maintenance dialysis.
- There are no potential risks or harms associated with the application of the guideline for serum albumin in adult patients with CKD on maintenance dialysis.
- Gold standard method for measuring albumin is nephelometry, which is not commonly used in practice due to cost and time. In patients with ESRD patients, bromocresol green (BCG) method should be used to estimate albumin, while in patients without ESRD bromocresol purple method is more accurate.

**Future research**

**General**

- Determine the incremental value of using one 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.

*Inflammatory markers*
- Determine whether systemic inflammatory markers may be used to assess nutritional status in adult patients with CKD stages 3-5, including those on maintenance dialysis and with kidney transplantation.

*nPCR*
- 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 using handgrip strength as a surrogate measure of protein-energy status and functional status when baseline data (prior measures) are available for comparison (2B).

**Rationale/Background**

Handgrip strength (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 and non-dialyzed patients.

**Detailed Justification**

Five studies examined relationships between HGS and comparative measures in patients with CKD, including one study with non-dialyzed patients, one study with incident dialysis patients, two studies with MHD patients, and one study with PD patients. Overall, HGS was a valid measure of nutritional status compared to malnutrition inflammation score (MIS) in MHD patients (sensitivity=70-87%, specificity=43-66%) and was negatively associated with MIS in non-dialyzed patients ($r=0.42; p<0.001$), but results may vary according to confounding variables. HGS was correlated with LBM assessed by other methods, but there was no correlation with other markers of body composition or nutritional status in PD patients. In incident dialysis patients, HGS had higher correlations with nutritional status and inflammatory markers, and was more predictive of mortality than muscle mass measured by dual energy X-ray absorptiometry (DEXA).

**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, PD and non-dialyzed patients.
- 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 (i.e. PD and pre-dialysis), 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.\textsuperscript{79}

**Monitoring and Evaluation**

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

**Future research**

The workgroup recommends further research on HGS to determine:

- the timing of the measurement (e.g. pre or post hemodialysis session, non-dialysis 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 (e.g. position of the arm, the evaluation period, 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 and post-transplant**, 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 wasting 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 those receiving renal replacement therapies such as MHD, PD or post-transplant. 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 over 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 under-estimate REE in earlier stages of CKD as well as those 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 healthy adults, but the evidence is limited. Recent research has shown that predictive energy equations specifically designed for patients with CKD on 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 six studies which tested REE equations in CKD patients and compared them to a reference standard of indirect calorimetry.\(^{80-85}\) Two of the six studies used indirect calorimetry data to derive a disease-specific equation.\(^{80, 85}\) The Harris-Benedict equation over-estimated REE in four studies across the spectrum of CKD; e.g., Dias Rodrigues et al. (MHD),\(^ {81}\) Kamimura et al. (non-dialyzed, MHD and PD),\(^ {82}\) Lee et al (CAPD)\(^ {83}\) and Neyra et al (CRF, MHD and PD),\(^ {84}\) but the Harris-Benedict equation underestimated REE in MHD participants in Vilar et al.\(^ {85}\) (MHD). Similarly, the Schofield equation over-estimated REE in Dias Rodrigues et al. (MHD)\(^ {81}\) and Kamimura et al. (non-dialyzed, MHD and PD),\(^ {82}\) but underestimated REE in Vilar et al. (MHD).\(^ {85}\) Byham-Gray et al. demonstrated that the Maintenance Hemodialysis Equation more accurately predicted REE than the Mifflin-St. Joer equation.\(^ {80}\) Vilar et al. also found that their created equation for REE was best predictor of REE when compared to traditional predictive energy equations.\(^ {85}\) Generally, agreement between equations and methods was low-to-moderate.

**Special discussions**
Among patients with stage 5 CKD on MHD or PD, there are several factors that may influence energy expenditure beyond the traditional determinants (age, sex, and fat-free mass), such as hyperparathyroidism, hyperglycemia, and chronic inflammation that should be considered into the overall energy prescription. Energy needs will be variable depending on the health status of the patient (e.g., acutely ill versus chronically managed) as well as overall health goals (e.g., weight maintenance, repletion or loss). Energy needs may be different depending on the stage of CKD and its respective treatment (dialysis versus transplantation). In the context of these recommendations, “metabolically stable” indicates absence of any active inflammatory or infectious diseases; no hospitalization within two 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 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, gender, weight status, disease-specific determinants, metabolic stressors, and treatment goals.

- Disease specific equations, such as the Maintenance Hemodialysis Equation, should be used when estimating energy requirements for the CKD population.
- Thermal effects of food may be decreased in individuals who are non-dialyzed compared to 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; i.e., 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 Statement 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 and post-transplant, Malnutrition Inflammation Score may be used to assess nutritional status (2C).

Rationale/Background
Assessment of nutritional status in adults diagnosed with CKD stages 1-5 must occur on a routine basis in order 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 on their validity and reliability. Most of the existing tools focus on identification of malnutrition risk; only one 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 exam, dietary intake assessment, and medical/psychosocial history. The availability of composite nutritional indices [e.g., the Subjective Global Assessment (SGA) or Malnutrition Inflammation Score (MIS)], collect such data and therefore assist the clinician in deciding about the individual’s nutritional status and eventual plan of care, and are specific to the unique nutritional requirements of this patient population.

Detailed Justification

COMPOSITE NUTRITIONAL INDICES: SCREENING TOOLS
Geriatric Nutrition Risk Index (GNRI)
Three studies reported on the use of GNRI to assess nutritional status, including two validity/reliability studies\textsuperscript{86, 87} and one prediction study in MHD patients.\textsuperscript{27} In one study, GNRI
had the greatest area under curve (using MIS as a reference) of the nutrition screening tools.\textsuperscript{87} 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 high inter-observer agreement score ($k=0.98$) and high intra-observer reproducibility ($k=0.82$).\textsuperscript{86} 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 to MIS and albumin levels.\textsuperscript{27}

**Malnutrition Universal Screening Tool/Malnutrition Screening Tool (MUST/MST)**

Two validity/reliability study reported on the use of MUST and MST tools to assess nutritional status in MHD patients.\textsuperscript{87, 88} A study by Lawson et al., reported on the validity and reliability of both MUST and MST tool in MHD patients.\textsuperscript{88} The sensitivity of both the MUST and MST tool 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 a high specificity (MUST=78.3\%; MST=85.5\%), so they are good at excluding individuals who are not malnourished. Reliability assessed by kappa was 0.58 for MUST (95\% CI, 0.20 to 0.80) and 0.33 for MST (95\% CI, 0.03 to 0.54). Both tools had an NPV or 60\% and 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., the authors compared results from various malnutrition assessment tools to the reference standard of MIS.\textsuperscript{87} MUST and MST scores were both significantly associated with MIS ($p<0.0001$ for each). The ROC 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 these may not be the best tools to discriminate nutritional risk in patients on MHD.

**Mini-Nutrition Assessment (MNA)**

Four studies reported on the use of MNA to assess nutritional status in MHD patients, three were validity/reliability studies\textsuperscript{87, 89, 90} and one was a correlational study.\textsuperscript{91} Afsar et al.
reported on the reliability of MNA tool compared to SGA 3-point scale.\textsuperscript{89} The reliability coefficients (alpha) for MNA was 0.93 (good degree of reproducibility). MNA might underestimate the nutritional status of patients on MHD who are not in an inflammatory state. Hence, MNA may not be as reliable as SGA in detecting PEM in the MHD population. Erdogan et al. compared MNA to Bio-electrical Impedance Analysis (BIA), 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).\textsuperscript{91} Authors concluded BIA is not as sensitive as MNA to detect early effects of secondary causes for malnutrition. Santin et al. 2015, compared SGA (7-point), MIS, MNA-Short Form (MNA-SF) to handgrip strength (HGS), albumin, c-reactive protein (CRP), and skinfolds. SGA and MNA-SF had fair agreement (kappa=0.24; p<0.001).\textsuperscript{90} 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 CKD population, whereas MNA-SF validity results were more comparable to non-CKD elderly individuals. Yamada et al., compared MNA to 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.\textsuperscript{87}

**Nutrition Impact Symptoms (NIS)**

One validity study reported on the use of NIS score for identifying those at risk of malnutrition in patients on HD and concluded that NIS score is a useful nutrition screening tool for identifying who are at risk of malnutrition.\textsuperscript{92} 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 subjective global assessment (PG-SGA), an abbreviated PG-SGA and NIS). Serum albumin was negatively correlated with NIS (Spearman Rho= -0.161; p=0.018).

**Nutrition Screening Tool (NST)**

One validity study reported on the use of NST to assess nutritional status in PD patients. In this study, NST had a sensitivity of 0.84 (range: 0.74 to 0.94; p<0.05) and specificity of 0.9 (range: 0.82 to 0.99; p<0.05) which is clinically acceptable.\textsuperscript{93}
Renal Nutrition Screening Tool (R-NST)
In another study by Xia et al. in PD patients, the R-NST was compared to SGA-7 point scale.94 Authors determined that the R-NST tool when compared to SGA-7 point scale is valid to detect risk of 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), 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 of undernutrition.

Protein Energy Wasting (PEW) score
Two predictive studies reported on the use of PEW score to assess nutritional status. Leinig and colleagues identified that SGA and albumin were significant predictors of mortality, but BMI, mid-arm muscle circumference (MAMC) and PEW score did not predict mortality at 24 months in PD patients.65 However, Moreau-Gaudry et al., a study conducted in patients on MHD recorded that PEW predicts survival. Each unit decrease in score was related with a 5-7% reduction in survival (p<0.01).95 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 (SGA)
Eleven studies examined the relationship between the 7-point SGA score and comparative measures, including three validity/reliability studies52, 53, 90 and six additional prediction and/or correlation studies.27, 61, 67, 96-98

Three studies examined the validity and/or reliability of the 7-point SGA score in MHD patients. In Visser et al., 7-point SGA score demonstrated fair inter-observer reliability [intra-class correlation (ICC) = 0.72] and good intra-observer reliability (ICC=0.88) in MHD patients.53 In Santin et al., 7-point SGA score had good agreement with MIS (κ=0.43; p<0.001) and MNA-SF (κ=0.24; p<0.001).90 In a study by Steiber, et al., SGA had fair interrater reliability (κ=0.5, Spearman’s Rho=0.7), substantial intra-rater reliability (κ=0.7, spearman’s Rho=0.8) (p<0001).52
Three cohort studies examined whether the 7-point SGA score was predictive of hard outcomes in patients on MHD. In Perez et al., SGA was a significant predictor of mortality at 2 years after adjustments for significant confounders. In a study by de Roij van Zuitedewijn et al., SGA was a significant predictor (p<0.001) for mortality at 2.97 years, but had lower predictive value for all-cause mortality compared to MIS and albumin levels. de Mutsert and others reported that hazard of mortality increased with SGA in a dose-dependent manner among patients on dialysis. Compared to normal nutritional status, persons who had a SGA of 4-5 had an increased HR (95% CI) at 7-year mortality of 1.6 (1.3, 1.9) and SGA of 1–3 had an HR of 2.1 (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 one unit increase in the 7-point SGA adapted for end-stage renal disease (ESRD)/continuous ambulatory PD patients, there was a 25% decreased 2 year mortality risk (p<0.05).

Six studies examined correlations between the 7-point SGA score and other measures of nutritional status. In Visser, et al., there was a strong correlation between the 7-point SGA score and BMI (r=0.79), % fat (r=0.77), and mid arm circumference (r=0.71) (all p<0.001) in MHD patients. In a study by Steiber et al., there were statistically significant differences in mean BMI and serum albumin according to SGA score in MHD patients (p<0.05). Tapiawala et al. assessed the 7-point SGA score in patients with CKD, ESRD and those on all types of dialysis. SGA scores were not correlated with dietary protein and energy intake or serum albumin levels, but anthropometric measures correlated with the SGA scores (skinfolds r=0.2, mid-arm circumference r=0.5 and MAMC r=0.5). Authors concluded 7-point SGA is a reliable method of assessing nutritional status. Malgorzewicz et al. compared near-infrared measurements and albumin levels to the SGA 7-point score in MHD patients. LBM measured by 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<.05). In Vannini et al., SGA were associated with traditional nutritional markers, reinforcing validity for use among patients on MHD. SGA score was not associated with CRP level. Jones et al. examined the relationship between 3-point SGA score and a composite nutritional score that included SGA (3 point and 7 point), BMI, % reference weight, skinfold and MAMC measurements and albumin levels in patients treated by MHD. Compared to 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\textsuperscript{99}, the authors utilized a version of the SGA that was adapted for patients on MHD, and in two studies\textsuperscript{65,100} the version of the SGA tool used was unclear. Garagarza et al. compared bioimpedance spectroscopy measurements to SGA scores from a version modified for MHD\textsuperscript{99} that included a 5-point score comprising weight changes, eating habits, gastrointestinal symptoms, functional activity and comorbidities. PEW measured by BIS extracellular weight (ECW)/body weight (BW) was positively associated with CRP (p=0.009) and SGA score (p=0.03). Leinig et al. examined the relationship between SGA score and mortality risk at 24 months in PD patients, but version of the SGA employed was unclear. SGA score was a significant predictor of mortality in PD patients.\textsuperscript{65} Passadakis et al. compared BIA measurements to SGA score in CAPD patients, but the version of SGA utilized was uncertain.\textsuperscript{100} 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 (MIS)**

Eight studies reported on the use of MIS to assess nutritional status, including two validity/reliability studies\textsuperscript{86,90}, four prediction studies\textsuperscript{9,27,97} and three correlation studies).\textsuperscript{71,76,101}

One study by Bebershavili et al. reported that MIS had moderate inter-observer agreement (k=0.62) and inter-observer reproducibility (k=0.77) and is a valid tool for longitudinal assessment of nutritional status of patients on MHD.\textsuperscript{86} Another study by Santin et al., indicated that MIS had good agreement with SGA (k=0.43, p<0.001) and worse agreement with MNA-SF (k= 0.14, p<0.004).\textsuperscript{90} 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.\textsuperscript{9,27,90,97} Three of the studies reported that in patients on MHD, MIS is a significant predictor of mortality.\textsuperscript{9,27,97} In one study, MIS was a significant predictor for mortality at 2.97 years (p<0.001), and best predictive
tool for all-cause mortality and secondary end-points like cardiovascular events in patients on MHD. Another study by Fiedler et al. also reported that MIS was predictive of both mortality and hospitalizations in patients treated by MHD with survival analysis indicated that MIS was one of the best predictors of mortality [HR 6.25 (2.82 – 13.87), p<0.001]. Perez et al. also indicated that MIS was a significant predictor for 2 year mortality in MHD patients. Finally, in Santin et al., while mild MIS did not predict mortality, severe MIS was a significant predictor of mortality in adjusted analysis [HR (95% CI): 5.13 (1.19, 13.7)].

Three studies reported on the use of MIS and correlation with other tools. Amparo et al. indicated that there was a significant negative correlation between hand grip strength and MIS (r= -0.42, p<0.001) in predialysis subjects. Hou et al. indicated that MIS was strongly correlated with modified quantitative subjective global assessment (r=0.924) and inversely correlated with BIA (r= -0.213) in MHD patients. Molnar et al. reported that MIS showed significant negative correlations with abdominal circumference (p= -0.144; p<0.001) and pre-albumin level (p= -0.165; P<0.001), whereas significant positive correlation was seen with IL-6 (p=0.231; p<0.001), TNF-a (p=0.102; p<0.001), and CRP levels (p=0.094; p=0.003) in kidney transplant recipients. All studies show that MIS is a useful tool to assess nutritional status in CKD patients.

**Other Composite Nutritional Indices**

**Nutrition Risk Score**

A prediction study reported that Nutrition Risk Score was a good predictor of mortality (HR 4.24 (1.92-9.38), p<0.001) in patients on MHD and was superior when compared to lab markers and BIA in predicting mortality.

**Protein Nutrition Index (PNI)**

A reliability study investigated PNI as a predictor of survival in PD patients. Compared to the reference standard (nPNA (nPCR) ≤0.91 as malnutrition), the sensitivity, specificity, positive and negative predictive value of PNI were 0.4, 0.978, 0.901 and 0.783, respectively. This study indicated that PNI is a good predictor of mortality (even after adjusting for age and comorbidities). An increase in PNI score by 1 led to a 16% decrease in mortality risk.
Composite Score of Protein Energy Nutrition Status (cPENS)

de Roij van Zuijdewijn et al. studied eight nutrition assessment tools used to predict all-cause mortality.27 Composite Score of Protein Energy Nutrition Status had a Harrell’s C statistics of 0.63 (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 et al. 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.103 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 score 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.97 This study indicated that SGA and MIS are better predictors of all-cause mortality at 15.5 months in this study and International Society of Renal Nutrition and Metabolism criteria was not able to predict mortality in this sample.

One correlation study investigated the relationship between body adiposity index (BAI), BIA, anthropometrics, and DEXA.104 The correlation coefficient was higher between DEXA vs. anthropometric measurements (r=0.76) and BAI (r=0.61) when compared to BIA (r=0.57) in the adjusted analysis (p<0.0001). Results suggest BIA estimates body fat with high accuracy in non-dialyzed CKD patients.

Special discussions

The large body of literature on nutritional assessment and composite nutritional indices have been completed in CKD 5D. While some of these tools may be relevant and can be translated to earlier stages (1-4) CKD, there is a need for the practitioner to conduct a comprehensive
More research is needed to examine which composite nutritional indices are appropriate for the recognition of a poor nutritional status (e.g., 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 a 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 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 mechanisms 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 non-dialyzed.

- More research is needed examining validity and reliability of the GNRI and SGA tools in elderly people with CKD.

- Further development and testing of screening and assessment tools for PEW are necessary, especially in terms of response to nutritional interventions.
1.6 Statement on Tools/Methods Used to Assess Protein and Energy Intake

Considerations when Assessing Dietary Intake
1.6.1 In adults with CKD 3-5D and post-transplant, it is reasonable to assess factors beyond dietary intake (e.g. medication use, knowledge, beliefs, attitudes, behavior and access to food, depression, cognitive function etc.) 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 non-dialysis 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) and 5D (2D), 24-hour food recalls, food frequency questionnaires and normalized protein catabolic rate (nPCR)/normalized protein catabolic rate (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, macro- and micro-nutrients 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 over-reporting of intake are a concern in this population.

Detailed Justification
A total of six studies reported on use of methods to assess protein and energy intake in CKD subjects.\(^{105-111}\)

Food Records/Diary
Based on the findings of four 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.\(^{107-109}\) Two studies used food diary/3-day food records to determine underreporting of energy intake in non-dialyzed and PD patients.\(^{105,106}\) Underreporting was
noticed in 72.5% of non-dialyzed CKD patients and 52.5% PD patients. Both the studies indicated that underreporting was more pronounced in overweight patients. Shapiro et al. compared energy intake measured by 3-day food record (dietitian interview-assisted) and REE measured by indirect calorimetry. Energy intake reported by interview-assisted food records were lower than measured REE.  

Food Frequency Questionnaires
Delgado et al. conducted a validation study comparing Block Brief 2000 food frequency questionnaire (BFFQ) against 3-day food diary records and found the Block Brief 2000 food frequency questionnaire under-estimated energy and macronutrient intake in patients on hemodialysis. However, the use of 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 protein catabolic rate (PCR) to assess protein intake in CKD patients, and found significant correlations with reference standards for measuring dietary intake (ex: 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 by PCR. In PD patients, PNA (PCR) normalized to desirable body weight was correlated better with BUN (r=0.702) and Kt/V (r=0.348).  

Special discussions
Despite the food record/diary being the most reliable and valid measure of dietary intake among patients diagnosed with CKD, it does rely 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 that 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 (e.g., elderly). In non-dialyzed CKD patients, 24-hour urine collection to measure urine urea nitrogen (UUN), sodium and potassium is more reliable to yield estimates of DPI, sodium and potassium. Dietary intake methods may need to be simplified, modified, or be combined with a few strategies in order to obtain reliable dietary intake data, with emphasis on them being
Implementation considerations

- Routine dietary assessment among adults diagnosed with CKD stages 1-5D should occur to allow for the identification and treatment of nutritional concerns related to nutrient intake.
- Assessing dietary intake using multiple, complementary methods, such as FFQ and 24-hr urine collection to measure urine urea nitrogen, sodium and potassium, may be useful to confirm 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 over-reporting of dietary intake in this population.
- Further development and testing of dietary assessment tools to integrate technology and assist individuals with limited literacy, 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, USA or international nutrition credential) in close collaboration with a physician, or other provider (nurse practitioner or physician assistant), provide medical nutrition therapy (MNT). Goals are to optimize nutritional status, and to minimize risks imposed by co-morbidities 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 and post-transplant**, it is reasonable to prescribe MNT that is tailored to the individuals’ needs, nutritional status and co-morbid conditions (OPINION).

MNT Monitoring and Evaluation

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

Rationale/Background

Individualized management of nutritional intake is a crucial aspect of care for individuals diagnosed with any stage of CKD, including those on 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 post-transplant period. The metabolic abnormalities and co-morbid 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, 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 RDN 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 (MNT)**

In 2002, the then American Dietetic Association published a nutrition care model that provided evidence-based, high-quality standardized care for patients with CKD, non-dialyzed and post-transplant. The document was later revised in 2010, which reported that nutrition care provided by an RD up to twice monthly over a one-year period can have a valuable role in the medical care of the CKD patients by:

- Providing nutrition assessment and interventions to delay kidney disease progression in addition to co-morbid conditions such as diabetes mellitus, cardiovascular disease, dyslipidemia, gout, nephrolithiasis;
- Utilizing 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, supporting 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 identifying medication errors and need for adjustment- in collaboration with nephrology Provider (Medical Doctor, Nurse Practitioner, 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. CKD patients are on a dynamic nutrition trajectory according to their disease stage and MNT is needed at each stage of CKD. Metabolic abnormalities, acid base, 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, they might stabilize potassium balance and have no need for potassium supplementation or dietary potassium restriction. This type of complicated CKD patients 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. However, these studies were heterogeneous in terms of the populations (five studies included patients who were non-dialyzed, nine included patients on MHD, one included patients on CAPD, and one included patients post-transplant); interventions (ex: RDNs utilized various methods of nutritional counseling among the studies); and outcomes (ex: protein intake, serum phosphate, serum albumin, BMI, and dyslipidemia. Intervention durations ranged from four weeks to two years.

**CKD Progression**

In four of the studies ranging from 4 weeks to 4 months, authors found no effect of MNT on CKD progression in non-dialyzed patients compared to participants receiving standard nutrition education for CKD, which may or may not have also been provided by an RDN. Interventions ranged from one in-person contact plus phone contacts with the RDN for 12 weeks (Stage 4 CKD)\textsuperscript{116} to a multi-disciplinary intervention including 4 weeks of weekly counselling with an RDN (Stages 3-4 CKD)\textsuperscript{117} to 2, two-hour cooking classes and a shopping tour (Stages 2-4 CKD)\textsuperscript{118} to nutrition counselling plus nutrition education for four months (Stages 3-5 CKD).\textsuperscript{119}

**SGA Scores**

Three RCTs, including two study populations, reported on the effect of MNT on SGA scores. Campbell et al. demonstrated that malnourished Stage 4 CKD patients’ SGA scores significantly improved in the intervention group compared to the control group, for whom malnutrition by SGA score increased.\textsuperscript{116} The intervention consisted of nutritional counselling
from an RDN for 12 weeks, with an emphasis on self-management techniques, face-to-face consultation at baseline, and telephone consultation every two weeks for the first month, and then monthly for the next 2 months. In Leon et al., MHD participants received monthly consultation by RDN for 12 months.\textsuperscript{120} Intervention RDNs 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 that had improved or decreased SGA scores between groups.

\textit{BMI}

Four RCTs examined the effect of MNT interventions on BMI, including two studies with non-dialyzed patients (Stages 3-5 CKD),\textsuperscript{117, 119} one study with MHD participants\textsuperscript{120} and one with post-transplant patients.\textsuperscript{121} Howden et al. examined the effect of a 12-month multi-disciplinary lifestyle intervention on BMI in patients with stages 3-4 CKD.\textsuperscript{117} 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 to the standard care group (p<0.01). Paes-Barreto et al., examined the effect of MNT on BMI\textsuperscript{119} in participants with stages 3-5 CKD who received individualized dietary counselling monthly for four months. In addition to the routine counselling, an intervention group received intensive counselling, 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 to the standard care group (p<0.01). In Leon et al., MHD participants received monthly consultation by an RDN to determine and address barriers to reaching normal serum albumin levels for 12 months.\textsuperscript{120} There was no effect on BMI, though this was not the objective of the intervention. Finally, in Orazio et al., intervention participants received RDN counselling using a Mediterranean-style diet, which consisted of a low glycemic index and moderate energy deficit. MNT counselling was based the Stages of Change Model.\textsuperscript{121} There was no difference in change in BMI between groups after 2 years.

In a meta-analysis of two studies, participants who received MNT had a greater mean (95\% CI) decrease in BMI compare to the control groups [-0.89 (±1.52, -0.25) kg/m\(^2\)].\textsuperscript{119, 121} Results
regarding 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 et al. and Lou et al., phosphorus-focused education, provided once and monthly for 6 months, respectively, significantly improved (decreased) mean serum phosphate levels.\(^{122,123}\) In Karavetian et al., weekly education nutrition counselling for 2 months also decreased phosphate levels (p<0.01).\(^{124}\) However, Morey et al. also used phosphorus-focused RDN counselling and education, monthly for 6 months, and found no difference in change in phosphate levels between groups at 6 months.\(^{125}\)

Participants receiving a multi-disciplinary nutrition education program did not have any changes in phosphate levels compared to participants receiving an oral nutrition supplement (ONS).\(^{126}\) In Reese et al., participants who were coached by a trained RDN about dietary and medication adherence (≥3 times a week) for 10 weeks were compared to patients receiving a financial incentive or usual care.\(^{127}\) There were no between-group differences in change in phosphate levels. There was no effect of MNT in the form of dietary counselling in CAPD patients\(^{128}\) or in the form of RDN counselling plus low-protein and low-sodium diet education in non-dialyzed patients\(^{119}\) on phosphate levels, but the objectives of these studies were to improve energy, protein and sodium intake.

Meta-analysis of four studies with comparable data revealed that, mean (95% CI) phosphorus/phosphate levels were decreased -0.715 (-1.395, -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,\(^{125,126,129}\) but effect on phosphorus/phosphate levels as well as the effect on calcium or potassium levels in non-dialyzed patients,\(^{119}\) was unclear.

*Lipid Profile*
Three RCTs examined the effect of MNT from an RDN on lipid profile.\(^{117,118,126}\) In Hernandez-Morante et al., MHD participants in the intervention group received a 12-session multi-disciplinary Nutrition Education Program over four months, including group and
individual therapy, while control participants received an oral nutrition supplement three days/week. Within group analysis showed no significant changes in mean triglycerides and total cholesterol 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) in both groups over the 4-month study period (p<0.001 for each measure). Between-group analysis was not reported.

Both Howden et al. and Flesher et al. examined the effect of MNT in Stages 3-4 CKD participants. In Howden et al., intervention participants received a multi-disciplinary 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 triglyceride or total, HDL or LDL cholesterol levels between the 2 groups. In Flesher et al., 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 total cholesterol level between the 2 groups. Pooled analysis confirmed no effect of MNT on total cholesterol and triglyceride levels. However, in pooled analysis, LDL levels were decreased by MNT (Mean (95% CI): -6.022 (-7.754, -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 CKD patients. Two of those studies targeted protein intake as their primary outcome of the MNT provided to the participants. Paes-Barreto et al. educated non-dialysis patients on eating a low protein diet (LPD), while Leon et al. counseled MHD participants on following a high protein diet. Both studies showed high compliance of recommended protein intake among the participants in the intervention group as compared to the control group. The other four 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 utilization of MNT protocols has the potential to preserve nutritional status, modify risk factors for progression of kidney disease, as well as assist with living with CKD from a diet
and lifestyle prospective through teaching patient’s 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 of 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\(^\text{130}\). This is particularly true for CKD patients as well as in other disease states and metabolic phenotypes such as obesity that affect CKD risk and exacerbation of CKD progression. While MNT outcomes research is still in its infancy, the studies that do 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 is currently in progress. In addition, the strength of the evidence in 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 do not replace individualized modification.
- Implementation of MNT for CKD patients requires the formation of a fiscal structure that will support the integration of MNT into routine medical management of CKD patients. 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.
• MNT may be delivered through telehealth options, in order to improve patient education and successful maintenance of nutrition interventions and adherence.

**Monitoring and Evaluation**
Monitoring and evaluation of MNT on patient’s nutritional parameters is an essential component of treatment and includes assessment of patient’s labs, nutritional status, etiology 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 co-morbid conditions is necessary.
• Patient outcomes pertaining to the individualized nutrition plan formulated for patients and /or group classes to evaluate the effectiveness of the therapy should be explored in future studies.
• Research examining access to MNT as well as methods (ex: fiscal, referral, etc.) that support MNT access for individuals with CKD.
GUIDELINE 3: PROTEIN AND ENERGY INTAKE

3.0 Statement on Energy Intake

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

3.1 Statements on Protein Amount

Protein Restriction, Non-Dialysis

3.1.1 In adults with CKD 3-5 who are metabolically stable, we recommend protein restriction with or without keto acid analogs, to reduce risk for ESRD/death (1A) and improve QoL (1C). Protein restriction should be supervised by a registered dietitian nutritionist (RDN) or equivalent in collaboration with a physician.

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

Dietary Protein Intake, Maintenance Hemodialysis and Peritoneal Dialysis

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

Dietary Protein Intake, Diabetes Mellitus

3.1.3 In the adult with CKD 3-5 and who have diabetes, it is reasonable to prescribe a dietary protein intake of 0.8 – 0.9 g /kg ideal body weight per day to maintain a stable nutritional status and optimize glycemic control (OPINION).

3.1.4 In adults with CKD on MHD and PD and who have diabetes, it is reasonable to prescribe a dietary protein intake of 1.0 -1.2 g /kg ideal 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).

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. This has been clearly identified for compounds such as P-cresylsulphate, indoxyl-sulphate, trimethyl aminoxide, fibroblast-growth factor 23, which are now considered as uremic toxins. Secondly, protein intake is responsible for a major fraction of kidney workload, and many experimental and clinical research have 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. 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 absence of any active inflammatory or infectious diseases; no hospitalization within two 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.

**Detailed Justification**

**Energy Intake**

Energy metabolism maybe impaired in patients with chronic kidney disease. Hence, maintaining adequate energy intake is necessary to prevent protein-energy wasting.

Evidence from ten controlled trials in pre-dialysis population and from 3 studies in MHD patients indicates that energy intake ranging from 30-35 kcal/kg/d helps maintain neutral nitrogen balance and nutritional status. However, it is important to remember that many other factors may influence energy expenditure beyond traditional determinants like age, sex, and fat-free mass. Some of these factors include hyperparathyroidism, hyperglycemia, and chronic
inflammation that should be considered into the overall energy prescription, health status (e.g., acutely ill versus chronically managed), overall health goals, and weight maintenance--repletion or loss.

There is still 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/d helped maintain neutral nitrogen balance and body composition. Another similar study in 6 individuals indicated that average intake of 38 kcal was desirable to maintain neutral nitrogen balance. Recent review articles not included in this evidence review, also suggest that energy intake in the range of 30-35 kcal/kg/d is appropriate to maintain maintains neutral nitrogen balance and nutritional status.

**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 too much protein (1.35 g protein/kg/d) as compared with their optimal daily needs, estimated to be 0.8 g protein/kg/day. Further, metabolic balances in healthy adults and CKD patients have confirmed that, provided a sufficient energy intake (e.g., above 30 kcal/kg/d), the protein intake level can be safely decreased to 0.55-0.6 g protein/kg/d. A further reduction in protein intake to 0.3-0.4 g protein/kg/d can be achieved with the addition of pills of keto acid analogs to ensure a sufficient balance of the essential amino acids (EAAs) normally brought by animal proteins, which are essentially absent in these low protein vegan-like diets.

**PROTEIN RESTRICTION ALONE**

In adults with CKD/kidney transplant, thirteen RCTs reported the effect of protein restriction only (no supplementation) on outcomes of interest. Duration of the follow-up in the included studies ranged from 3 months to 48 months. (Appendix – study characteristics table)

*Survival/Renal Death*

Research reports a beneficial effect of protein restriction (0.55-0.6 g/kg/d) on ESRD/death in
adults with CKD. In adults with CKD, 5 RCTs reported findings on effect of protein restriction on survival/deaths. Three studies clearly indicated a beneficial effect of moderate restriction in dietary protein on the development of ESRD/death.\textsuperscript{140, 151, 155} Rosman et al. indicated people consuming 0.6 g/kg/d of protein had better survival (55%) compared to patients consuming free protein intake (40%).\textsuperscript{155} Hansen et al. indicated that death or ESRD was significantly lower in low protein intake group (0.6g/kg/d) (10%) compared to usual protein intake (27%).\textsuperscript{151} Locatelli et al. also showed that LPD (0.6 g/kg/d) had fewer events (27/192) compared to usual protein intake (1g/kg/d) (42/188), borderline significant (p<0.06).\textsuperscript{140} Whereas, Cianciaruso et al. indicated that cumulative incidences of death and dialysis therapy start were unaffected by the diet regimen, and low protein intake group (0.55 g/kg/d) does not seem to confer a survival advantage compared with a moderate protein intake group (0.80 g/kg/d) but may be explained by a relatively small sample size.\textsuperscript{148} Pooled together, results from the secondary analysis on the number of events of death/ESRD combined from the three studies indicated a beneficial effect of protein restriction on death /ESRD (OR 0.621 CI: 0.391, 0.985).\textsuperscript{140, 148, 151}

Quality of Life
Research reports an improved quality of life of a protein restricted diet in one study. In adults with CKD, one RCT examined the effect of protein restriction on quality of life.\textsuperscript{143} QoL scores at the end of the study indicated that the protein restricted group had significantly higher scores for general health (MD 4.0, 95% CI: 3.1, 4.86) and physical status (MD 10.0, 95% CI: 9.1, 10.9) compared to the control group (0.6 g/kg/d vs 46.3g protein/day; p<0.05).

Glomerular Filtration Rate
In adults with CKD, 5 RCT’s reported on effect of protein-restricted diet on GFR. Results from the all the studies indicated that LPD (0.55-0.6 g/kg body weight) had no significant effect on GFR compared to the control group (0.8 g/kg protein). Hansen et al. indicated that at a 6-month follow-up time, there was a comparable and significant decline in GFR in both groups.\textsuperscript{151} However, the difference between groups was insignificant (p=0.87). Sanchez et al. indicated that GFR rates decreased by 17.2% in the control group compared to only 6.9% in low protein group (NS between groups).\textsuperscript{143} Cianciaruso et al. indicated no effect of diet assignments was noted on eGFR and proteinuria (0.55g/kg/d vs 0.80 g/kg/d).\textsuperscript{148} Juesudason et al. reported that dietary treatment had no effect on changes in eGFR.\textsuperscript{152} Meloni et al. (stage 3) also indicated no
effect of protein restriction on eGFR decline (0.6g/kg/d).\textsuperscript{157} Decline in GFR was reported by three studies, a pooled analysis of these studies indicated no clear effect of protein restriction without supplementation on eGFR (SMD -0.002, CI: -0.192, 0.188).

\textit{Phosphate Levels}

In adults with CKD, two RCT’s reported mixed results regarding the effect of protein restriction on serum phosphate levels.\textsuperscript{149,154} Rosman et al. 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).\textsuperscript{154} Whereas, Cianciaruso et al., indicated that phosphate levels were similar in the two groups throughout the entire period of follow-up (0.55 g protein/kg/d group vs 0.8 g protein/kg/d).\textsuperscript{149}

\textit{Dietary Intake}

Seven randomized controlled studies\textsuperscript{136,143,144,150-152,157} and 1 NRCT\textsuperscript{138} reported on dietary intake. Dietary intake was used as a compliance measure in most of the studies. These studies indicated that protein intake was lower in groups assigned to low-protein diet (0.6 g/kg/d) compared to control or standard groups (0.8-1.3 g/kg/d). In one study, the average protein intake during the entire duration of follow-up was higher than expected in both the groups (CPD=1.03 ± 0.18, LPD=0.78 ± 0.17 g protein/kg/d).\textsuperscript{150} Follow-up of at least 1.5 years indicated that compliance to diet did not change in time in either group. Hansen et al. reported an estimated dietary protein intake at 4 years significantly lower in LPD compared to
usual PD group (p=0.005).\textsuperscript{151} Jesudason et al. showed that the moderate protein intake group increased their protein intake (NS) and standard protein group decreased their protein intake.\textsuperscript{152} In the study by Kloppenburg et al. the protein intake during the high protein diet was higher than during the regular protein diet.\textsuperscript{136} Kuhlmann et al. reported that protein intake was not significantly different among the groups.\textsuperscript{138} However, total energy intake significantly differed among each other. In the Meloni et al. study, patients in the low protein group were maintaining their intake at 0.68 g protein/kg/d level which was significantly lower than the free protein diet group.\textsuperscript{157} Phosphate intake was also significantly lower in the LPD group. Sanchez et al. showed that protein intake in the LPD group decreased significantly from baseline to end of the study (p<0.05).\textsuperscript{143} Energy intake tended to decrease during the study duration in both the groups but it was non-significant. In Williams et al. study, compared to control, only dietary protein and phosphate restriction group had significantly lower protein intake level.\textsuperscript{144} Finally, Cianciaruso et al. reported that the 2 groups (LPD vs MPD) 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.\textsuperscript{148} Dietary intake can be used as a compliance index to the diet.

\textit{Nutritional status}

Research findings indicated that protein restriction did not affect serum albumin levels or anthropometrics in adult CKD patients. In adults with CKD, 2 RCTs reported no effect of protein restriction (0.55-0.9 g protein/kg/d) on serum albumin levels compared to control group (0.8-1.3 g protein/kg/d).\textsuperscript{136,148} In adults with CKD, one RCT reported no effect of protein restriction (55-70 g/d) on anthropometrics compared to control group (90-120 g/d).\textsuperscript{152}

\textit{Blood pressure}

Two RCT’s reported no effect of protein-restriction (0.6 g/kg body weight vs usual) on BP values.\textsuperscript{151,152} Hansen et al. reported that BP changes were comparable in the two groups during follow-up period.\textsuperscript{151} BP was equally and significantly reduced during the study compared to baseline in both groups. Jesudason et al. reported no overall changes in BP for both the groups. However, there was a time-by-treatment interaction (p<0.05) for diastolic BP.\textsuperscript{152} Diastolic BP was lower throughout the follow-up period in the moderate protein intake group.
Lipid profile

Research reported an improvement in serum lipid profile during a LPD. Coggins et al. determined that an intervention diet providing 0.28 kg/kg/d showed significant decreases in total cholesterol, HDL, and LDL between baseline and 6-month follow-up (p<0.05).\textsuperscript{158} The diet providing 0.575 g/kg/d reported trends for decreases in total and LDL-C between baseline and 6-month follow-up (p<0.10). Cianciaruso et al. showed a significant decrease in LDL values in the LPD group, but not in the moderate protein intake group.

PROTEIN RESTRICTION + KETOACID ANALOGS SUPPLEMENT

In international settings where ketoacid analogs (KAA) are available, a very-low protein-controlled diet may be considered. For adults with CKD without diabetes, not on dialysis, with an eGFR below 20ml per minute per 1.73m\textsuperscript{2}, a very-low protein diet (VLPD) providing 0.28g to 0.43g protein/kg/d with addition of keto acid (KA) analogs to meet protein requirements may be recommended.

In adults with CKD including kidney transplant, fourteen studies reported the effect of protein restriction + KA supplementation on outcomes of interest. One non-randomized controlled trial (NRCT),\textsuperscript{132} and 13 RCTs were included.\textsuperscript{133, 135, 137, 139, 141, 142, 158-164}

Survival/renal death

In adults with CKD (stages 3 to 5), 4 RCTs reported mixed effect of protein- restricted diet+ KA on renal survival/RRT.\textsuperscript{134, 141, 162, 163} Garneata and Mircescu et al. indicated a significantly lower percentage of patients in the VLPD+ KA group required RRT initiation throughout the therapeutic intervention.\textsuperscript{134, 141} Whereas, Levey and Malvy et al. indicated no effect, but Malvy study was unpowered.\textsuperscript{162, 163} Pooled analysis of two studies that reported RRT incidence indicated that protein restricted diet + KA has a lower risk ratio for incidence of RRT (RR 0.412, CI: 0.219, 0.773).\textsuperscript{134, 141} Levey et al. 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.\textsuperscript{162} Malvy et al. also indicated no effect of protein restriction +KA on renal survival.\textsuperscript{163} Whereas, Mircescu et al. indicated a statistically

Guideline on Nutrition in CKD  Page 87
significantly lower percentage of patients in the VLPD+KA group required RRT initiation throughout the therapeutic intervention (4% vs. 27%);141 and Garneata et al. also indicated a delay in dialysis initiation.134 Both Garneata and Mircescu are newer studies134, 141 and shorter in duration (12 to 15 months) compared to Levey and Malvy (Levey-2.2 years).162, 163 When pooled together, there is probably an overall benefit of dietary protein restriction + KA supplementation on RRT/renal survival in CKD stage 3 to 5 patients (RR 0.65, CI 0.49 to 0.85, p<0.001).

eGFR
A VLPD supplemented with keto-analogue (0.28-0.4 g protein/kg/d) could help preserve renal function in stage 3 to 5 CKD patients. One study was conducted in PD patients, and GFR was preserved. In adults with CKD, 1 NRCT132 and 4 randomized controlled trials134, 141, 142, 161, 162 reported on effect of protein-restricted diet+ KA analog (0.28 - 0.4g/kg body weight) on eGFR. Results from the all the 6 studies indicated that VLPD +KA (0.3-0.4 g/kg body weight) supplementation helped preserve eGFR, whereas, subjects assigned to LPD only (0.58-0.68 g/kg protein) did indicate decline in eGFR. All studies were conducted in subjects in stages 3 to 5. Pooled analysis for all five studies was not possible to conduct.

Bellizzi reported that GFR significantly decreased in the control group.132 Garneata et al. indicated that the decrease in eGFR was less in KA group compared with LPD.134 Klahr et al. indicated that compared with usual protein group, the low-protein group had a more rapid GFR decline in the first four months (p=0.004) but slower decline from the first four months to the end (p=0.009).161 Among patients with GFR of 13-24 ml/min/1.73m² (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. (post-hoc analysis of MDRD) 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/yr (p=0.063).162 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. indicated that eGFR did not change significantly in patients receiving VLPD+KA but significantly decreased in the LPD group (p<0.05), suggesting renal protection for VLPD+KA.141 Prakash et al. also indicated that eGFR
stayed unchanged in the KA supplemented group, however, it significantly decreased in the placebo group (p=0.015). Keto-supplemented diet over the 9-month period helped preserve the eGFR.\textsuperscript{142}

\textit{Electrolyte levels}

VLPD supplemented with keto-analogues (0.28-0.4 g protein/kg/d) could potentially decrease serum phosphate and improve some markers of bone metabolism (calcium, parathyroid hormone). Four randomized controlled studies (stages 4-5)\textsuperscript{133, 141, 154, 163} indicated a decrease in serum phosphate levels at the end of intervention among LPD+ KAA groups. One study with MHD patients also demonstrated a decrease in serum phosphate in the LPD +KAA group.\textsuperscript{139} Feiten et al. indicated that serum phosphate did not change in the LPD group but tended to decrease in the VLPD + KA group (within VLPD, p=0.07). Serum PTH concentration did not significantly change in the VLPD + KA group; however, it increased significantly in the LPD group (p=0.01).\textsuperscript{133} Li et al. in MHD patients indicated that in the LPD +KA group, no significant changes in serum calcium were observed, however, mean serum phosphate levels significantly fell at the end of the study (p<0.001) compared to the NPD group.\textsuperscript{139} Mircescu et al. in stages 4 and 5 patients indicated that in the VLPD+KAA group a significant increase was seen in serum calcium levels post intervention (p<0.05); serum phosphate levels decreased (p<0.05); whereas no statistical changes were observed in the LPD group.\textsuperscript{141} In the study by Rosman et al., patients in the LPD group showed significantly lower serum phosphate levels and used less phosphate binders (p<0.05).\textsuperscript{154} In a recent meta-analysis, it was reported that serum phosphate levels were lower in patients supplemented very low protein intake in two randomized studies from China.\textsuperscript{165}

\textit{Dietary intake}

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

In Bellizi (stage 4 and 5), at 6 months, protein intake and salt intake were significantly lower in VLPD than LPD (p<0.0001). Feiten et al. (stage 4) reported a reduction in protein intake in the VLPD supplemented group; energy intake did not change in both groups during the whole study, and was low (approximately 23 kcal/kg/d). Phosphorus intake decreased significantly only in the VLPD + KA group. Calcium intake was low and did not change during the intervention period for both groups. In Herselma et al. study, protein intake during intervention was significantly reduced from baseline in both groups. In the study of Jian et al. in PD patients, dietary protein intake between groups LP and HP was different in the 6th and 10th month (p<0.05). Kopple et al. looked at both protein and energy intake (CKD stage 3 and 4), compared to usual protein diet, low-protein diet had significantly lower dietary protein intake in study A (p≤0.001). Compared to LPD, VLPD had significantly lower dietary protein intake in study B (p≤0.001). Dietary energy intake in low-protein diet was significantly lower in study A (p≤0.001) compared to usual protein diet, however, there was no significant difference between LPD and VLPD in study B (p>0.05). Mircescu et al. (CKD Stages 4 and 5) results indicated that compliance with prescribed diet was good throughout the study in both arms.

*Nutritional status*

Research reports that a VLPD supplemented with keto-analogues (0.28-0.4 g protein/kg/d) 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 and 1 NRCT reported no effect of very LPD and KA intervention on serum albumin levels. Jian et al. and Garneata et al. were the only studies that studied effect of protein restriction + ketoanalogues supplementation on SGA and no statistically significant effect was noticed. Both the studies indicated that nutritional status was maintained.

In the study by Kopple et al., (MDRD study B, CKD stages 3 and 4), no significant differences in anthropometrics measurements were observed between groups (p>0.05). Malvy et al. reported that for the patients in the VLPD group, a significant weight loss was observed at the
end of the study (p<0.01) and lean and FM were reduced in this group at the end of study. Moderate protein group indicated no difference for weight variables. Garneata et al. in a larger and more recent study, reported no differences throughout the study period in both groups for BMI, MAMC, and TSF.134

Blood pressure

The effects of a VLPD supplemented with keto-analogue (0.28-0.40 g protein/kg/d) on blood pressure are inconclusive. In adults with CKD, 1 NRCT132 and 2 RCTs135,141 reported mixed effect of a protein-restricted diet (0.3-0.4 g/kg/d) + KA supplements on BP. Only one study showed a significant reduction in systolic BP and diastolic BP.132 In this study, the VLPD had antihypertensive effect in response to the reduction of sodium intake, type of protein intake and ketoanalogue supplements, independent of actual protein intake. The other two studies reported no effect of protein-restricted diet + ketoanalogue on BP.135,141

Lipid Profile

Research indicates that a VLPD supplemented with ketoanalogue (0.28-0.40 g protein/kg/d) could improve serum lipid profile of CKD patients. In adults with CKD, 1 NRCT132 and 4 RCTs reported on the effects of a protein-restricted diet (0.3-0.4 g/kg/d) + ketoanalogue on serum lipid profile.133,134,158,163 Feiten et al. and Malvy et al. reported no effect of VLPD + ketoanalogue on serum lipid profile,133,163 whereas, Bellizi et al. indicated a decrease in TC and TG only in the VLPD group. Coggins et al. indicated a significant decrease in TC, HDL, LDL in the VLPD group.158 Garneata et al. showed that cholesterol levels remained stable during the entire duration of the study however patients were taking statins/fibrates as standard therapy.134

Dietary Protein Intake, Diabetes Mellitus

Nutrition play a significant role in the management of individuals with diabetic kidney disease (DKD) in conjunction with pharmacological 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 that 0.8 g/kg body weight/day among those with CKD stages 1-4 and also for CKD stage 5.166 However, KDIGO guidelines suggested that more liberalization with protein restriction and recommended that 0.8 g/kg body weight/day be maintained and avoiding levels above 1.3 g/kg/body weight.167

Guideline on Nutrition in CKD
Evidence from controlled trials in this non-dialyzed DKD population has been conflicting.\textsuperscript{151, 157, 168-173} Recent meta-analysis does show small beneficial impact of LPD on eGFR decline; however, the heterogeneity was really high (the type of diabetes, stages of CKD, types on interventions, duration, adherence to recommendations).\textsuperscript{174, 175}

For the DKD patients receiving dialysis, evidence from observational studies indicated low dietary protein intake is associated with higher hospitalization rates and higher risk of mortality.\textsuperscript{176, 177} The KDOQI guideline for dialysis patients suggests dietary protein intake of >1.2 g/kg body weight/day to manage the protein catabolism and losses of protein in dialysate.

Ko et al. 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/day was advised for DKD not on dialysis and dietary protein intake >1.2 g/kg body weight/day was advised for DKD patients on dialysis.\textsuperscript{178}

**Special discussions**

These diets should be progressively installed to allow a careful dietary counselling and adequate compliance. 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 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 source and moving towards more vegetal 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/d) supplemented with KAs.

Are LPD/VLPD+ ketoanalogues indicated for CKD patients with PEW? This question cannot easily be answered since 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 etiology of wasting and protein intake should be increased until the wasting state improves. An LPD/VLPD + KA diet should not be
started during a catabolic state in CKD patients.

Do LPD and VLPD+ ketoanalogues have impact on the nutritional status? In a post-hoc analysis of the MDRD study, the authors compared the randomized groups (LPD versus VLPD+ ketoanalogues) for various outcomes related to nutritional status. Overall, the results demonstrate the safety of dietary protein restriction over two to three 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 randomized groups in some of these changes. In both LPD and VLPD+ ketoanalogues, both protein and energy intake declined. Serum albumin rose, while serum transferrin, body weight, percentage of body fat, arm muscle area and urine creatinine excretion declined. In a longitudinal study looking at body composition, a VLPD+ ketoanalogues diet 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 improve slightly thereafter. Other short-term studies did not show noticeable effects of LPD and VLPD+ ketoanalogues on nutritional parameters. Nevertheless, small anthropometric measurement’s decline observed in some studies are of concern since, in routine practice, LPD and VLPD+ ketoanalogues are used on the long term and because of the adverse effect of protein-energy wasting in patients with end-stage renal disease. This is why physicians who prescribe low-protein diets must regularly monitor patients' protein and energy intake and nutritional status.

**Implementation considerations**

**Energy intake**

- 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, gender, 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 on maintenance dialysis (hemodialysis or peritoneal dialysis), there are several factors that may influence energy expenditure, beyond the Guideline on Nutrition in CKD
traditional determinants (age, sex, and fat-free mass), such as hyperparathyroidism, hyperglycemia, and chronic inflammation that should be considered into the overall energy prescription

- Energy needs will be variable depending on the health status of the patient, e.g., acutely ill versus chronically managed and overall health goals, weight maintenance, repletion or loss.

- Energy needs may be different depending on the stage of CKD and its respective treatment (dialysis vs transplantation).

- 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 and many other methods. [Caution: Not generalizable to the CKD population and data-gathering methods were not standardized.]. The IBW can also be estimated as follows: in males as 50.0 kg + 2.3 kg for each inch over 5 ft (each 2.5 cm over 152.4 cm) and in females as 45.5 kg + 2.3 kg for each inch over 5 ft.

**Protein restriction**

- Increase the training and number of specialized renal dietitians worldwide who could effectively and safely implement low and very low protein diets.

- Promote low protein products to simplify dietary counseling and help achieving LPD.

- BE more aggressive with the dietary interventions to improve symptoms when chronic dialysis is not a treatment option or need to be postponed (vascular access maturation, organizing preemptive renal transplant).

- The need for food information is important to obtain a good compliance to the restricted protein intake. However, therapeutic education can help patients to improve personal motivation, and can even become a personal goal to achieve. Getting more interested in food harvesting, preparation, and cooking may improve quality of life. In addition, postponing initiation of dialysis undoubtedly maintains a better quality of life rather than undergoing chronic dialysis.
**Monitoring and Evaluation**

Compliance to diets should be monitored frequently during the first year of dietary intervention by dietary interviews (3 is optimal) and 24-hour urine collection for urine urea nitrogen content. Then yearly follow-up may be recommended until start of maintenance dialysis.

**Future research**

- Determine whether a LPD has an additive or a synergistic effect to that of renin angiotensin aldosterone antagonists or newer nephroprotective agents (i.e. SGLT2 inhibitors) on proteinuria and nephroprotection through RCTs.
- Examine the impact of a low and very-low protein dies with or without KA on digestive microbiota in CKD patients.
- Investigate at what is the best CKD stage to start dietary protein intake modification.
- Examine ways to improve adherence and compliance with LPD, VLPD+KA diets
3.2 Statement on Protein Type

3.2.1 In adults with **CKD 1-5D (1B) and post-transplant (OPINION)**, there is inadequate 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 (VPD) may have beneficial effects on health. A recent population-based study suggested soy or soy isoflavones intake significantly reduced the risk of postmenopausal breast cancer.\(^{181}\) Oxidative stress significantly decreased in postmenopausal women when treated with VPD (soy isoflavones) and in vitro experiments have shown that VPD protects against inflammation in vascular endothelial cells.\(^{182}\) These findings lead to the development of preventive strategies for human health and disease. For example, the US Food and Drug Administration suggested that the intake of 25 g soy protein daily may prevent the risk of coronary heart disease due to reduced serum lipids and lipoproteins.

In CKD patients, VPD may have positive biological actions and possibly clinical benefits through a variety of mechanisms. In vitro studies showed that VPD reduce the expression of renin-angiotensin.\(^{183}\) Studies in rodents demonstrated that VPD retard the development and progression of CKD, vs animal protein diets (APD),\(^{184}\) 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 predialysis CKD patients.\(^{185}\) As a result, it was thought that VPD may be used in helping to reduce phosphorus load and potentially CKD progression in this group of patients.

**Detailed Justification**

Three randomized controlled trials (CKD 5D) and two randomized crossover (Stage 3-4 CKD) trials compared the impact of vegetable-based protein (VPD) vs animal-based (APD) protein 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., serum albumin significantly increased after both VPD and APD, compared to the pre-study
diet, but there was no significant difference on serum albumin between VPD and APD. Fanti et al. found no significant difference between VPD and APD on serum albumin levels. Tabibi et al. found a significant (p<0.05) increase in serum albumin levels within both groups, but no significant difference found between groups. Finally, Chen et al. found no significant differences in serum albumin between groups. However, the power to discriminate might have been insufficient due to the small number of patients enrolled. In pooled analysis of four studies, there was no effect of protein type on serum albumin levels.

**Protein catabolic rate (PCR)**

VPD may be associated with a decrease in PCR after 6 months, but evidence was limited. In Saroka et al., PCR was significantly (p<0.05) lower after 6 month of VPD compared to the pre-study diet, but there were no changes in the APD diet. In a secondary analysis, there was a mean difference (95% CI) of -0.10 (-0.17, -0.03) g/kg/d in PCR values in the VPD vs the APD. This might have been the consequence of a slightly reduced absorption of protein from vegetal source (estimated to be 90% of animal protein).

**Pre-albumin levels**

VPD did not affect serum pre-albumin levels compared to a control group, but evidence was limited. Fanti et al. found no significant difference between VPD and APD on serum albumin or pre-albumin levels after receiving soy protein for 8 weeks, compared to the control group.

**Inflammatory Markers (CRP, IL-6, TNF-α)**

Protein type did not affect inflammatory markers. Fanti et al. compared the impact of a soy protein vs 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. VPD for 7 days to 6 months did not affect plasma/serum phosphate levels, but did decrease 24-hour urinary phosphate levels by a mean difference of -126.6 (-200.4, -52.7) mg. Soroka et al. found no significant difference between VPD, APD, or pre-study diet on urinary sodium, potassium or
Phosphorus can be obtained from a variety of sources, including dairy products, legumes, and green vegetables. In a small randomized crossover trial in predialysis patients, Moe et al. demonstrated that plasma phosphate levels were significantly higher in the APD group at day 7 (p=0.02), but there was no difference in urinary phosphorus excretion. There were no differences in plasma calcium or urinary calcium excretion levels between groups. In pooled analysis of these 2 studies, there was no effect of VPD, compared to APD, on serum/plasma phosphate. However, VPD did decrease 24-hour urinary phosphate levels by a mean difference (95% CI) of -126.6 (-200.4, -52.7) mg.

Total, LDL and HDL Cholesterol, Triglyceride levels

Protein type did not affect lipid profile in Stage 4 and 5D CKD patients. Three studies examined the effect of VPD vs APD on blood lipid panel. Chen et al. compared the impact of a soy protein vs a milk protein supplement on plasma lipids during 12 weeks in MHD patients with and without hyperlipidemia. In patients without hyperlipidemia, no significant differences were found in total cholesterol, LDL-C, HDL-C and triglycerides levels within or between groups. In hyperlipidemic patients however, soy protein lead to a significant decrease in total cholesterol, LDL cholesterol and triglyceride levels, compared to milk protein, whereas HDL significantly increased. Tabibi et al. compared the impact of a soy protein supplement vs control in PD patients and found no significant impact on total cholesterol, LDL-C, HDL-C and triglycerides levels in the intervention group. Soroka et al. found no significant differences after VPD, APD or pre-study diet on total cholesterol, LDL-C and triglycerides TG, in stage 4 CKD patients. HDL-C level was significantly lower after VPD compared to the pre-study diet. In pooled analysis of 3 studies, there was no mean difference in total, LDL or HDL-C levels or triglyceride levels between groups.

Special discussions

VPDs have been studied to test metabolic hypotheses in CKD patients. Particularly, the fact that phosphorus may be less absorbed during a VPD diet may benefit calcium and phosphate metabolism. This becomes more important since currently processed food contains much added inorganic phosphorus as compared with VPD. The fat content of VPD possesses a healthier profile and may benefit patients in long-term studies. Finally, toxic middle molecules

Guideline on Nutrition in CKD
such as P-cresyl sulfate, indoxyl-sulfate and trimethylamine oxide (TMAO), almost exclusively produced from animal source protein, could be reduced by VPD and this hypothesis should be tested in long-term clinical trials in CKD patients. As demonstrated in other subtopics of this guideline, VPD has shown reduction in acid load, increase in dietary fiber intake, reduction of phosphorus, and body weight. There is increasing interest in the role of VPD in CKD due to the benefits of this dietary pattern on cardiovascular disease risk factors in the general population. However, current evidence from RCTs specifically comparing benefits of VPD vs APD in CKD patients is limited.

Implementation considerations

- Work with patients to help them meet their individualized dietary protein intake needs.
- Based on CKD patient’s preference for animal or plant-based protein ensure that they meet their dietary protein needs and that their diets provide adequate essential amino acids.

Monitoring and Evaluation

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

Future research

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

Mediterranean Diet

3.3.1 In adults with CKD 1-5 (non-dialysis) and post-transplant, 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 which represent habitual dietary intake. Particular dietary patterns, including the Mediterranean diet, the Dietary Approach to Stop Hypertension (DASH), plant-based and diets high in fruits and vegetables (including Vegetarian diets) are examples of healthy dietary patterns which have been the subject of interest in nutritional epidemiology. A whole -diet approach considers the synergistic effects of nutrients resulting in cumulative effects on health and disease.

CKD presents many challenges for nutrition management, including increased risk of death and appreciable cardiovascular disease 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. However, these relationships have not been explored conclusively with the CKD population.

Detailed Justification
While various dietary patterns were investigated (Fruits and Vegetables, Mediterranean Diet, Low Fructose Diet, Hypolipidemic, Carbohydrate restricted- low iron, polyphenol-enriched diet (CR-LIPE), 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**

*eGFR*

One RCT reported on the effect of Mediterranean dietary pattern on eGFR.\(^{195}\) Mekki et al. indicated no clear effect of Mediterranean dietary pattern on eGFR at 90 days post intervention in adults with CKD stage 2. Additional research on the effect of Mediterranean dietary pattern is needed.

*Lipid profile*

Limited evidence from three studies, two of which examined non-dialyzed patients (CKD stages 2 and 3) and one of which examined post-transplant patients, demonstrated that the Mediterranean diet improved lipid panel by decreasing total cholesterol (TC), low-density lipoprotein (LDL-C) and triglyceride (TG) level compared to control groups.

Two controlled trials reported on the effect of Mediterranean dietary pattern on lipid profile in non-dialyzed patients.\(^{195,196}\) In the RCT, Mekki et al. (stage 2) reported a 35% reduction in TC (p<0.05) in the Mediterranean diet group, whereas, no change in TC was observed in the control group. LDL-C levels and TG levels were also reduced compared to standard care.\(^{195}\) In an NRCT, Daniele et al. reported a significant reduction in TC in both Mediterranean diet group and organic Mediterranean diet group.\(^{196}\) However, most reduction was noted in the organic Mediterranean diet group. In post-transplant patients, one RCT reported that Mediterranean diet led to significant reduction in TC, TG and LDL-C levels compared with a low-fat diet.\(^{195,197}\)

*Other Outcomes*

Compared to a control group, the Mediterranean Diet had no clear effect on BP in post-transplant patients\(^{197}\) or on CRP levels in stage 2 patients.\(^{195}\)

However, one NRCT reported on the effect of Mediterranean dietary pattern on albuminuria in stage 2 and 3 CKD adults, and both Mediterranean diet groups
(normal and organic) had significant reductions in albuminuria values compared to low protein group.196

High Fruit and Vegetable Dietary Pattern

CKD Progression
In adults with stages 3-4 CKD, fruits and vegetables dietary pattern has mixed effects on eGFR compared with oral bicarbonate supplementation.198, 199

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. reported that the group following the fruit and vegetable dietary pattern had greater net body weight loss than both oral bicarbonate and standard care groups (p<0.05).199 Goraya et al. reported lower body weight in adults with CKD stages 3-4 following a fruit and vegetable dietary pattern compared to oral bicarbonate supplementation group at 1-year follow up (p<0.01). (Mean Difference= -5.09 kg, 95% CI - 7.73,2.44; I²=56%).198

Blood Pressure
Three studies (2 RCT, 1 NRCT) reported on the effect of increased fruit and vegetable intake on BP in adults with CKD. All three studies indicated that increased intake of fruit and vegetable had a significant effect on lowering systolic BP compared to oral bicarbonate supplement intake group or standard care group.198-200 Goraya et al. indicated reductions in systolic BPs in all groups, however, the 3-year value for the fruits and vegetables group was lower than those in HCO₃ and control.199 Goraya et al. showed that compared to HCO₃ group, the fruit and vegetables group had lower systolic BP at 1-year follow up (p<0.01).198 Goraya et al. (NRCT) showed that fruit and vegetable intake, but not control or HCO₃, significantly decreased systolic BP in individuals with CKD Stages 1 and 2 (p<0.001).200 Pooled analysis of data from Goraya et al. 2013 and Goraya et al. 2014 indicated a Mean Difference (95% CI) of -5.6, CI: -8.3, -2.8 mmHg. Increased intake of fruits and vegetable
dietary pattern lowered systolic BP compared to oral bicarbonate supplement intake or standard care group in adults with CKD stages 1 - 4.

Comparison with recent research

A recent systematic review (SR) examined the effect of dietary patterns on CKD outcomes using cohort studies. In agreement with the current analysis of controlled trials, Kelly et al. found no effect of dietary pattern on CKD progression in studies with follow-ups ranging from 4 to 6.4 years. However, unlike the current SR, Kelly et al. 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 (95% CI): 0.73 (95% CI, 0.63 to 0.83)].

A recent Cochrane review of 6 RCTs evaluated dietary patterns in CKD (one study (n=191) of a carbohydrate-restricted low-iron, polyphenol enriched diet, two studies (n=355) of a Mediterranean diet, two studies (n=181) of increased fruit and vegetable intake and one 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 systolic and diastolic BP, and higher GFR and albumin levels following dietary interventions.

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. A recent study confirmed that intake of nuts, low-fat dairy products, and legumes are protective against the development of CKD. 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

- Safety of various dietary patterns, including the DASH and Mediterranean diet, 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 intake.
- Individualized support and follow-up may be required to support patients in implementing 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 pattern in CKD patients to determine the effect on clinical outcomes including kidney disease progression and cardiovascular disease.
- Evaluate the association of multiple dietary patterns with CKD progression in a large cohort with established CKD over a longer duration than currently available (i.e. >10 years).
4.1 Statement on Oral, Enteral and Parenteral Nutrition (IDPN) Supplementation

Oral Protein-Energy Supplementation

4.1.1 In adults with CKD 3-5D (2D) and post-transplant (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 counselling 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 and Intradialytic Parenteral Nutrition (IDPN) Protein-Energy Supplementation

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

Rationale/Background

Protein-energy wasting (PEW) is common among patients with CKD, especially those undergoing maintenance dialysis therapy, and is associated with increased morbidity and mortality. The etiology 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. As a result, patients with CKD may develop an imbalance between dietary intake and nutritional requirements. Indeed, many patients with CKD consume less protein and energy than their recommended intakes even when individualized dietary counselling is provided by a renal dietician.
intake and the target requirements in patients with CKD, provision of oral nutritional supplements (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 quality of life in patients with CKD.

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

**Detailed Justification**

This evidence review included fifteen clinical trials, twelve of which were RCTs and three NRCTs. Most of the studies examined the effect of ONS in patients on MHD. However, Moretti et al. included patients on MHD and PD with the results merged; Gonzalez-Espinoza et al. and Teixido-Planas et al. studied patients on PD only; and Wu et al. 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. used a glucose-polymer ONS and Wu et al. used a non-protein calorie ONS. Four studies used renal-specific protein-energy ONS. A major drawback of the literature was the limited use of a placebo group, though most studies did include a comparator group which was defined as participants not receiving ONS or receiving only nutritional counselling. Study durations ranged from 12 weeks to 13½ months. Seven of the RCTs included participants with some level of malnutrition at baseline. In contrast, five studies did not actively enroll malnourished patients. Of the NRCTs Sezer et al. enrolled malnourished patients as defined by serum albumin or weight loss, Cheu et al. enrolled patients with hypoalbuminemia, and Scott et al. did not actively recruit patients with malnutrition.

*Mortality, Hospitalizations, and Quality of Life*

Guideline on Nutrition in CKD
One NRCT examined the effect of ONS on mortality in 276 patients on MHD who received for ONS for a low serum albumin versus 194 similar patients who refused ONS or in whom treatment was deemed inappropriate.\textsuperscript{218} No difference in mortality [HR (95% CI); 0.70 (0.36, 1.35)] was noted over a median duration of 13.5 months.

Two RCTs\textsuperscript{213, 216} and one NRCT\textsuperscript{218} evaluated the effect of ONS on hospitalization over a period of 6 to 13.5 months in patients on MHD or PD. A pooled analysis of the two RCTs\textsuperscript{213, 218} found no significant difference in odds of hospitalization by group assignment, but a NRCT\textsuperscript{218} reported a 34% reduction in hospitalization risk [0.66 (0.50, 0.85)] by 12 months in patients receiving ONS compared to controls.

Three studies (two RCTs\textsuperscript{209, 210} and one NRCT\textsuperscript{219}) each of three months’ duration examined the effect of ONS on quality of life (QOL) measures in patients on MHD. One RCT\textsuperscript{209} and one NRCT\textsuperscript{219} reported that patients receiving general\textsuperscript{209} or renal-specific\textsuperscript{219} protein-energy ONS had higher QOL scores in the domains of physical functioning\textsuperscript{209, 219} and bodily pain\textsuperscript{209} compared to receiving dietary advice only\textsuperscript{209} or no supplementation,\textsuperscript{219} but another RCT\textsuperscript{210} reported that renal-specific protein-energy ONS did not influence QOL scores in any domain. A pooled analysis of the two RCTs\textsuperscript{209, 219} found that ONS did not significantly influence bodily pain, physical functioning, or general health QOL domain scores.

\textit{CKD Progression}

A RCT\textsuperscript{217} 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 a low-protein diet. While no difference in serum creatinine or eGFR was observed between ONS and controls, there was a comparative reduction in proteinuria in the ONS arm (p<0.05).

\textit{Composite Nutritional Scores & Biochemical Markers of Nutritional Status}

A 3-month RCT in 18 patients on MHD examined the effect of a food-based ONS on Subjective Global Assessment (SGA) scores.\textsuperscript{209} Authors describe a significantly greater SGA improvement in patients receiving ONS compared to patients receiving nutritional guidance only. One NRCT found that ONS over a six-month period did not influence the Malnutrition Inflammation Score (MIS) as compared to dietary advice.\textsuperscript{220}
Fifteen studies (twelve RCTs\textsuperscript{207-211, 213-217, 222} and three NRCTs\textsuperscript{218-220}) examined the effect of ONS on serum albumin in patients with 3-5D. These included eleven in patients on MHD 3 to 13.5 months’ duration, one RCT\textsuperscript{213} in patients on MHD and PD of 6 months’ duration, two RCTs\textsuperscript{211, 214} in patients on PD of 6 months’ duration, and one\textsuperscript{217} 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\textsuperscript{207-214, 217, 219, 220} that included patients with CKD 3-5D found that ONS modestly improved serum albumin as compared to controls [mean difference (95% CI); 0.121 (0.006, 0.236) g/dL]. However, a subgroup analysis found the effect to be significant only when using protein-energy ONS\textsuperscript{209, 210, 212, 214, 219, 220} [mean difference (95% CI); 0.16 (0.08, 0.24) g/dL] and not energy\textsuperscript{207, 217} or protein-based\textsuperscript{208, 211, 213} supplements. Heterogeneity of results in the pooled analysis was high (I\textsuperscript{2}=68.3%, p<0.001) so results should be interpreted cautiously.

One RCT\textsuperscript{210} in 86 patients on MHD reported that ONS did not influence serum pre-albumin levels as compared to dietary advice. Two RCTs of 3-6 months’ duration in patients on MHD reported conflicting effects of ONS on total protein, perhaps related to type of ONS.\textsuperscript{207, 208} The first study of 30 patients reported a positive effect on total protein using an amino acid-based ONS\textsuperscript{208} while a second of 21 patients found no effect of a 6-month energy-based ONS intervention.\textsuperscript{207} Two studies (a RCT\textsuperscript{207} and a NRCT\textsuperscript{219}) in patients on MHD of 3-6 months’ duration found no effect of ONS on serum transferrin, 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 one study\textsuperscript{207} that used an energy based ONS.

**Body Mass Index (BMI):** Seven studies (six RCTs\textsuperscript{207-212} and one NRCT\textsuperscript{220}) evaluated the effect of ONS on BMI over a 3-6-month period. Six of the studies were conducted in patients on MHD\textsuperscript{207-210, 212, 220} and one in patients on PD.\textsuperscript{211} A pooled analysis demonstrated no overall effect of ONS on BMI though the study using an energy-based ONS noted a rise in
BMI. 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 on MHD, PD, and with CKD 3-4. Overall, ONS was linked to increased body weight but mainly in patients on MHD consuming an energy-based supplement. However, one RCT in patients on PD that used a protein-based ONS reported increased body weight. A pooled analysis of all six studies found higher body weight in the ONS group compared to the control arm [mean (95% CI); 2.77 (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 and 1 NRCT) in patients on MHD 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 one NRCT reported an increase in target weight using a renal-specific protein-energy ONS as did one RCT using a protein-based ONS. A pooled analysis of three studies found no overall effect. Hiroshige et al. reported results in a figure and could not be included in pooled analysis.

**Lean Body Mass/Fat Free Mass/Muscle Mass:** Seven trials (six RCTs and NRCT) in patients on MHD, PD or PD studied the effect of ONS on markers of lean mass over 3 to 6 months. Overall, ONS increased LBM or fat free mass only in patients on MHD who received an energy based ONS. In patients on MHD, the effect of protein based ONS on LBM was mixed. In a pooled analysis of 6 studies ONS was associated with a significant increase in LBM or fat free mass [mean difference (95% CI); 1.18 (0.16, 2.20) kg] compared to the control arm, but a subgroup analysis found the effect to be significant only in patients on MHD using energy-based ONS.

**Body Fat:** Seven studies (six RCTs and one NRCT) in patients on MHD evaluated the effect of ONS on body fat over a period of 3 to 6 months. A pooled analysis of six studies reported no overall effect of ONS on body FM though subgroup
analyses demonstrated that energy\textsuperscript{207} and protein-energy\textsuperscript{209,212,220} based ONS significantly increased body FM compared to controls, but protein-based ONS had no effect.

\textit{Skinfold Measurements:} Five studies (four RCTs\textsuperscript{207, 209, 211, 214} and one NRCT\textsuperscript{220}) in patients with CKD on MHD\textsuperscript{207, 209, 220} or PD\textsuperscript{211, 214} examined the effect of ONS on skinfold measurements over a 3 to 6-month period. A pooled analysis of 4 studies\textsuperscript{207, 211, 214, 220} reported that ONS significantly increased skinfold measurements [mean difference (95\% CI); 3.91 (0.93, 6.90) mm] compared to dietary counselling or no supplementation, but this effect was significant only in patients on MHD using energy based ONS.

\textit{Arm or Muscle Circumference:} Four RCTs in patients on MHD\textsuperscript{207, 209} or PD\textsuperscript{211, 214} evaluated the effect of ONS on arm or muscle circumference over a 3 to 6-month period. None of the studies showed any effect.

\textit{Dietary Intake}

\textit{Protein:} Ten studies (nine RCTs\textsuperscript{207-211, 213, 214, 217, 222} and one NRCT\textsuperscript{220}) examined the effect of ONS on protein intake as estimated by nPCR/nPNA (nPCR), 24-hour dietary recall or multiple-day food records with study durations of three to six months. Overall, protein-based supplements (AA\textsuperscript{208} or BCAA\textsuperscript{222}) increased reported protein intake and nPCR in patients on MHD and PD but energy\textsuperscript{207, 217} or protein-energy supplements did not influence either marker in patients with CKD 3-5D. A pooled analysis of seven studies\textsuperscript{208-211, 213, 214, 220} found that ONS significantly increased nPCR in patients on dialysis [standardized mean difference (95\% CI); 0.29 (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\textsuperscript{208, 211, 213} but not protein-energy based ONS.\textsuperscript{209, 210, 214, 220} Similar results were noted in a pooled analysis of three studies\textsuperscript{210, 211, 214} examining the effects of ONS on reported protein intake where ONS increased reported protein intake only in one study that supplemented egg albumin protein.\textsuperscript{211}

\textit{Energy}

Six RCTs\textsuperscript{207, 210-212, 217, 222} with study duration of 3 to 6 months examined the effect of ONS on energy intake in patients on MHD\textsuperscript{207, 210, 212, 222} on PD,\textsuperscript{211} and with CKD, stages 3-4.\textsuperscript{217} Overall ONS raised energy intake though the effect was limited to patients on MHD receiving

Guideline on Nutrition in CKD
renal-specific protein-energy ONS. Four out of five studies in patients on dialysis reported that ONS increased energy intake. However, a subgroup analysis found the effect to be significant only for patients on MHD receiving protein-energy ONS, but not receiving protein- or energy-based ONS alone. The only study in patients with CKD 3-4 found no improvement in energy intake using a non-protein calorie ONS.

Phosphorus and Calcium

An RCT of 3 months’ duration in patients on MHD found no effect on phosphorus or calcium intake.

Other Biochemical Markers (CPR, anemia indices, electrolyte levels)

Seven studies (six RCTs and one NRCT) of 3-6 months’ duration in patients on MHD and CKD 3-4 found no effect of ONS on CRP. Seven studies (five RCTs and two NRCTs) in patients on MHD or PD 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 (four RCTs and one NRCT) examined the effect of ONS on serum calcium, phosphate, and potassium levels over 3 to 6 months. Three of the trials were in patients on MHD, one was in patients on PD, and one was in patients with CKD 3-4. None of the studies found any effect on ONS on these electrolytes. Five studies (four RCTs and one NRCT) examined the effect of ONS on plasma lipids over 3 to 6 months.

IDPN

This evidence review encompassed three studies that examined the effects of IDPN on nutritional status and clinical outcomes in MHD patients, including one NRCT and two RCTs. In all these studies, participants were malnourished. In Hiroshige et al., participants in the intervention group received dietary counselling from an RDN and an IDPN infusion of 200 ml 50% dextrose, 200 ml 7.1% EAAs, and 200 ml 20% lipid emulsion, providing 2400 kcal and 42.3 g amino acid for one year. Results were compared to a group receiving dietary counselling only (control group). In Cano et al. all participants were given an oral nutritional supplements (ONS) providing 25 g/protein/day and 500 kcal/day for one year, and the intervention group additionally received IDPN to meet target ranges of 30 to 35
kcal/day and 1.2 g/protein/kg/day; and included a standard lipid emulsion of 50% glucose, 50% non-protein energy supply, and a standard amino acid solution. In Toigo et al., participants in the intervention group were given (EAAs) IV formula for 6 months. Results were compared to participants in the intervention group where they received an isonitrogenous standard formula containing both non-essential amino acids (NEAAs) and EAAs for 6 months. Both groups simultaneously received 500ml of 10% glucose. Participants were followed up for an additional 6 months.

Mortality and hospitalization

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

Anthropometric measurements

The three studies examined the effect of IDPN therapy on anthropometric measurements in malnourished MHD patients. The findings from these studies indicated that IDPN, in combination with dietary counselling or ONS, increased BMI, dry body weight, skinfold measurements, and MAMC compared to dietary counselling only. However, similar improvement in BMI was observed when adequate and comparable protein and energy were given to patients receiving ONS only. Compared to a standard IDPN formulation of both EAAs and NEAAs, an IDPN formulation with EAAs did not affect % desirable body weight, skinfold measurements, and AMA.

Laboratory markers of nutritional status (albumin, pre-albumin, transferrin, and nPCR)

Three studies 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 counselling or ONS increased albumin, pre-albumin, or transferrin levels, but similar improvements in albumin and pre-albumin levels were observed when adequate and comparable protein and energy were provided to patients.
receiving ONS only.\textsuperscript{223} Compared to a standard IDPN formulation of both EAAs and NEAAs, an IDPN formulation with EAAs only did not affect albumin and transferrin levels.\textsuperscript{224}

*Other laboratory markers (inflammation (CRP); hemoglobin, lipid profile)*

One study evaluated and found no effect of IDPN on inflammation in malnourished hemodialysis patients. Cano et al. reported no change in CRP levels in either ONS only or IDPN+ONS groups, although data was not provided.\textsuperscript{223}

One study examined and found no effect of IDPN therapy with EAAs only vs standard IDPN formulation with both EAAs and NEAAs on hemoglobin levels in malnourished MHD patients after 6 months.\textsuperscript{224}

Two studies examined the effect of IDPN on lipid profile. The results from these studies showed that combining IDPN with dietary counselling\textsuperscript{221} or ONS\textsuperscript{223} did not affect total cholesterol\textsuperscript{221} or triglyceride levels.\textsuperscript{221, 223}

*Dietary intake (energy and protein intake)*

Two studies\textsuperscript{221, 223} 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 prior to considering ONS and should be repeated at regular intervals during the supplementation period.

IDPN therapy does not alter patient’s eating behavior, nor does it encourage healthy eating habits. Patients on IDPN may suffer from time-limitation due to MHD frequency and duration. 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 via ONS or dietary counselling. If the difference can be met by the IDPN regimen, the workgroup felt that IDPN should be considered in conjunction with ONS or dietary counselling.

This evidence reviews suggested that IDPN offers no further 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. However, a direct comparison between IDPN and ONS was lacking, this would only imply that ONS is equally effective as IDPN when oral intake is possible. Since ONS was included in the intervention arm as well, the inferiority of IDPN over ONS cannot be confirmed.

A recently published a RCT investigating the effect of IDPN therapy on pre-albumin and other biochemical and clinical nutritional markers in malnourished MHD patients demonstrated that IDPN therapy increased pre-albumin levels and was superior to nutritional counselling after 16 weeks. This study was not included in this evidence review because the date of publication was beyond the cut-off time for study inclusion. In this study, patients randomized to the intervention group received standardized nutritional counselling plus IDPN three 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).

**Implementation Considerations**

- ONS should be prescribed two to three times daily and patients should be advised to take ONS preferably 1 hour after meals rather than as a meal replacement in order to maximize benefit.

- Monitored in-center provision of high-protein meals or ONS during MHD may be a useful strategy to increase total protein and energy intake. 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.

- Energy-dense and low-electrolyte, renal-specific ONS may be necessary to increase protein and energy intake and avoid fluid and electrolyte derangements.

- Increased risk of infectious complications and the high cost of IDPN are the greatest barriers for regular use of IDPN.

- MHD patients meeting all of the following three criteria may benefit from IDPN therapy:
  1) evidence of protein-energy malnutrition 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 oral or enteral route.

- If IDPN therapy in conjunction with oral intake does not achieve the nutritional requirements of the patient, or the gastrointestinal tract is malfunctioned, then total parenteral nutrition (TPN) given on a daily basis should be considered.

**Monitoring and Evaluation**

Gastrointestinal side effects can influence adherence to ONS\textsuperscript{227} and extended periods of monotonous supplementation can lead to flavor and taste fatigue as well as non-adherence to the prescribed ONS. Therefore, regular monitoring and evaluation during the supplementation period is 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 in order to evaluate effectiveness of ONS.

Ongoing monitoring and evaluation of nutritional status during IDPN therapy is necessary. Serum glucose should be closely monitored during and post MHD. In the case of insulin requirement, the use of subcutaneous short-acting insulin analogs should be chosen to avoid post-dialytic hypoglycemia. The ultrafiltration rate should be adjusted 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 quality of life 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 compared to ONS on nutritional status, morbidity, mortality and quality of life are required.
4.2 Statement on Nutrition – Dialysate

Dialysate Protein-Energy Supplementation

4.2.1 In adults with CKD on peritoneal dialysis with protein-energy wasting, we suggest not substituting conventional dextrose dialysate with amino acid dialysate as a general strategy to improve nutritional status (2C), although in selected cases of protein-wasting when energy intake is adequate, 1.1% amino acid dialysate with alkali supplements may ameliorate protein deficits (OPINION).

Rationale/Background

Protein-energy wasting is common among patients on maintenance PD, and is associated with increased morbidity and mortality. 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 protein-energy wasting. Intraperitoneal amino acids (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. IPAA supplementation may also reduce the infused carbohydrate load, thereby reducing the risk of hyperglycemia and the tendency to hypertriglyceridemia.

Detailed Justification

This evidence review included three studies that examined the effect of IPAA supplementation on nutritional status in malnourished PD patients, including two RCTs and one non-randomized crossover trial. In the two RCTs, results were compared between those receiving traditional 1.5% dextrose dialysate vs those who replaced one to two daily exchanges of 1.5% dextrose dialysate with 1.1% amino acid dialysate. Study durations ranged from 3 months to 3 years. In the non-randomized crossover trial, Misra et al. utilized the same study design in which the participants were assigned to each exposure (amino acid dialysate for one exchange/day or dextrose dialysate only) for 6 months. In all of these studies, PD patients demonstrated some level of malnutrition or protein energy wasting. In Misra et al., the majority of patients were presented with hypoalbuminemia; in Li et al., all patients were malnourished; and in Jones et al., 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. MAMC, triceps skinfold measurements and FM were maintained at 3 months and 3 years in both 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 and one non-randomized crossover trial examined the effect IPAA supplementation on serum albumin, pre-albumin, and transferrin levels in malnourished PD patients. One randomized-controlled trial evaluated the effect of IPAA supplementation on total protein level. The findings from these studies concluded that substituting amino acid dialysate for dextrose dialysate in malnourished PD patients did not affect serum albumin, pre-albumin, transferrin, and total protein levels compared to those receiving dextrose dialysate only.

Electrolyte levels (phosphorus/phosphate, bicarbonate, and potassium levels)

One RCT and one non-randomized crossover trial 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. showed that serum potassium and phosphate levels decreased significantly in IPAA group and levels were different between groups at 3 months (p<0.05 for each measure). In contrast, Misra et al. showed no within-group changes in potassium, phosphate or bicarbonate levels in either 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 secondary analysis, the IPAA groups in Jones et al. and Misra et al. demonstrated a mean difference (95% CI) of -0.50 (-0.87, -0.13) mEq/L in potassium and -1.10 (-1.43, -0.77) mmol/L in bicarbonate levels respectively when

Guideline on Nutrition in CKD
compared to the dextrose dialysate group. In pooled analysis, there was a mean difference (95% CI) of -0.55 (-0.70, -0.41) mg/dL in phosphate levels in the IPAA group compared to the dextrose dialysate group.

*Dietary intake (protein and energy intake)*

One randomized-controlled trial examined the effect of IPAA supplementation on total and oral protein and energy intakes in malnourished PD patients.\(^{232}\) Compared to 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 IPAA and dextrose dialysate groups. Compared to 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 two randomized-controlled and one non-randomized crossover trials. The included studies only assessed intermediate nutrition-related outcome measures, including dietary intake (total energy and protein intakes, and oral energy intake); laboratory markers of nutritional status (serum albumin, pre-albumin, transferrin, and total protein levels); and anthropometry (MAMC, triceps skinfold and FM). The effects of substituting amino acid dialysate for conventional dextrose dialysate on patient survival, hospitalization, other clinical outcomes and quality of life have not been adequately evaluated. The long-term effect of IPAA therapy remains unclear.

**Implementation considerations**

- IPAA supplementation decreased bicarbonate levels,\(^{233}\) and mild acidosis may occur in some patients,\(^{229, 230}\) although it is readily treatable.
• In diabetic patients on PD with uncontrolled hyperglycemia, substituting amino acid for glucose in PD solutions may serve as an immediate strategy for glycemic control.

**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 quality of life in PD patients at risk or with PEW.
4.3 Statement on Long Chain Omega-3 Polyunsaturated Fatty Acids

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

4.3.1 In adults with CKD on MHD or post-transplant, we suggest not routinely prescribing long-chain 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 on PD, it is reasonable not to routinely prescribe long-chain 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 on MHD, we suggest that 1.3-4 g/d long-chain 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 on PD, it is reasonable to consider prescribing 1.3-4 g/d long-chain n-3 PUFA to improve the lipid profile (OPINION).

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

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

4.3.6 In adults with CKD 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 with kidney allograft, we suggest not routinely prescribing long-chain 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 PUFA) include eicosapentaenoic (EPA) and docosapentaenoic and docohexaenoic acids (DHA), both of which are obtained primarily from dietary sources like cold-water fish (i.e. 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 biologic effects that mediate 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 PUFA on record,\textsuperscript{234} thus making them potentially very suitable candidates for supplementation interventions. In fact, LC n-3 PUFA supplementation has been studied as possible therapy for a number of conditions commonly observed in patients with CKD including dyslipidemia, hemodialysis access failure, cardiovascular disease 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 on MHD as the target population, though one study also included patients on PD.\textsuperscript{235} Nearly all the interventions used fish oil as the main source of LC n-3 PUFA but flaxseed oil\textsuperscript{235} and ground flaxseed\textsuperscript{236} 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 PUFA supplemented, the type of placebo used, and study duration makes it more difficult to provide conclusive evidence for or against the use of LC n-3 PUFA as a treatment option.

**All-Cause Mortality and Cardiovascular Events**

Despite the putative overall benefits of LC n-3 PUFA and the elevated risk of death in patients with CKD, three RCTs demonstrated no improvement in mortality with supplementation. However, the studies were heterogeneous in terms of study population (one in patients with MHD\textsuperscript{237}, two in patients with CKD with kidney allografts\textsuperscript{238,239}, the dose of LC n-3 PUFA (Maachi et al. 1.44g/d EPA + 0.96g/d DHA; Berthoux et al. 1.62g/d EPA+1.08g/d DHA; Svensson et al. 2006 0.77g/d EPA+ 0.64g/d DHA) and the 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 on MHD reported
mixed results on the effect of LC n-3 PUFA supplementation on cardiovascular events.\textsuperscript{237,240} Lok et al.\textsuperscript{240} reported that 4 g/day fish oil (1.6 g/d EPA, 0.8 g/d DHA) for 12 months as compared to corn oil-based placebo significantly lowered the cardiovascular event rate 0.41 (0.20 to 0.85) (p=0.02) and improved cardiovascular event-free survival 0.43 (0.19 to 0.96) (p=0.04) but did not influence the number of patients with one or more events 0.78 (0.55 to 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. reported that 1.7 g/d fish oil (0.77 g/d EPA and 0.64 g/d DHA) for two years had no effect on the primary combined endpoint of cardiovascular events or death as compared to olive oil-based placebo\textsuperscript{237} but did improve the secondary endpoints of myocardial infarctions (0.30 (0.10, 0.92) (p=0.036) and major coronary events (0.40 (0.17, 0.97) (p=0.043).

\textit{Hemodialysis Access}

Previous studies have suggested that LC n-3 PUFA, in particular those derived from fish oil, have anti-proliferative, antioxidant, and vasodilatory effects. This was the impetus for the four RCTs that examined whether LC n-3 PUFA supplementation could improve patency of arteriovenous grafts (AVG) or fistulas (AVF) in patients on MHD. Of the three RCTs\textsuperscript{240-242} studying AV graft survival, the two smallest (using 0.96-1.76 g/d EPA and 0.6-0.96 g/d DHA) had mixed results with one showing no benefit at six months (n=29)\textsuperscript{241} and the other (n=24) reporting higher primary patency rates compared to placebo group at 1 year (p<0.03).\textsuperscript{242} The third and much larger trial (n=201) noted a borderline statistically significant improvement in the loss of native patency at one year 0.78 [0.60-1.03](p=0.064) after providing 1.6 g/d EPA and 0.8 g/d DHA.\textsuperscript{240} While the overall results are not clearly positive they do suggest at a possible beneficial effect. However, by far the largest study in this field (n=567), which examined patency rates in new AVF at 12 months\textsuperscript{243}, reported that fish oil 4 g/d (1.84 g/d EPA and 1.52 g/d DHA) had no benefit.

\textit{Rejection Episodes and Graft Survival in Kidney Allografts}

While LC n-3 PUFA have been reported to mediate the immunologic response, they have not yet demonstrated any benefits on kidney transplant. Two RCTs\textsuperscript{239,244} with differing study interventions (2.4g/d EPA + DHA for one year, 9 vs 18 g/d EPA for 26 weeks) found no benefit on rejection episodes or a relationship between supplementation dose and rejection.
Supplementation using approximately 2.5 g/d EPA+DHA also did not influence graft survival.238,239

**Glomerular Filtration Rate and CKD Progression**

Based on six RCTs with widely differing study design and populations (CKD stage 3, MHD, kidney allografts),238,239,244-247 fish oil supplementation was not found to influence estimated or measured GFR. In the study by Guebre Egziabher et al, participants received 1.8g of n-3 fatty acids, but authors do not describe EPA or DHA amount.246 In the study by Bennett et al, participants received “9 or 18g/d EPA capsules”.244 In the remaining studies, EPA dose ranged from 0.46-1.62g/d and DHA ranged from 0.25-1.08g/d.

Similarly, fish oil supplementation for 8-12 weeks did not influence serum creatinine levels in three studies of non-dialyzed patients who used placebo or non-placebo-based control groups. In the study by Guebre Egziabher et al, participants received 1.8g/d of n-3 fatty acids, but authors do not describe EPA or DHA amount.246 In the remaining studies, EPA amount ranged from 0.69-1.44g/d and DHA amount ranged from 0.25-0.96g/d.245,246,248

**Blood Pressure (BP)**

Five RCTs examined the effect of LC n-3 PUFA supplementation on BP, two in non-dialyzed patients (no stage reported),247,248 two in patients on MHD,240,249 and one in patients with CKD with kidney allografts.244 The results were mixed. In non-dialyzed patients, Svensson et al. reported that fish oil (0.96g/d from DHA and 1.44g/d EPA) for 8 weeks did not affect BP,248 while Mori et al. found that fish oil (0.38g/d DHA and 0.46g/d EPA) for 8 weeks lowered both systolic (mean±SEM, -3.3 (±0.7)) and diastolic (-2.9 (± 0.5)), (p<0.0001 for each change) blood pressures.247 A pooled analysis of these two trials did not find an overall beneficial effect. In patients on MHD, Lok et al. reported an improvement in systolic BP in patients on MHD with fish oil (0.8g/d DHA and 1.6g/d EPA) for one year [Mean Difference (95% CI): -8.10 (-15.4, -0.85), p=0.014]240 and a reduction in the number of BP medications but no effect on diastolic BP. In contrast, Khajehdehi et al. found no effect at all on BP of 1.5 g/day fish oil (DHA and EPA content not reported) as compared to placebo for two months.249 Data from these two trials could not be pooled. Bennett et al. randomized patients with CKD with kidney allografts and reported no benefit of “9 or 18 g EPA capsules” per day versus placebo for 26 weeks244 on systolic BP but did note a reduction in diastolic BP in both EPA arms (p<0.05 for Guideline on Nutrition in CKD
each) only.

**Lipid Profiles**

Nineteen separate RCTs (though one without a true control group\textsuperscript{250}) addressed the impact of LC n-3 PUFA supplementation on lipid levels. Thirteen studied patients on MHD\textsuperscript{235, 236, 241, 251-259} (with one study also including patients on PD\textsuperscript{179}), four studied patients with CKD 2-5\textsuperscript{185, 186, 199, 200}, and two studied patients with CKD with kidney allografts\textsuperscript{244, 260}. The studies ranged greatly in terms of the type of supplement (seventeen with fish oil, two with flaxseed oil or ground flaxseed (2 g/d oil in Lemos and 40g/d seed in Khalatbari)) and duration (3-6 months). Additionally, amount and reporting of dosing was inconsistent. Studies reporting amount of specific LC n-3 PUFAs described doses ranging from 0.42-1.8g/d EPA and 0.25-0.82g/d DHA. The specific amounts of EPA and DHA were not clear in several studies.\textsuperscript{244, 246, 249, 252, 257, 258}

**Triglycerides:** Eighteen RCTs studied the impact of LC n-3 PUFA on serum triglycerides. Seven of the thirteen trials studying patients with MHD found no effect\textsuperscript{235, 241, 251, 252, 255, 256, 258} and six reported a reduction in levels.\textsuperscript{235, 236, 249, 254, 257, 259} In a pooled analysis of twelve of these studies, LC n-3 PUFA supplementation lowered triglyceride levels by an average (95% CI) of -33.78 (-63.21, -4.36) mg/dL as compared to placebo/controls, though heterogeneity was high (I\textsuperscript{2}=92.36%, p<0.001). While outcomes did not appear to be related to study quality or duration, triglyceride lowering tended to be associated with using lower doses of LC n-3 PUFA (0.42-0.96g/d EPA and 0.24-0.6g/d DHA daily), flaxseed oil (2g/day) or ground flaxseed (40g/day), a counterintuitive finding. Interestingly, positive results were more consistent in non-dialyzed patients\textsuperscript{245, 247, 248, 250} where fish oil supplementation (1.8g/d total or 0.46-1.44g/d EPA with 0.25-0.96g/d DHA) for 8-12 weeks consistently lowered triglycerides.

**Total Cholesterol:** The literature did not suggest a beneficial effect of LC n-3 PUFA supplementation on total cholesterol. Eleven of thirteen studies in patients on MHD reported no effect (0.42-1.8g EPA and 0.24-1.14g DHA per day for 4 weeks-6 months)\textsuperscript{235, 241, 249, 251, 252, 254-259}, while the two studies supplementing with flaxseed oil (2g/d for 120 days)\textsuperscript{235} or
ground flaxseed (40 g/d for 8 weeks)\textsuperscript{236} noted a significant reduction in total cholesterol levels (though one study did not compare differences between groups \textsuperscript{236}). A pooled analysis of all 13 studies did not find any effect on mean total cholesterol but did note a high level of heterogeneity in the data ($I^2=95.77\%, \ p<0.001$). Three of four supplementation studies in non-dialyzed patients reported no effect on total cholesterol levels\textsuperscript{237, 247, 250} while the fourth demonstrated a reduction at three months ($p<0.05$) with no difference between arms.\textsuperscript{245} Results could not be pooled for these four studies. While Ramezani et al.\textsuperscript{260} reported lower cholesterol levels in CKD patients with kidney allografts compared to placebo after 6 months of supplementation with 1.76g/d EPA with 0.96g/d DHA in fish oil, Schmitz et al.\textsuperscript{242} found no such benefit in a similar population.

**LDL Cholesterol**

Eight of twelve studies in patients on MHD found no benefit of supplementation,\textsuperscript{235, 251, 252, 254, 256-259} while four reported a reduction in LDL.\textsuperscript{235, 236, 241, 249} Two of the four positive studies supplemented with fish oil (1.5g total in Khajehdehi et al.\textsuperscript{249} and 0.96g/d EPA with 0.6g/d DHA in \textsuperscript{241} while the other two used flaxseed oil or ground flaxseed.\textsuperscript{235, 236} (with both latter studies observing a drop in LDL).\textsuperscript{235, 236} Study quality or duration or the type of comparison group used did not influence the outcome. A pooled analysis of all twelve studies noted an improvement in LDL only when excluding the flaxseed-based supplement studies [mean difference (95% CI): -5.26 (-9.51, -1.00) mg/dL] and even then, the result was clinically marginal. In non-dialyzed patients, four studies of 8-12 weeks length using fish oil found no effect on LDL (1.8g/d total in Guebre-Egziabher et al. and 0.46-1.44g/d EPA with 0.25-0.96g/d DHA),\textsuperscript{237, 245, 247, 250} In patients with CKD with kidney allografts, one study reported that EPA “9g capsules” per day increased LDL levels (but a higher dose did not) while another study reported negative results.\textsuperscript{242, 244}

**HDL Cholesterol**

Seventeen RCTs included HDL as an outcome. Though HDL may be influenced by physical activity, smoking status, and gender, the preponderance of these studies did not control for these factors. Of the twelve studies in patients on MHD six reported negative results\textsuperscript{235, 251, 252, 254, 256, 258} and six found that HDL levels were increased.\textsuperscript{235, 236, 241, 249, 257, 259} Effects were not clearly influenced by study quality or duration. However, the positive studies tended to use lower doses of LC n-3 PUFA (0.72-0.96g/d EPA with 0.42-0.6g/d DHA),
flaxseed oil (2g/day), or ground flaxseed (40g/day). In a pooled analysis of all twelve studies, LC n-3 PUFA supplementation was found to raise HDL by a mean (95% CI) of 7.1 (0.52, 13.63) mg/dL. However, the heterogeneity was high overall. Results were mixed in the four trials of pre-dialysis patients, with two showing a benefit\textsuperscript{248, 250} and two reporting no effect.\textsuperscript{245} 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 CKD patients with kidney allografts showed no benefit.\textsuperscript{244}

**Inflammatory Markers**

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

**C-Reactive Protein**

Fifteen RCTs studied the effect of fish oil supplementation on circulating CRP. In pre-dialysis patients throughout the stages of CKD, fish oil either compared to placebo\textsuperscript{247, 261} or at varying doses\textsuperscript{250} had no effect. The pattern in patients on MHD was similar. A pooled analysis of ten studies\textsuperscript{235, 236, 241, 251, 254-256, 262-264} found no effect of LC n-3 PUFA supplementation (nine using fish oil containing 0.42-1.8g/d EPA with 0.24-1.14g/d DHA, one using 2g/d flaxseed oil) on circulating CRP as compared to placebo (MD -1.73 mg/L, 95% CI: -3.54, 0.09). Ewers et al. 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 (p=0.01) after 12 weeks as compared to non-supplemented patients.\textsuperscript{252}

**Interleukin-6**

Six RCTs studied the effect of LC n-3 PUFA on circulating IL-6. Neither of the two studies in predialysis patients comparing fish oil supplementation to placebo or at varying doses found a significant effect on IL-6 (one study reported 1.8g/d n-3 PUFAs total and one reported 1.4g/d EPA with 1.0g DHA)\textsuperscript{250, 265}, nor did a pooled analysis of four studies in patients on MHD (MD 5.32 pg/ml, 95% CI: -5.637, 16.275) in which participants received 0-1.93g/d EPA with 0.72-0.97g/d DHA.\textsuperscript{254, 262, 264, 266}

**Special discussions**

Guideline on Nutrition in CKD
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 the 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.\textsuperscript{234, 267}

**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 raise blood levels of α-linolenic acid then supplementation should focus on soybean, flaxseed, and other oils as well as meat and dairy products. If it is to raise EPA or DHA blood/tissue levels then the primary dietary sources must be sardine, mackerel, salmon and other high-content marine-based foods.\textsuperscript{268} Potential limitations to dietary supplementation include their relatively high cost and difficulty in 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) has lower LC n-3 PUFA compared to wild fish, while frying fish could alter the n-3/n-6 ratio which may be of clinical significance.\textsuperscript{269}

- Capsule-based supplementation involves a set of different considerations. While dozens of commercial LC n-3 PUFA supplements are available, quality control is often lacking.\textsuperscript{270} This makes precise dosing recommendations difficult. An alternative route is to have the patient obtain supplements via physician prescription (e.g. icosapent ethyl, omega-3 ethyl esters). For either option cost could be an issue. Achieving high dose supplementation will be easier with capsules then through dietary consumption. Adverse effects of capsule-based supplementation may lead to gastrointestinal side effects like stomach upset and eructation (though the latter can be masked by different formulations). Theoretical risks like 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\textsuperscript{271}
Monitoring and Evaluation

There is no need to routinely monitor dietary LC n-3 PUFA intake other than in the context of general dietary counselling. An exception would 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 PUFA reduces 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.272

- 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 in any study design. For example, a recent RCT found that a highly purified form of EPA ethyl esters (with no ALA or DHA included) at a high dose (4 g/daily) available only in prescription form was effective in reducing cardiovascular risk.273 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 and post-transplant, 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 and post-transplant, 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 (DRIs) 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 prescription may limit vitamin-rich foods (particularly water-soluble vitamins), dialysis procedure may contribute to micronutrient loss, improper absorption of vitamins, and certain medications and illness. Due to these concerns, there is a trend for routinely prescribing multivitamin supplements. Findings from the DOPPS study indicate that more than 70% of MHD patients in United States take supplements. However, there is insufficient evidence to indicate whether micronutrients or multivitamin supplementation is beneficial or detrimental in this population.

Guideline on Nutrition in CKD
**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,\textsuperscript{274-276} riboflavin,\textsuperscript{277} vitamin B-6 \textsuperscript{278-280}, vitamin C,\textsuperscript{281, 282} Vitamin K,\textsuperscript{283-285} and/or vitamin D\textsuperscript{286}. 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 for those on peritoneal dialysis or post-transplant.

This SR 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 B12- 4 trials, vitamin c- 8 trials, thiamine- 1, Zinc- 10 trials, Selenium- 7 trials). Some of the good quality evidence from these articles led to 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 SR 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 synthesize evidence. Also, the 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. On the other hand, there is some evidence to support that there might be some individuals who are at higher risk of certain micronutrient
deficiencies. Taking all these issues into consideration, the expert panel felt that it was important to draft expert opinion-based recommendations 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 SR. Tucker et al., in a detailed review of micronutrients in patients on MHD, states that there is insufficient evidence to support routine supplementation and instead supplementation should be individualized and based on clinical judgement.287 Similarly, Jankowska et al. and Kosmadakis G et al., 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.288,289

**SPECIAL DISCUSSIONS**

Certain CKD population might be at higher risk of micronutrient deficiencies, and this must be taken into consideration. For example, pregnant women, gastric bypass surgery patients, patients with anorexia 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 if signs and symptoms of certain vitamin and mineral deficiency are present. These can be used in combination with lab measures to get a complete picture of problem.

If patients with CKD are meeting their recommended intake as assessed by 24-hr recall and have poor nutritional status, then 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 (ex: Recommended Dietary Allowance) unless there are specific considerations requiring modification.

- Assess Dietary intake, including consideration of fortified foods.
- Supplementation dose should be individualized based on each patient’s needs and risk profile.

**Future research**

- Well-designed trials are needed to investigate if supplementation improves outcomes. These trials should limit inclusion to a certain baseline status (ex: 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 & Vitamin B12

Folic Acid Supplementation for Hyperhomocysteinemia

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

Folic Acid Supplementation for Folic Acid Deficiency and Insufficiency

5.1.2 In adults with CKD 1-5 D (2B) and post-transplant (OPINION), we suggest prescribing folate, Vit 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 one-carbon donor. Folic acid is reduced to methylfolate 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. Even though intake of food 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.287 Because folate, vitamin B12 and vitamin B6 assist in the conversion of homocysteine to methionine (and therefore reduce serum homocysteine levels), they have received considerable attention as a putative treatment for cardiovascular disease 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 B6 and B12 on hard outcomes, including all-cause mortality and/or cardiovascular events in patients with stage 5 CKD, on MHD or PD, and post-transplant. Folic acid and other B-vitamin supplementation ranged from 2.5-40 mg/d folic acid, 1.4-100 mg/d B6, 150 μg/week- 2 mg/d B12 for a duration of 2-5 years.

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

Supplementation with folic acid in combination with other B-vitamins did not improve total cholesterol levels, intima media thickness (IMT) or BP in MHD patients. Doses ranged from 5 mg to 15 mg folic acid and a B-complex vitamin for 3 to 6 months.

CKD Progression

One RCT examined the effect of folic acid supplementation on CKD progression. In a sub-study of a larger primary stroke prevention trial including 15,104 participants with CKD Stage 3 diagnosed with hypertension and taking the angiotensin converting enzyme inhibitor enalapril being randomized to receive 0.8 mg/day of folic acid or placebo for a median of 4.4 years. Compared to the group receiving enalapril and placebo, the enalapril + folic acid group significantly reduced the adjusted risk of CKD progression (Hazard Ratio (95% CI): 0.45 (0.27, 0.76); p=0.003), which was the sub-study’s primary outcome. 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 B6 and B12 on the risk of dialysis initiation/ESRD in participants with stages 3-5 chronic kidney disease and those post-transplant.
Serum Homocysteine Levels

Fourteen studies examined the effect of folic acid supplementation alone on plasma homocysteine levels.\textsuperscript{294-299, 302-309} Participants included were those with CKD, non-dialyzed (4 studies), on MHD (10 studies) and PD (4 studies), and post-transplant (1 study). In the ten RCTs, folic acid supplements ranged from 0.8-60 mg/day and duration varied from 4 weeks to 4.4 years in patients of various stages of CKD. All but one study concluded that folic acid supplementation significantly decreased homocysteine levels.\textsuperscript{295}

Thirteen RCTs examined the effect of supplementation with folate and other B-vitamins on homocysteine levels.\textsuperscript{290-293, 300, 301, 310-316} Serum homocysteine level was a primary outcome of interest in eight studies.\textsuperscript{300, 301, 310-312, 314-316} Twelve out of 13 studies found that folic acid with other B vitamin supplementation decreased homocysteine levels in participants with CKD Stages 3-5, on MHD, PD and post-transplant. Supplementation doses in these studies ranged from 2.5-40 mg/d folic acid (one study utilized 3 mg IV folic acid/week), 1 µg/d oral to 1000 mg/week IV B12, and 1.4-100 mg B6 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 a RCT that included 121 patients on MHD.\textsuperscript{300}

Folic acid and B12 Levels

Six RCTs reported that supplementation of folic acid alone increased serum folic acid levels in participants with stages 3-5 CKD and those on MHD and PD.\textsuperscript{294, 299, 302, 305, 306, 309} When folic acid with vitamins B6 and B12 was provided, it is worth noting that serum folic acid level 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. study that included patients on MHD, serum folic acid significantly increased with an intake of 2.5 mg after 2 years of supplementation as compared to the control group.\textsuperscript{293} In Chiu et al., a supplementation of 3 mg folic acid weekly via IV for 3 months did not result in a significant increase in serum folic acid levels in participants with stage 3 – 5 CKD or were on MHD and PD.\textsuperscript{312}
Of the ten studies that examined the effect of supplementation of folic acid with B-complex, nine found a significant increase in serum folic acid levels.\textsuperscript{291-293, 300, 301, 310, 311, 313, 316} Doses ranged from 2.5-60 mg 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 the plasma, serum, or red blood cells. Serum or plasma folate levels reflect recent dietary intake, so deficiency must be diagnosed by repeated measures 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 (i.e. longer-term folate status). Usually, RBC folate concentrations diminish after about 4 months of low folate intake reflecting the 120-day life span of RBC 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 neurological disease. Based on the 2015 USRDS annual report, more than 2/3 (38.9\%) of the patients who are on dialysis are 65 years or older. Older people have a higher risk of impaired gastrointestinal function. Since absorption of vitamin B12 is dependent on Intrinsic Factor and normal gut function and since the latter is often at least partially impaired in older individuals, assessment of serum vitamin B12 may be necessary if folate supplementation is considered.

Serum homocysteine levels, vitamin B12 and folate levels monitoring may be considered for patients who take certain medications such as methotrexate, nitrous oxide, 6-azaridine, phenytoin, carbamazepine, oral contraceptives, and 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 B12 should be considered if folate supplementation is considered.
administered.

- High folic acid intake may mask signs of pernicious anemia and undetected progression of neurological disease, and thus levels of folate and vitamin B12 should be monitored if folate is being supplemented.
- Suggested vitamin intake should be based on recommendations for the general population (ex: Recommended Dietary Allowance) 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 since adults over 50 years may have increased needs due to the prevalence of atrophic gastritis in this population.

**Monitoring and Evaluation**

Serum/plasma/RBC folate level, serum vitamin B12 should be assessed as appropriate

**Future research**

- Conduct dose response studies for folic acid intake especially in people undergoing chronic dialysis and persons who are taking medications that interfere with the intestinal absorption, serum levels, or actions of folate and/or vitamin B12.
- 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 one 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 and post-transplant** 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 levels of vitamin C required to maintain nutritional health, reverse deficiency, and to avoid toxicity are unclear. Studies included for this current review evaluated the effect of vitamin C supplementation on nutritional status, inflammation, anthropometrics, micronutrient levels, electrolytes levels, fluid status, serum uric acid levels, lipid levels, morbidity events, quality of life, mortality and hospitalizations. Limited data from a very small number of studies prohibit definitive evidence-based conclusions for all the above surrogate and hard outcomes. Therefore, we suggest that individualized decision-making is the best clinical approach to determine if vitamin C supplementation, or termination of supplementation, is required for adults with CKD stages 1-5D and post-transplant.

**Detailed Justification**

Nine studies examined the effect of vitamin C on nutrition-related outcomes in the CKD population, including five RCTs, 317-321 one randomized crossover trial322 and three comparative studies.322, 323 All studies examined MHD patients. Two studies (Canavese et al. and Singer et al.) also included PD patients and those with eGFR <20mL/min.321

*Quality of Life (QoL), Mortality, and Hospitalizations*

In adults with CKD, one RCT (250 mg oral ascorbic acid 3x/week for 3 months)321 and one comparative study323 (500 mg oral vitamin C/day for 2 years) measured the effect of vitamin C supplementation, compared to either a placebo or control, on hard outcomes, including all-cause mortality, QoL or hospitalizations events.
Singer et al. reported no changes in symptom, cognitive, or nausea sub-scales of the 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 et al., 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 endpoints could not be provided.

**Nutritional Status Parameters: serum Albumin, Pre-albumin, Transferrin, and Protein**

**Nitrogen Appearance**

Three studies examined the effect of vitamin C supplementation on nutritional status in MHD participants: one RCT, one randomized crossover trial, and one comparative study. However, nutritional status was not the primary outcome of interest. In Zhang et al., all patients were vitamin C-deficient at baseline, while in DeVriese, et al. 44% of participants were deficient at baseline. In Fumeron et al., 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/week for 2 months to 1500 mg/week for 3 months.

All three studies reported no effect of supplementation on albumin levels, as did pooled analysis of two of the RCTs. Zhang et al. measured the effect of vitamin C supplementation on pre-albumin levels in a randomized crossover trial with MHD participants. While one supplemented group experienced an increase in pre-albumin levels after three months of supplementation with 200 mg vitamin C, pre-albumin levels did not change in the other group after the same intervention. Therefore, the effect of vitamin C supplementation on pre-albumin levels is unclear. Fumeron et al. supplemented MHD participants with 750 mg/week of vitamin C for 2 months. There were no significant changes in transferrin levels in either
group. DeVriese et al. measured nPNA (nPCR) in a NRCT and found no effect of vitamin C supplementation on nPNA (nPCR) following supplementation with 360mg/week or 1500mg/week for 9 months in MHD patients.\(^{322}\)

**CRP levels**

Three studies examined the effect of oral vitamin C supplementation on CRP levels in MHD participants \(^{282, 317, 322}\) and found no significant effects compared to placebo or control groups, but evidence was limited.

**Vitamin C Levels/deficiency**

Four RCTs\(^{262, 317, 319, 321}\) and two comparative studies\(^{322, 323}\) examined the effect of Vitamin C supplementation in doses ranging from 360-3500 mg/week 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 (cut-offs were 11.44 and 23.0 µmol/L). However, in pooled analysis of three 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 non-dialysis CKD 1-5, PD and post-transplant 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 200-250 mg daily or three times weekly in most studies. The study by Ono that dosed MHD patients with daily 500 mg oral Vitamin C daily for 2 years reported an aggravation of hyperoxalemia.\(^{323}\) De-Vriese et al. had subjects dosed as 360 mg per week for 0-3 months followed by 1500mg/week dosing x 3-6 months and then no supplementations for 6-9 months in MHD patients. This study reported an increase in plasma malondialdehyde.\(^{322}\) Supplementation with vitamin C increased the low levels but there is a potential risk of toxicity that requires monitoring.

*Lipid Levels: Total Cholesterol, Triglycerides, LDL, HDL-C, LDL:HDL Ratio*
The results of three trials, \(^{317, 320, 322}\) demonstrated that vitamin C supplementation of 125-200 mg/d for 3 months may decrease total cholesterol and LDL cholesterol levels, but there was no effect on triglyceride or HDL cholesterol levels. Vitamin C supplementation of 125-200 mg/day decreased LDL:HDL 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. included supplementing patients with potentially toxic doses of ergocalciferol, 50,000 IU daily x 3 months. \(^{320}\) 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 post-transplant are not known and are based on those from the general population. The prevalence of vitamin C deficiency may vary according to the stage of CKD and dialysis modality. Toxicity is a possible concern for excessive vitamin C supplementation.

The above findings do not however preclude the importance of assessing for vitamin C supplementation or when to discontinuing 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 the nephrology 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 of the subject’s nutritional status, dietary intake, co-morbid conditions and dialysis modality.
- Suggested vitamin intake should be based on recommendations for the general population (ex: Recommended Dietary Allowance) 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 of medical history, co-morbid conditions, and concomitant medications. Measurement of serum oxalate levels 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 utilize serum levels of vitamin C, but reliability is unclear.
- Ascertain the optimal vitamin C status of CKD population including CKD stages 1-5D and those with kidney transplant.
- Confirm the recommended dietary allowance for vitamin C in various CKD population and the supplemental vitamin C dose that will prevent vitamin C deficiency without increasing risk of toxicity.
- If feasible, evaluate the effect of vitamin C supplementation on hard outcomes including survival, hospitalization, cardiovascular events as well as quality of life measures with RCTs in CKD population.
5.3 Statements on Vitamin D

Vitamin D Supplementation for Vitamin D Deficiency and Insufficiency

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

Vitamin D Supplementation with Proteinuria

5.3.2 In adults with CKD 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 D2 (ergocalciferol) and Vitamin D3 (cholecalciferol) are recognized as a pro-hormones 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. The classic actions of vitamin D are the regulation of calcium and phosphorus homeostasis contributing to bone health. More recently, there has been a growing interest in the potential pleiotropic actions of vitamin D on immune, cardiovascular and neurological systems and on antineoplastic activity since extra-renal organs possess the enzymatic capacity to convert 25 (OH)D to 1,25(OH)2D.

Insufficiency/deficiency of vitamin D, assessed by serum concentration of calcidiol [25(OH)D], has been found to be common in the general population and even more prevalent in patients with CKD stages 3-5D. For most experts, vitamin D insufficiency is defined as a serum 25(OH)D level between 20–29 ng/mL, deficiency is considered as 25(OH)D levels of less than 20 ng/mL and sufficiency serum 25(OH)D equal or greater than 30 ng/mL.

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 (DBP), impaired tubular 25(OH) reabsorption and dietary restrictions.\textsuperscript{329-332} Considering the high prevalence of vitamin D deficiency/insufficiency in CKD/ESRD and the potential benefits of restoring the vitamin D status the K/DOQI (2003) and KDIGO (2017) Clinical Practice Guidelines for CKD-MBD have proposed ergocalciferol or cholecalciferol supplementation.\textsuperscript{333, 334}

**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 concentration in 14 RCTs, including in the form of ergocalciferol\textsuperscript{335, 336} and cholecalciferol.\textsuperscript{337-348} This effect was demonstrated in HD patients (8 studies), HD and PD patients combined (1 study), stages 1-4 CKD patients (4 studies) and in 1 study with any CKD participants. Five studies reported that ergocalciferol using doses 50,000 IU/week and dose dependent on status\textsuperscript{335, 336} and cholecalciferol in doses ranging from 25,000-50,000 IU/week improved vitamin D status.\textsuperscript{337, 338, 341, 345} There were significant effects noted after three months of supplementation. However, there was no difference in vitamin D deficiency status between non-dialyzed groups receiving two different dosing regimens.\textsuperscript{343}

A meta-analysis was conducted to determine odds of vitamin D sufficiency according to vitamin D supplementation, which included Bhan et al. (each group compared to the placebo group), Delanaye et al., Massart et al., and Alvarez et al.\textsuperscript{335, 337, 341, 345} Participants that were supplemented with vitamin D had an OR (95% CI) of 9.31 (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 eight studies were pooled to determine mean difference (95% CI) in vitamin D levels according to vitamin D supplementation. There was a mean increase of 21.06 (17.46, 24.66) ng/mL in the vitamin D supplemented groups compared to 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*

Guideline on Nutrition in CKD
In adults with chronic kidney disease, twelve studies examined the effect of vitamin D intake on biomarkers and/or health outcomes. 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 effect of calcium levels in doses of 50,000 IU/week or /month or in individualized doses. The effect of cholecalciferol on calcium levels was unclear with seven studies finding no effect on calcium levels and three studies determining supplementation increased calcium levels. In Massart et al., there was no effect of 25,000 IU weekly cholecalciferol on proportion of HD participants reaching target levels at 3 months. There was no clear pattern of effect according to participant population, deficiency status or vitamin D dosage. In pooled analysis of four studies in which data could be combined, there was no effect of vitamin D supplementation on calcium levels [MD (95% CI): 0.07 (-0.18, 0.31) mg/dL].

Vitamin D supplementation had no effect on phosphorus levels with ergocalciferol supplementation (2 studies with doses of 50,000 IU/week or /month or in individualized doses) or cholecalciferol doses ranging from 50,000 IU/day to 50,000 IU/month (10 studies). In pooled analysis of five RCTs, there was no effect of vitamin D supplementation on phosphorus levels [MD (95% CI): -0.15 (-0.44, 0.15) (mg/dL)].

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 non-dialyzed, on hemodialysis or peritoneal dialysis, and renal transplant recipients. However, whether such improvements translate into clinically significant outcomes is yet to be determined.

Cross-sectional analysis of Third National Health and Nutrition Examination Survey (NHANES III) showed progressively higher prevalence of albuminuria with decreasing 25(OH)D levels. In a prospective cohort study vitamin D deficiency was associated with a higher incidence of albuminuria. There are limited randomized clinical trials investigating the effect of cholecalciferol or calcifediol on proteinuria in CKD and the results are inconclusive.

**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 is not well defined but is 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 a serum 25(OH)D level between 20–29 ng/mL, deficiency is considered as 25(OH)D levels of less than 20 ng/mL and sufficiency serum 25(OH)D equal or greater than 30 ng/mL.

- Both the Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) experts recommend checking and supplementing low serum 25(OH)D levels in CKD and dialysis patients. In the most recent update of the KDIGO guidelines on bone mineral disorder, it is suggested based on low quality evidence that patients with CKD stage 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.333

- 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 1000–2000 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.354

- 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.355 Since 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 levels (UL) proposed by the Institute of Medicine (IOM) for the general population is 4,000 IU/day.356 There is no recommendation of safe dose of cholecalciferol or ergocalciferol supplementation to prevent for toxicity or adverse effects such as hypercalcemia or hyperphosphatemia in CKD. However, periodically measurement of serum calcium and phosphorus should be considered especially for patients who are on calcium-containing phosphate binders and/or on vitamin D active analogs.

**Future Research**

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

- Optimal definition of vitamin D adequacy
- 25(OH)D thresholds for supplementation
- Dosing, timing of administration and type of vitamin D analogues 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 E and A

Vitamins A and E Supplementation and Toxicity

5.4.1 In adults with CKD on MHD or PD, it is reasonable to not routinely supplement vitamin A or E because of the potential for vitamin toxicity. However, if supplementation is warranted, it is reasonable to use caution and monitor patients for toxicity (OPINION).

Rational/Background

Vitamin E is a fat-soluble nutrient recognized for antioxidant properties. There are eight known naturally occurring forms of vitamin E, 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 (DRI) for vitamin E is only available for alpha-tocopherol. The RDA for vitamin E was determined by identifying serum levels of vitamin E that provided protection to erythrocyte survival when exposed to hydrogen peroxide.

While vitamin E supplements are typically provided as alpha-tocopherol, products containing other tocopherols and tocotrienols have been reported. The potency of synthetic alphatocopherol (RRR-alpha-tocopherol, labeled as D or d) is not identical to the natural form. This is because synthetic alpha-tocopherol contains eight 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 IU to receive a dose equivalent to the natural source. Most supplements provide vitamin E as alpha-tocopherol in a 100-400mg dose.

Vitamin E is a fat-soluble vitamin. The potential risk of vitamin E toxicity is primarily related to the use of supplements. High doses of vitamin E supplements in the form of alphatocopherol have been reported to cause bleeding and/or disrupt blood coagulation in vivo and there are some in vivo data that suggest alpha-tocopherol inhibits platelet aggregation. The RDA for vitamin E for normal adult men and woman is 15mg 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 1500 IU and 1100 IU/day respectively. While 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, blood pressure during dialysis and oxidative stress. However, results were inconclusive. Data regarding the effect of vitamin E coated dialyzers on hemoglobin, lipid profile and nutritional status were inconclusive and study design for these trials and the meta-analyses were of low quality.

Studies examining daily vitamin A requirements for individuals with various stages of CKD are lacking. Optimal serum levels of vitamin E are not defined for this population. Daily vitamin E required to maintain nutritional health, reverse deficiency, and to avoid toxicity in CKD population 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 intravenously, which was considered beyond the scope of this guideline.

**Detailed Justification**

The eight studies included for this review examined the effect of oral vitamin E supplementation in adults with CKD on serum indices and health outcomes. In three of these studies, vitamin E supplementation was combined with α-lipoic acid supplementation (ALA). All studies examined MHD patients as the target population, except for Ramos et al., who examined Stages 3-5 CKD subjects. Subjects in Hodkova et al. were vitamin E repleted, but baseline vitamin E status was not reported for any of the other studies.

**All-Cause Mortality and Cardiovascular Disease Outcomes**

Participants with CKD (serum creatinine ≥1.4 to 2.3 mg/dL) and high risk for cardiovascular events were given 400 IU daily oral vitamin E for a median of 4.5 years. Compared to the placebo group, there was no difference in total mortality between groups. Additionally, there
was no difference in the relative risk of myocardial infarction (MI), stroke, death from CV causes, unstable angina, heart failure hospitalizations, heart failure, TIA or composite or MI, stroke, or death from cardiovascular causes between groups.

Boaz et al. examined the effect of vitamin E supplementation on CVD endpoints (primary outcome) and all-cause mortality. MHD subjects with pre-existing CVD were supplemented with daily oral 800 IU oral vitamin E for a median of 519 days. Risk of all-cause mortality was not significantly different between groups. The vitamin E group had a significantly decreased risk of experiencing a CVD endpoint compared to the control group, but the RR for fatal and non-fatal MIs, ischemic stroke and PVD 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. Participants received either tocotrienols (90 mg) and tocopherols (20 mg) for 16 weeks or 400 IU oral vitamin E/day, 600 mg alpha lipoic acid (ALA)/day, or both for 2 months. While there were no changes in albumin levels between groups in the former study (Daud et al.), in Ahmadi et al., SGA score was improved in the vitamin E, ALA, and combined supplementation groups compared to placebo. SGA 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. 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 (Interleukin-6)

Five studies examined the effect of vitamin E supplementation on inflammatory biomarkers, particularly CRP and IL-6 levels.\textsuperscript{361, 363-365, 367} In three of the studies these inflammatory markers were the primary outcomes of interest.\textsuperscript{361, 365, 367} Himmelfarb et al. and Ramos et al. gave vitamin E supplementation in combination with $\alpha$-lipoic acid,\textsuperscript{364, 367} and Ahmadi et al. examined vitamin E supplements alone and in combination with $\alpha$-lipoic acid.\textsuperscript{361} 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 400-800 IU oral vitamin E per day (with or without 600 mg $\alpha$-lipoic acid) 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.\textsuperscript{363, 364, 367} Ramos et al. (Stages 3-5 CKD) and Himmelfarb et al. (MHD patients) both supplemented with daily oral 666 IU mixed tocopherols (Vitamin E) + ALA 600 mg for 8 weeks and 6 months, respectively.\textsuperscript{364, 367} Neither found an effect of supplementation on serum IL-6 levels. However, Ahmadi et al. found that oral vitamin E alone (400 IU per day) or in combination with 600 mg $\alpha$-lipoic acid per day, reduced IL-6 cytokine levels in MHD participants.\textsuperscript{361} In pooled analysis of two RCTs that utilized vitamin E alone or with $\alpha$- lipoic acid, there was no effects on IL-6 levels compared to the placebo groups.

Serum Vitamin E Levels

Two RCTs examined the effect of daily oral vitamin E supplementation on vitamin E levels.\textsuperscript{362, 365} Both studies included MHD patients. Hodkova et al. found that serum vitamin E levels increased in the vitamin E supplemented group ($\alpha$-tocopherol 400 mg/888 IU) after 5 weeks, but no change in the control. Between group differences were not reported.\textsuperscript{365} Boaz et al. found that the vitamin E supplemented group had significantly higher vitamin E levels compared to the placebo group when MHD participants with pre-existing CVD were supplemented with 800 IU oral vitamin E/day for a median of 519 days, but between group differences were not reported.\textsuperscript{362} In pooled analysis of the two RCTs that examined vitamin E supplementation alone, there was no significant effect of supplementation compared to 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 four months \(^{363}\) and 200 mg for three months (Khajehdehi et al.) did not change serum triglyceride, total cholesterol or LDL (low density lipoprotein) levels but demonstrated efficacy of increasing HDL-C levels.\(^{253}\)

**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 CKD patients. The nutritional requirements or Recommended Dietary Intake of vitamin E for individuals with CKD stages 1-5, those undergoing chronic dialysis and post-transplant are unknown. Dose response studies identifying the relation between Vitamin E intake and serum levels of vitamin E are not available. The prevalence of vitamin E deficiency in 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 those patients who are being supplemented. High doses of vitamin E supplementation has the potential to increase risk of hemorrhagic stroke and impair platelet aggregation. Vitamin E interacts with anticoagulant and antiplatelet medications and therefore caution is advised on vitamin E supplementation for CKD patients already receiving these medications.

Vitamin A was investigated in this SR, however there were no trials examining dietary intake of vitamin A, and supplementation trials included IV vitamin A, which the WG determined qualified it as a medication vs 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 vitamins A or E supplementation in CKD population. An individualized approach is required in considering the need to supplement...
vitamins A or E supplementation or terminate supplementation in adult CKD population and there is also a need to monitor for toxicity with supplementation.

**Implementation considerations**

- Implementation of vitamin E supplementation should consider individual patient’s nutritional status, dietary intake, concomitant medications, co-morbid conditions particularly with regard to baseline cardiovascular disease, and lipid levels.
- Oral doses $\geq 400$ 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 utilize serum levels of vitamin E, but the sensitivity and reliability of this approach are unclear.
- Ascertain the optimal vitamin E status of CKD population including CKD stages 1-5, those on dialysis and those that 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 of toxicity, including investigation of the effects of larger doses of oral vitamin E (i.e. 800 IU/day).
- Examine the effects of vitamin E supplementation on hard outcomes including cardiovascular disease, morbidity and mortality using RCTs.
5.5 Statements on Vitamin K

Anticoagulant Medication and Vitamin K Supplementation

5.5.1 In adults with CKD 1-5D and post-transplant, it is reasonable that patients receiving anticoagulant medicines known to inhibit vitamin K activity (e.g., 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 (VSMCs) 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 (BMP-2) thereby blocking the differentiation of VSMCs towards osteochondrogenic type cells.

Vitamin K participates in the enzymatic carboxylation of proteins controlling bone calcium deposition (e.g., 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 clothing, 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 K1) and menaquinones (vitamin K2).\textsuperscript{368} Phylloquinone is found primarily in foods, especially green and leafy vegetables (e.g., spinach, kale, cabbage, broccoli), plant based oils found in many food products, and cow’s milk. There are more than
10 menaquinones which 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. 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.

**Detailed Justification & Special Discussion**

The United States Institute of Medicine states that the Adequate Intake of vitamin K is 120 and 90 micrograms per day for adult men and women, respectively. 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 micrograms/day. These recommendations do not differentiate phylloquinone from menaquinone intake. At the time the US Institute of Medicine recommendations were set, the food composition databases on which these recommendations were made only contained 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 and lower serum albumin concentrations were associated with more severe elevation in prothrombin time in patients taking antibiotics. Vitamin K supplements may return prothrombin time to normal in such patients. Patients receiving antibiotics who have poor intake and at higher risk of bleeding (e.g., surgical patients) may be considered for vitamin K supplements, particularly if they have acute kidney injury or chronic kidney disease. However, the foregoing conclusions were essentially based on observational studies of small number of patients.

A study of the NHANES data indicated that 72.1% of adults with mild-moderate CKD (eGFR-EPI 58 mL/min/1.73m2) had vitamin K intake below the recommended adequate Intake (AI) level (mean, 97.5 µg/day; 95%CI, 89.7-105.3). Studies in Italy confirmed that daily intake of
vitamin K1 in MHD patients is commonly below recommended levels.\textsuperscript{372} Several observational studies in advanced CKD (stages 3-5) or MHD patients indicated that serum vitamin K1 (phyloquinone) and vitamin K2 (menaquinone) concentrations were frequently low and that serum levels of other uncarboxylated compounds which, when elevated, indicated vitamin K deficiency were increased.\textsuperscript{376, 377}

The recommended dietary vitamin K intake for patients with CKD 1-5, including those with the nephrotic syndrome, those who are undergoing MHD or PD or those who are post-transplant recipients 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 are commonly elevated.\textsuperscript{303, 304}

**Vitamin K Levels**

Only one short term randomized controlled study has been published that examined the effects of vitamin K supplements on vitamin K status in MHD patients.\textsuperscript{377} No such studies have been carried out in other stages of CKD or in PD patients or those post-transplant. The study involved small number of patients who received, by random assignment, supplements of 45, 135 or 360 micrograms per day of vitamin K2 (menaquinone-7) for only six weeks. In general, there was a dose dependent increase in serum vitamin K2 and decrease in serum \textit{dpucMGP}, \textit{ucOsteocalcin} and PIVKD-II. Mean serum vitamin K2 rose to previously reported normal values with the 45 \(\mu\)g/day dose and to modestly above normal values with the 135 and 360 \(\mu\)g/day doses. Serum \textit{dpucMGP}, \textit{ucosteocalcin} and PIVKD-II decreased most with the 360 \(\mu\)g/day 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.\textsuperscript{283, 378, 379} (Clinical Trials Identifier: NCT01528800; NCT01742273; NCT2610933; NCT02870829; UMIN000011490; UMIN000017119). 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 K
supplements should not receive anticoagulant medicines that inhibit vitamin K activity (e.g., warfarin compounds).

Implementation Considerations

- Patients receiving antibiotics who have poor intake and at higher risk of bleeding (e.g., surgical patients) may be considered for vitamin K supplements, particularly if they have acute kidney injury or chronic kidney disease. However, the foregoing conclusions were essentially based on observational studies of small number 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 CKD patients 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 value, if any, for routine vitamin K supplements in patients with different types and stages of CKD and with vascular calcification.
- Examine the confounding effects of different co-morbid 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 chronic 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 K1 and vitamin K2 have any different clinically important effects.
5.6 Statement on Trace Minerals – Selenium and Zinc

Selenium and Zinc Supplementation

5.6.1 In adults with CKD 1-5D, we suggest not routinely supplementing 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 like 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.380-383 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.382

Zinc is an essential micronutrient and forms a component of bio-membranes. It functions not only as an antioxidant but also has anti-inflammatory effects and prevents free radicals-induced injury during inflammation. There is some suggestion that marginal zinc intake may be associated with an increased risk of cardiovascular disease in general population384 and zinc has been shown to protect against atherosclerosis by inhibiting the oxidation of low-density lipoprotein cholesterol in animal studies.68 Zinc deficiency has been shown to increase oxidative stress and NF-κB DNA-binding activity and induce inflammation in experimental models.385-387 Zinc is also essential for insulin synthesis and release and glucose homeostasis388 and zinc deficiency has been suggested to impair insulin secretion and decrease leptin levels.389 Studies have reported a high prevalence of zinc deficiency in hemodialysis patients.390-392

The current Recommended Dietary Allowance (RDA) for zinc is 8 mg/d for women and 11 mg/d for men in the general population and for selenium is 55mcg/d for women and men. Whether similar amount of intake is recommended in various CKD stages and maintenance dialysis population is currently not known.
Detailed Justification

Selenium
In adults with chronic kidney disease (CKD), seven studies have examined the effect of selenium intake on biomarkers and other surrogate health outcomes. Most of the studies utilized oral selenium supplementation and all studies were performed in MHD patients. Koenig et al. examined the effect of intravenous selenium supplementation\textsuperscript{393} and Stockler-Pinto examined the effect of selenium supplementation in the form of a Brazil nut.\textsuperscript{394} Selenium dosages generally ranged from 175-1400 μg per week. The selenium dosage in Stockler-Pinto et al. was not described (1 Brazil nut/day) and in Koenig et al., the parenteral dose of selenium used was much higher (400 mg 3 times a week) compared to other studies. Study duration ranged from 14 days to 6 months. In Temple et al., participants’ selenium status at baseline was normal.\textsuperscript{395} In a study by Tonelli et al., 28% of treatment group versus 15% of placebo group had low selenium levels after supplementation.\textsuperscript{396} Around 20% of participants were selenium deficient in Stockler-Pinto et al., and the remaining studies did not report selenium status at baseline.\textsuperscript{394}

Nutritional Status
Only one very short-term (12 weeks) randomized placebo-controlled study examined the effect of oral selenium supplementation of 200μg per day on nutritional status in 80 MHD patients.\textsuperscript{397} The study reported a significantly greater reduction in SGA and malnutrition-inflammation score in the selenium group compared to the placebo group. However, no significant difference was observed in serum albumin concentrations between the two groups.\textsuperscript{397} The same study by Salehi et al. did not observe any difference in the median changes of CRP levels between selenium and placebo groups. Although a smaller increase in interleukin-6 levels was observed in selenium group compared to placebo group,\textsuperscript{397} 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 two short-term small randomized controlled studies provided some evidence that selenium supplementation may be useful in increasing plasma and erythrocyte selenium levels,\textsuperscript{395,398} it is not known if selenium supplementation may impact on any patient health-related or hard clinical outcomes. Only one short-term randomized study by Salehi et al. examined the effects of oral selenium supplementation on lipid levels. The results showed no difference between selenium group and control group in any of the lipid parameters including triglyceride, total cholesterol, low density lipoprotein- and high-density lipoprotein-cholesterol.\textsuperscript{397}

**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 11mg, 50mg to 100mg elemental zinc.\textsuperscript{399-401} In the study by Argani et al., serum albumin levels increased in the zinc supplemented group but there was no change in the placebo group.\textsuperscript{399} Guo et al. examined zinc supplementation of 11mg daily for 8 weeks in a cohort of 65 MHD patients with low baseline zinc level (<80mg/dL). Descriptive quantitative data was not provided but the authors concluded that protein nitrogen appearance and albumin levels significantly increased in zinc supplemented group but not in control group.\textsuperscript{400} Jern et al. showed that protein catabolic rate increased with 50mg zinc supplementation for 90 days but no change in placebo group.\textsuperscript{401} Between group differences were not provided in these studies. The data from these three 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.\textsuperscript{399,402-404} The studies by Argani et al. and Rahimi-Ardabili et al. administered 100 mg oral zinc daily to MHD patients for two months.\textsuperscript{399,403} Argani et al. showed no changes in cholesterol and triglyceride levels with zinc supplementation.\textsuperscript{399} Rahimi-Ardabili et al. showed that cholesterol levels increased significantly in the placebo group but no change in the treatment group and total
cholesterol levels were not different between the two groups after 2 months’ study. In the other two studies, Roozbeh et al. and Chevalier et al. both supplemented MHD patients with 50 mg zinc daily for six weeks and 90 days, respectively. All patients in both these two studies were zinc deficient at baseline (<80ug/dL). Both studies showed that total cholesterol, LDL-C, HDL-C and serum triglyceride levels increased in 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. Pakfetrat et al. examined the effect of 50 mg oral zinc per day for 6 weeks in MHD patients, and found that significantly decreased homocysteine levels decreased in the zinc supplemented group compared to the placebo group. Two studies examined the effects of zinc supplementation on inflammatory parameters, but results were inconclusive. Data on the effects of zinc supplementation on body weight and BMI were mixed and limited.

Zinc Levels

Six RCTs examined zinc supplementation in relation to serum zinc levels in MHD patients. All except Tonelli’s study described zinc deficiency at baseline. The dosage of zinc supplementation used ranged from 11mg to 110mg. Study duration ranged from 5 weeks up to 6 months. In the study by Tonelli and co-workers, zinc levels in the medium dose (50mg per day) but not the low dose (25mg per day) group were significantly higher than the non-supplemented group at 90 days and 180 days after supplementation. A pooled analysis of these 6 studies showed a mean (95% confidence intervals) increase of 30.97 (17.45, 44.59) ug/dL of serum zinc levels after supplementation compared to control group. However, heterogeneity was high. Furthermore, it is not known if zinc supplementation in deficient patients may impact on any health-related outcomes or clinical hard outcomes in 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.

Implementation considerations

- Suggested intake should be based on recommendations for the general population (ex: Recommended Dietary Allowance) unless there are specific considerations requiring
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 CKD Stage 3-5D patients.

Future research recommendations

- Conduct population-based cohort studies to determine the prevalence and importance of selenium and zinc deficiency across different stages of CKD and kidney transplant patients 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 CKD and maintenance dialysis patients may improve various surrogate markers of inflammation and protein energy wasting, lipid parameters, wound healing, dysgeusia and other health outcomes in dose dependent manner. Limited data suggest that further randomized trials should recruit specifically selenium deficient patients.
- The safety of prescribing zinc in non-deficient dialysis patients also needs to be determined.
6.1 Statements: 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 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 proteins, and trapping ammonia that is generated as 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. 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 adverse nutritional impact on the patient accompanied by an increase in protein catabolic rate.

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
four RCTs,198, 199, 410, 411 one NRCT,200 three non-controlled studies,412-414 two prospective
cohort studies,415, 416 and one retrospective cohort study.417

*CKD Progression; effect of reducing net acid production*

Studies aimed at evaluating the effect of reduction in net acid production (NEAP) have been
two-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, four RCTs,198, 199, 410, 411 one non-RCT,200 two non-controlled studies,413,
414 two prospective cohort studies,415, 416 and one retrospective cohort study417 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 per 1.73 m2 in available studies) higher quartiles
of net endogenous acid production (NEAP) were associated with greater I125iothalamate
glomerular filtration rate (iGFR) decline (p-trend=0.02).416 In CKD stages 3-5 not on dialysis
(≤ 60 mL/min per 1.73 m2) higher NEAP is associated with CKD progression (p<0.05 for all
quartile groups).417 In CKD stages 3-4 (≥15 or <60 mL/min per 1.73 m2) compared to lowest
dietary acid load tertile, highest dietary acid load had greater relative hazard of ESRD
(p=0.05).415

Studies reducing NEAP by the use of administration of oral sodium bicarbonate are not
confounded by alteration in dietary protein composition and easier to study in randomized
controlled prospective manner. In studies involving patients with CKD Stages 4-5, the oral
sodium bicarbonate group had significant greater creatinine clearance after 18 and 24 months
(p<0.05). Rapid CKD progression (creatinine clearance loss of >3ml/min per 1.73m2/yr) was
lower in the oral sodium bicarbonate group (RR: 0.15; 95% CI: 0.06-0.40). Development of
ESRD was lower in the oral sodium bicarbonate group (RR: 0.13; 95% CI: 0.04-0.40).410 In
another study of CKD Stages 4-5: not on dialysis, there was no significant difference in
creatinine clearance between before and after intervention (p>0.05).414 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, lesser reduction in eGFR was observed with HCO3 group or fruits
and vegetables than usual care group.199
In a study by Goraya et al., in patients with CKD Stage 4 using either fruits and vegetables or NaHCO3 as the intervention, plasma creatinine levels were comparable between the subjects treated either with HCO3 or fruits and vegetables at baseline and 1-year follow-up (p=0.99, 0.49, respectively), eGFR were comparable between the two groups at baseline and 1-year follow-up (p=0.84, 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 not as definitive. This may in part be due to the fact that 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 three groups in CKD Stage 1 patients (p>0.05). However, in CKD Stage 2 patients, fruits and vegetables had greater decrease in net urine albumin excretion than both HCO3 and control (p<0.05) and HCO3 group had greater decrease in net urine albumin excretion than control (p<0.05). It should be noted that a change in diet towards higher intake of fruit and vegetables is a different and more complex intervention than change in NEAP since the amino acid load and composition is 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 CKD patients were mixed, though evidence is limited. In adults with chronic kidney disease, two RCTs examined the effects of oral bicarbonate supplements on hospitalization. Among CKD Stage 5D (peritoneal dialysis), compared with placebo group, intervention group had lower hospital
admission (trend) and hospital length of stay (p=0.07 and 0.02, respectively). In CKD Stages 4-5; pre-dialysis, there was no significance difference in hospitalization for heart failure between the two groups (p= N/A).

**Nutritional Status**

In CKD patients Stages 3-5 including ones on maintenance dialysis, oral bicarbonate supplements improved nutritional status (e.g., SGA scores, nPCR, albumin, and prealbumin) in most studies. Oral bicarbonate supplements increased overall SGA scores (2.7 g/day) and lowered nPNA (nPCR) (de Brito-Ashurst ~1800 mg/day). Except for Kooman et al., (dialysate bicarbonate and oral sodium bicarbonate (1500-3000 mg) if pre-dialytic bicarbonate did not reach desired level), the other three studies observed positive effects of oral bicarbonate supplements on serum albumin or prealbumin levels (de Brito-Ashurst ~1800 mg/day; Movilli et al., - mean dose 2.7±0.94 g/day; 1–4 g/day; Verove et al. – mean dose 4.5±1.5g/d). Oral bicarbonate supplements also had no effects on TSF measurements. de Brito-Ashurst et al., (~1800 mg/day) noted significant increases in mid arm muscle circumference (MAMC) measurements with oral sodium bicarbonate, while Kooman et al. did not.

Two RCTs and three non-controlled studies examined the effects of oral bicarbonate supplements on nutritional status in adults with CKD. In CKD Stage 5; peritoneal dialysis, the oral bicarbonate group had higher overall SGA scores starting at 24 weeks (p-value <0.0003). In CKD Stages 4-5; pre-dialysis, 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 at 12 and 24 months (p<0.05).

In contrast, in a group of CKD Stage 5; hemodialysis patients, there was no significant difference in serum albumin among time points (p>0.05). In CKD Stage 5; hemodialysis, oral sodium bicarbonate increased serum albumin level (p=0.01).

Among CKD patient Stages 4-5; pre-dialysis, oral sodium bicarbonate increased both serum albumin and prealbumin levels between before and after intervention (p<0.05). Among
CKD Stages 1-2 compared to control and HCO3, fruit and vegetable group had 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). No difference between HCO3 and control.200 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 to HCO3 group, FV group had lower weight at 1-year follow up (p<0.01) – baseline weight did not differ between the two groups (p=0.24).198 In CKD Stage 3, fruits and vegetables had greater net body weight loss than both HCO3 and control (p<0.05) and control group had greater net body weight loss than HCO3 group (p<0.05).199

**Special discussions**

In Stage 5 MHD patients, higher bicarbonate in the dialysate bath is associated with increased mortality in epidemiological studies.418 In an analysis of the DOPPS data, it was reported MHD patients with either very low bicarbonate (≤17) or very high predialysis bicarbonate (>27) concentrations are at the greatest mortality risk.419 Paradigms that may apply to patients with residual renal function or those undergoing continuous therapy, such as peritoneal dialysis, do not directly apply to hemodialysis patients who are experiencing large changes in acid base equilibrium rapidly and/or discontinuously. Higher bicarbonate concentration in hemodialysis patients may also be reflective of lower protein intake.

Research on this topic is complicated by the fact that 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, since the effects of specific amino acids or other dietary constituents on both renal outcomes as well as vascular and bone pathophysiology (Calcium/Phosphorous) 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 fruits and vegetables. The latter can be accomplished by reduction in dietary protein intake and changing its composition. 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 randomized to low protein intake exhibited a significant increase in serum bicarbonate, 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 composition on outcomes is challenging.

- When increasing fruits and vegetables intake to correct acid load please use caution and monitor potassium levels.

**Monitoring and Evaluation**

Clinical trials have demonstrated compliance with expected changes in acid base status as evaluated by measurement of serum bicarbonate:

Consuming fruit and vegetable in the amount that could reduce dietary acid by 50% generally had positive effects on acid-base biomarkers. Fruit and vegetable increased plasma total CO2 (though not significant in one study) and decreased potential renal acid load and 8h NAE. Except for Goraya et al., (0.5 mEq/kg/day), oral bicarbonate supplements also had positive effects on acid-base biomarkers by increasing plasma total CO2 or bicarbonate levels and decreasing potential renal acid load and 8h NAE in six studies with different supplement combinations and dosages.

No hyperkalemia events were noted in the studies of Goraya et al. 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 RAS inhibitors. While 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 diets is to be recommended to control metabolic acidosis. A close monitoring of serum/plasma Guideline on Nutrition in CKD
potassium levels is encouraged, and fruit/vegetable consumption should be temporarily limited if the patient is considered at risk of hyperkalemia. Monitoring of circulating potassium is specially recommended in patients with CKD stage 4 or more, including those on dialysis, as this is the kidney function range where inabilities to compensate 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 effect 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 composition, carbohydrate composition from the control diet from the effects of acid load.
- Increasing pH during intermittent hemodialysis does not improve clinical outcomes. It is important to establish 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 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 (OPINION).

Rationale/Background

Calcium is a multivalent cation important for many biologic and cellular functions. Approximately 99% of total body calcium is found in the skeleton and the remainder 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 calcitropic hormones triggered by demand for calcium.

Serum calcium concentrations are maintained in the normal range until very late in CKD when it decreases slightly. 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. On the other hand, calcium excess may promote extra-osseous calcification contributing to increasing the risk of cardiovascular disease and mortality of these patients. In kidney transplant, calcium balance is even more complex and depends on several factors such as the post-transplant renal function, the persistence of hyperparathyroidism, the previous bone disease and the immunosuppressive therapy.

Detailed Justification

Guideline on Nutrition in CKD
Serum calcium levels do not reflect the overall body calcium balance and may not be very informative except at extremes. The maintenance of serum calcium 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 amount of dietary calcium is challenging and depends on the investigation of calcium balance.

The evidence review included three small short-term clinical trials in pre-dialysis CKD patients that investigated the effect of calcium intake in food or supplements on mineral bone biomarkers and on calcium balance. No other outcomes were investigated in these studies.

**Calcium Balance and other Lab Measures**

In an NRCT, 51 patients in the early stage of CKD (creatinine clearance: 66 to 82 mL/min) were placed in a low protein (40g/d) and low phosphorus (600 mg/d) diet supplemented with or without 0.5 g/d of elemental calcium for 10 days. A decrease in intact parathyroid hormone (iPTH) was observed only in the group receiving calcium supplementation and no changes in serum calcium, phosphorus and calcitriol were found in the other groups.

In a crossover study, six patients with CKD stages 3 and 4 consumed controlled high (2,000 mg/d) and low calcium diets (800 mg/d) for 9 days. 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 iPTH and 1,25-dihydroxivitamin D decreased in the high calcium diet.

In a 3-week randomized cross-over balance study, eight patients with CKD stages 3 and 4 were randomized to a controlled calcium intake of 2457 mg/day (1,500 mg of elemental calcium from calcium carbonate used as phosphate binder + 957 mg/day of dietary calcium) versus placebo (957 mg/day of dietary calcium). The calcium balance was neutral in the placebo
and positive in the calcium carbonate groups (508 vs. 61 mg/d, respectively, p=0.002). Serum calcium, phosphate and iPTH concentrations were unchanged in both groups.

Despite the small number of patients investigated, these well performed balance studies showed that a dietary calcium intake of approximately 800 to 1,000 mg/d may be adequate to maintain calcium balance in patients CKD stages 3 and 4 who are not receiving active vitamin D analogs, at least at short term.\textsuperscript{427} These values are close to the current estimated average requirement (EAR-800-1000 mg/d) and the recommended dietary allowance (RDA- 1000-1200 mg/d) for healthy individuals proposed by the Institute of Medicine.

**Special Discussions**

In maintenance dialysis patients, calcium balance is more complex. In addition to dietary calcium load and use of vitamin D analogs, calcium concentration in the dialysate and mode of dialysis also determine the mass balance of calcium. Studies using a mathematical modeling have shown a positive calcium balance mass in patients on MHD.\textsuperscript{428, 429} According to estimates and assumptions made, extracellular fluid calcium increased with an elemental daily calcium intake \textgreater 1.5 g and was numerically more positive when patients are given active vitamin D analogs.\textsuperscript{428} 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.\textsuperscript{430}

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 on maintenance dialysis. Notably in KDIGO (CKD-MBD) 2009 and 2017 there is no recommendation regarding calcium intake for patients on maintenance dialysis or with kidney transplantation.\textsuperscript{333, 431}

**Implementation considerations**

Hypercalcemia is relatively common in patients on maintenance dialysis. Evidence has been accumulated linking higher serum calcium concentrations to increased nonfatal cardiovascular
events\textsuperscript{422} and mortality.\textsuperscript{433-436} In the event of hypercalcemia the following adjustments are recommended: \textsuperscript{334}

- In patients taking calcium-based phosphate binders the dose should be reduced or therapy switched to a non-calcium phosphate binding.
- In patients taking active vitamin D analogs the dose should be reduced or therapy discontinued until serum concentration of calcium return to normal.
- If hypercalcemia persists, consider using low dialysate calcium (1.5 to 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.\textsuperscript{437, 438}

**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 of 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 different sources of calcium (dairy foods, fortified foods and calcium supplements) on serum calcium concentrations should be studied.
6.3 Statements on Phosphorus

Dietary Phosphorus Amount

6.3.1 In adults with CKD 3-5 and on MHD, 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 and post-transplant, it is reasonable when making decisions about phosphorus restriction treatment to consider the bioavailability of phosphorus sources (e.g. animal, vegetable, additives) (OPINION).

Phosphorus Intake with Hypophosphatemia

6.3.3 For adult kidney transplant recipients 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 as an approved ingredient added during food processing. Because of difficulties of persons with CKD (CKD) to clear excess phosphorus, additional means of serum phosphate control is 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 promote phosphorus excretion to avoid phosphorus accumulation and hyperphosphatemia is generally seen when estimated glomerular filtration rate (eGFR) level decreases below 45 mL/min, being less common in earlier CKD stages. In the setting of anuria in patients on maintenance dialysis, hyperphosphatemia risks are particularly heightened, with a prevalence as high as 50%.

Detailed Justification

How much should dietary phosphorus/phosphate be restricted in adult patients with CKD is not
well established. Traditionally, CKD-specific recommendations suggest maintaining phosphorus intake between 800-1000 mg/day in patients with CKD stages 3-5 and those in maintenance dialysis in order to maintain serum phosphate in the normal range. The workgroup notes, however, that the efficacy of this recommendation has not been established. Further, such dietary phosphorus intake range is higher than current recommended dietary allowance for phosphorus in the adult general population (700 mg/d).

While dietary intake influences serum phosphate in CKD patients, 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 workgroup prefers not suggesting specific dietary phosphate ranges, and instead emphasize on 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), or the use of phosphorus additives in processed foods.

With the goal to better understand the effect of dietary phosphate control, the workgroup 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 dietary protein restriction-the major source of dietary phosphorus) may be recommended to prevent / treat complications related to high phosphate load patients with CKD stages 3-5 and maintenance dialysis. This can be achieved by intensified patient educational strategies or individualized dietary plans. 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:

*Phosphate restriction regimes in non-dialysis CKD*: Two RCTs 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 a LPD,
and observed significant reductions in serum phosphate, and urinary phosphorus excretion post-intervention.

**Reducing phosphorus by limiting protein intake in non-dialysis CKD:** Five RCTs in CKD patients not undergoing dialysis stages 4-5\textsuperscript{133, 134, 14, 154, 163} evaluated the effect of a low LPD or a VLPD supplemented with keto-analogs on serum phosphate levels. All five studies reported statistically significant\textsuperscript{134, 141, 154, 163} or borderline-significant\textsuperscript{133} 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 regimes in maintenance dialysis:** Two RCTs\textsuperscript{123, 450} examined the effects of limiting dietary phosphorus in patients with CKD undergoing MHD. Lou et al. tested the effect of 3-month intensified dietary counseling in order to achieve 800 – 900 mg/d of dietary phosphorus and observed a greater decrease in serum phosphate concentration compared to standard care.\textsuperscript{123} Sullivan et al. tested the effect of patient education on identifying foods with phosphorus additives and observed, compared to standard care, a significant reduction in serum phosphate levels after 3 months.\textsuperscript{450} No studies were identified that included PD patients.

Although dietary phosphorus restriction may be a valid stand-alone strategy in patients with CKD-stage 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 one in the armamentarium of interventions to maintain serum phosphate levels in the normal range. For other non-dietary phosphate management strategies, the interested reader can consult recent guidelines on the management of mineral and bone disorders of CKD.\textsuperscript{147, 333, 334, 442-444} Aligning with those guidelines, we recommend decisions to restrict dietary phosphorus be based on the presence of progressively or persistently elevated serum phosphate (that is, 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. studied impact of a dietary phosphorus restriction (alone or in combination with protein restriction) on creatinine clearance among 90 CKD patients of unreported etiology or CKD stage over a median intervention time of 19 months.\(^{144}\) Compared to routine care, dietary protein and phosphate restriction or phosphate restriction only did not show any significant difference in the mean rate of fall of creatinine clearance. In an observational analysis from the Modification of Diet in Renal Disease (MDRD) study, greater 24-hr urinary phosphate excretion (taken in this study as an estimate of dietary phosphorus intake) was not associated with the future risk of ESRD.\(^{451}\) 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 CKD patients stages 2-5 observed that higher phosphorus excretion per creatinine clearance was associated with a higher 3-year risk of CKD progression (defined as the composite of ESKD or 50% reduction of eGFR).\(^{452}\)

It has been proposed that hyperphosphatemia in non-dialysis patients stages 2-5 may reduce the antiproteinuric effect of ACE inhibition\(^{453}\) or of VLPDs.\(^{454}\) In a post hoc observational analysis from the Ramipril Efficacy In Nephropyathy (REIN) trial, Zoccali et al. evaluated the relationships between serum phosphate concentration at baseline, disease progression, and response to ACE inhibition among 331 patients with proteinuric nephropathies.\(^{453}\) Independent of treatment, patients with higher phosphate progressed significantly faster either to ESRD or to a composite endpoint of doubling of serum creatinine or ESRD compared with patients with phosphate levels below the median, and the renoprotective effect of ramipril decreased as serum phosphate increased (P ≤ 0.008 for interaction). In another post hoc study from a non-randomized, study in which 99 proteinuric CKD patients who sequentially underwent low-protein diet (LPD; 0.6 g/kg/day) and VLPD (0.3 g/kg/day) supplemented with keto-analogues, each for periods longer than 1 year, Di Lorio et al. observed that 24-h proteinuria was reduced modestly in patients who maintained relatively higher serum phosphate levels or relatively

Guideline on Nutrition in CKD
higher phosphaturia to be maximal in those who achieved the lowest level of serum and urine phosphate.\textsuperscript{454}

\textit{Mortality}

In observational studies involving CKD patients, the associations of dietary phosphorus intake on mortality are mixed, impacted 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 non-dialysis CKD.\textsuperscript{451, 455, 456} Murtaugh et al.\textsuperscript{455} evaluated the association between 24-h dietary recall estimation of phosphorus intake in participants with eGFR<60 ml/min/1.73m\textsuperscript{2} from the community-based U.S survey National Health and Nutrition Examination Survey III, and observed no association between dietary phosphorus and mortality. Palomino et al. examined myocardial infarction patients from the Heart and Soul Study, the majority of which with 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).\textsuperscript{456} Selamet et al. involved nephrology referred patients with CKD from the MDRD study and failed to observe an association between 24-hr urinary phosphorus excretion and mortality.\textsuperscript{451}

One study in MHD patients that examined the association between dietary phosphate (as estimated from 3-day food recalls) and mortality.\textsuperscript{457} Patients with higher dietary phosphorus intake were associated with greater 5-year mortality risk (p-trend across tertiles=0.04). Lynch et al.\textsuperscript{458} explored the between prescribed dietary phosphorus restriction and mortality in a post hoc analysis of the Hemodialysis (HEMO) study, which included 1751 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 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 subjects prescribed 1001 to 2000 mg/d and those with no specified phosphate restriction: hazard ratios (95\% CIs) 0.73 (0.54 to 0.97) and 0.71 (0.55 to 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 fibroblast growth factor 23 (FGF23).459-461

It has been proposed that dietary intensification of phosphorus can solve this complication; one small randomized controlled trial154 examined the effects of 12-week dietary phosphorus supplementation by means of a neutral phosphate salt (disodium phosphate) in patients with early post-transplantation hypophosphatemia. The authors observed that, compared to 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 intervention.

The serum phosphate level at which supplementation should be considered in these patients or the dose of replacement to be given is, however, 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 of limiting the intake of other nutrients, particularly protein, which is the main source of phosphate in the diet.458,462,463 These concerns are particularly relevant to patients treated with dialysis because of protein losses in dialysate and greater protein catabolism from hypermetabolic stress.205 Dietary counselling that includes information on not only the amount of phosphate but also on 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.464
• Advise choosing natural foods that are lower in bioavailable phosphorus. Animal- and plant-based foods contain the organic form of phosphate. While animal-based phosphate is absorbed in the GI tract by 40-60%, the absorption of plant-based phosphorus is lower (20-50%). In line with this, a small crossover trial including CKD patients’ stage 4 found that a 7-day vegetarian diet led to lower serum phosphate levels and decreased FGF23 levels than a 7-day meat-based diet. Furthermore, foods with only organic phosphorus typically are more nutrient dense and have a higher nutritional value compared with processed foods containing phosphate additives, which tend to have a lower nutritional value, and are often paired with sodium and potassium additives.

• 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, to emulsify ingredients and enhance flavor, and to stabilize foods. Phosphorus additives contain, however, inorganic phosphorus with a close to 100% intestinal absorption. Meat and poultry products that report the use of additives have an average phosphate-protein ratio much higher than additive-free products. The most-commonly used phosphorus additives in food industry can be found, for instance, in bakery products, enhanced meats, and processed cheeses.

• Advise choosing natural foods that have low amount of organic phosphorus versus high amount of protein. The content of organic phosphorus per gram of protein varies widely among foods. Nutrient composition tables reporting on phosphorus/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.
• 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.\textsuperscript{471, 472} Slicing the meat prior to boiling and the use of a pressure cooker has been shown more effective in terms of achieved protein to phosphorus content.\textsuperscript{471} At the same time, these methods may remove other minerals (e.g. potassium) of concern for patients with CKD.\textsuperscript{473} Such practices, however, result in reduced palatability and texture of the food.

The work group emphasizes to individualize recommendations after appropriate evaluation of the patient daily intake. It requires nutrition expertise (preferably consultation with a renal dietitian) and should take into consideration culturally appropriate food substitutions. Nutritional counselling 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.\textsuperscript{124} 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.\textsuperscript{449, 450} A meta-analysis suggested that nutritional counselling based on a structured behavioral change are, in general, successful in controlling hyperphosphatemia in these patients.\textsuperscript{124} In this meta-analysis, however, only about half of 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 to the many studies exploring pharmacological management of this electrolyte disorder (e.g. use of phosphate binders), the amount of evidence on the effectiveness of dietary control is low. The workgroup recommends future studies to better define the effect of this simple and cost-effective strategy. Examples of still unanswered questions are:

• Study if dietary phosphorus restriction is able to normalize serum phosphate levels in PD patients.
● Research if dietary phosphorus intake level is associated with worse clinical outcomes such as cardiovascular events, progression of kidney disease or mortality.

● 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 non-dialysis CKD stage 3-5 and maintenance dialysis.

● Study the effects of nutritional counseling with focus on organic vs inorganic phosphorus sources on the diet quality and metabolic balance of maintenance dialysis patients beyond serum phosphate control.
6.4 Statement on Potassium

Dietary Potassium Amount

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

Dietary Potassium in Hyperkalemia

6.4.2 In adults with CKD 3-5D and post-transplant who exhibit hyperkalemia, it is reasonable to consider lowering dietary potassium intake as a therapeutic strategy (OPINION).

Potassium Intake for Hyperkalemia or Hypokalemia

6.4.3 In adults with CKD 3-5 on MHD (2D) and post-transplant (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 and 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 (i.e. adrenergic system, insulin, aldosterone, and urinary clearance) are commonly impaired in patients with CKD and ESRD 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 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 (GI) problems like vomiting, diarrhea, constipation and bleeding. All these factors should be considered when formulating a strategy to keep the serum Guideline on Nutrition in CKD
potassium within the normal range.

The consequences of dietary potassium intake in patients with CKD are not known. Indeed, 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 urine potassium excretion or other surrogates for dietary intake to assess the following outcomes. While we acknowledge that urine potassium excretion may not necessarily represent dietary potassium in these patients, the studies showed:

**Mortality**

Data on the association between dietary and urinary potassium excretion and mortality in adults with CKD were mixed. A study in MHD (stage 5), found that compared to the lowest quartile of dietary potassium intake (879 mg or 22.5 mEq/24hr) as measured by the Block Food Frequency Questionnaire, higher quartiles of intake were associated with a stepwise increase in risk of 5-year mortality (p-trend=0.03). Another study in pre-dialysis (Stage 2-4) there was no significant association noted between quartiles of urinary potassium excretion and all-cause mortality. Compared to the highest quartile of urinary potassium excretion (mean 3600 mg or 92.1 mEq/24hr) persons in the three lowest quartiles had higher all-cause mortality (hazard ratio (95% CI) of 1.53 (1.15-2.02), 1.7 (1.25-2.31), 1.71 (1.23-2.38) for quartiles 3, 2, and 1, respectively). Results remained similar even after using time-updated average urine potassium excretion.

**CKD Progression**

Data on the association between urinary potassium excretion and CKD progression in adults with CKD were mixed. In Stage 2-4; pre-dialysis urinary potassium excretion in the highest quartile (≥67.1 mmol or 2617 mg/24 h) was significantly associated with CKD progression (defined as incident ESRD or halving of eGFR from baseline) (1.59, 95% CI: 1.25-2.03) compared to levels in the lowest quartile (<39.4 mmol or 1541 mg/24 h). In another study in Stage 2-4; pre-dialysis, baseline urinary potassium excretion was not significantly associated with kidney failure (defined as dialysis therapy or transplantation) even when using time-updated average urine potassium.
Nerve Function

One randomized study examined the effects of dietary potassium restriction on progression of peripheral neuropathy in CKD patients. In 42 patients randomized to either dietary potassium restriction vs. usual diet (change in dietary potassium -854 vs. -343, 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.477

Special Discussions

Research on this topic is complicated by the fact that potassium handling by the kidney will vary by disease state and CKD stage. In patients with pre-dialysis CKD the acute and chronic effects of dietary potassium loading are not consistently reflected in serum potassium levels due to compensatory mechanisms that are triggered to maintain homeostasis.478-480 Research and evidence on this area is also limited because of difficulties in obtaining reliable data on 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 diet in terms of potassium (i.e. fruits and vegetables). However, none of the pivotal trials examining potassium binders evaluated dietary potassium intake, and currently there is no known study that investigates how potassium intake should be modified when taking potassium binders. Since the focus of this guideline was dietary intake, rather than pharmacological treatments, potassium binders were outside the scope of this guideline.

Implementation considerations

- Potassium is widely distributed in foods, but the main sources are fruits, vegetables, legumes and nuts. As these foods are major sources of fiber, vitamins, minerals and other important nutrients, efforts should be made to avoid restricting dietary potassium. In particular reduced fiber can lead to constipation which could lower potassium excretion. For these issues, consult the guideline statements on fiber and fruit/vegetable intake.
When treating hyperkalemia clinicians are advised to first try and identify contributing factors that can be corrected such as a hypoinsulinemic state or certain medications. This is true in light of the physiological benefits high potassium intake may confer, such as putative antihypertensive effects.\textsuperscript{481} If hyperkalemia cannot be reversed, the next step is to identify the most important dietary sources of potassium by interviewing the patient and dietary recalls. Clinicians preferably assisted by a renal dietitian should educate patients about hyperkalemia regarding fruits, vegetables, and other foods with low potassium content that ideally still contain higher levels of fiber and other micronutrients. Published food composition tables can be helpful in this regard.\textsuperscript{482} In addition, potassium content in vegetables can be lowered by boiling and reductions in food taste and palatability associated with this strategy can be partially improved with the use of aromatic herbs.\textsuperscript{409,410}

\textbf{Future research}

It will be necessary to approach pre-dialysis and dialysis populations separately in light of the great differences in potassium handling.

- There is a need for studies on what constitutes an optimal dietary potassium intake and how dietary potassium intake influences blood potassium content and clinical outcomes.
- There is a need for studies investigating optimal means of adjusting dietary potassium intake when taking potassium binders.
- In addition, in patients on 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 (non-dialyzed) (1B), maintenance dialysis (1C), and post-transplant (1C), we recommend limiting sodium intake to less than 100 mmol/day (or <2.3 g/day) to reduce blood pressure and improve volume control.

Sodium Intake and Proteinuria

6.5.2 In adults with CKD 3-5 (non-dialyzed), we suggest that reduced sodium intake (100 mmol/day or <2.3 g/day) be prescribed to reduce proteinuria (2A).

Sodium Intake and Dry Body Weight

6.5.3 In adults with CKD 3-5D, we suggest reduced 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. 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 ECF 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. However, this system may be compromised with excessive sodium intake, and/or inadequate excretion, which may occur with chronic kidney disease.

Chronic high sodium intake may impact on a number of physiological functions relating to the vasculature, heart, kidneys and sympathetic nervous system. Excessive sodium intake is thought to exert toxic effects on blood vessels through mediating factors such as oxidative stress, inflammation and endothelial dysfunction. Of particular interest in CKD is the role of sodium reduction in improving the pharmacological 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 mmHg systolic BP and 2.82 mmHg diastolic BP) with 100mmol/d reduction in sodium intake. Indications from a small number of long-
term studies (>6 months) suggest a benefit for CV-morbidity and mortality, although the studies were underpowered to adequately examine these outcomes. The following will explore the evidence within CKD.

**Detailed Justification**

Overall, the evidence for reducing sodium intake comes from randomized controlled trials 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 upon 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 randomized controlled trials, 1 parallel and 4 cross-over studies examined the effects of reduced dietary sodium intake in CKD (Stage 2 to 5, non-dialysis). The cross-over studies utilized supplemental sodium or provided meals on the background of a low sodium diet to generate consistent intake in the high (180 mmol to 200mmol/d, with ~100-120mmol/d supplemented) vs low sodium intake group (placebo, total 50 to 0 mmol sodium per day). The parallel RCT was the longest study duration (six months) conducted in a sample of Bangladeshi immigrants in the UK (n=48). Participants were randomized 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 260mmol, the intervention group achieved 138mmol/day (a reduction of over 120mmol), whilst usual care stayed largely stable (to 247 mmol/d).

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

Guideline on Nutrition in CKD
between usual and sodium restricted intakes.

Four trials were conducted in the maintenance dialysis population. One RCT in peritoneal dialysis (PD), and two RCTs in MHD and one non-randomized trial in both PD and MHD. In the MHD study, there was no significant reduction in BP. The difference with this study, compared to 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 low and high intake groups (100mmol.d or 2.3g sodium difference).

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

In the vast majority of trials, the target sodium restriction was 80-100 mmol/day (or 2-2.3g/day). 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 200mmol or 4g 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 endpoints is derived from observational studies as there were no RCTs in sodium reduction in CKD that reported CKD progression cardiovascular events, mortality outcomes. This is attributable to the small sample sizes and the longest trial duration only six months.

The post-hoc analysis of two observational cohort studies showed mixed results investigating
the association between sodium intake (measured by dietary recall) and subsequent mortality in MHD and PD patients. 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 as 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 1770 MHD patients, McCausland et al. found higher dietary sodium intake associated with increased mortality.

More consistent results were demonstrated from a large high-quality prospective cohort (CRIC study) of predialysis Stage 2-4, using urinary sodium excretion. In He et al., 24-hour urinary sodium excretion was associated with greater all-cause mortality and CKD progression (defined as incident ESRD or halving of eGFR from baseline). Sodium excretion was also associated with composite CVD (heart failure, myocardial infarction, stroke).

**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 cross-over trials) of short duration (1 week to 6 months), evaluating the effect on reducing sodium intake (typically to a level of <2g or 90mmol/d) on BP. In fact, lower sodium intake significantly decreased systolic BP in all but one study, which reduced intake by only 34mmol/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 pre-dialysis CKD, however the BP benefits were also apparent in trials in dialysis and transplantation populations.

Although this review was unable to derive a summary estimate, a Cochrane review on this topic published in 2015 showed dietary sodium reduction (MD -105.9, 95% CI -119.2 to - 92.5mmol/day) resulted in significant reduction in systolic BP (MD -8.76, 95% CI -11.35 to - 3.80 mm Hg). These short-term studies showing clinically meaningful systolic BP reductions ranging from 2-12mmHg systolic BP and 1-8mmHg

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**Guideline on Nutrition in CKD**

Page 190
diastolic BP in trials one week to six months in duration.\textsuperscript{505}

\textit{Inflammatory Markers}

Sodium reduction may make little to no difference to inflammation (low certainty evidence). Two RCTs, a parallel RCT in MHD,\textsuperscript{498} and a crossover in Stage 3 and 4,\textsuperscript{491} investigated the impact of sodium restriction on inflammation, measured by CRP, IL-6, TNF-alpha. In the Telini study there was a significant reduction in all inflammatory markers within the intervention group, however not reported between group differences (and no difference within control group).\textsuperscript{498} The single crossover study in Stage 3-4 showed no difference in inflammation comparing high and low sodium intake.\textsuperscript{491}

\textit{Body weight and fluid}

Sodium restriction may slightly reduce body weight and total body fluid in non-dialysis CKD (low certainty evidence). However, it is uncertain whether sodium restriction reduces body weight and body water in dialysis. The evidence from non-dialysis CKD comes from two randomized-crossover trials, one using sodium supplementation to compare intake of 60-80mmol/d to 180-200mmol/d for 2 weeks\textsuperscript{491} together with a more recent investigation by Saran et al. evaluating the effect of sodium restriction <2g/day vs usual diet for 4 weeks (with a 2-week washout in-between).\textsuperscript{495} Both trials demonstrated a reduction in extracellular volume. Furthermore, in maintenance dialysis, two RCTS demonstrated no significant difference in body weight with salt restriction in peritoneal\textsuperscript{496} or both hemodialysis and peritoneal dialysis.\textsuperscript{506} In one non-randomized study in hemodialysis, the group advised to restrict sodium (<3 g/day) and fluid (<1 L/d) intake demonstrated within group decrease in interdialytic fluid gain, but there was no change in the control group, and between group difference was not significant.\textsuperscript{497}

\textit{Kidney function (including proteinuria)}

Restriction of sodium intake may slightly reduce kidney function markers of creatinine clearance\textsuperscript{490, 492, 493, 504} and eGFR\textsuperscript{507} demonstrated in short-term cross-over trials in the stage 1-5 non-dialysis population (low certainty evidence). In the single parallel RCT over 6 months of sodium restriction, deBrito-Ashurst found no difference in eGFR.\textsuperscript{489} The Guideline on Nutrition in CKD \textsuperscript{500} states that the recommendation is based on small, short-term clinical trials.
inconsistency in results may be due to the short-term cross-over trials demonstrating acute hyper filtration 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 cross-over trials.\textsuperscript{491-493, 507} This evidence is supported by further parallel RCTs and observational studies. Meuleman et al. demonstrated a reduction in proteinuria over 3 months self-management intervention using a sodium intake <100mmol/d that reversed to baseline proteinuria after cessation of the dietary sodium restriction.\textsuperscript{494} In addition, in a post-hoc analyses of clinical trials (REIN I & II) in proteinuric patients with established CKD have demonstrated participants consuming a higher sodium diet was associated with an increased risk of progressing to ESKD compared to a lower sodium diet <100mmol/d.\textsuperscript{508}

**Implementation considerations**

- Achieving a reduced sodium intake in CKD is recommended, however can be particularly challenging to achieve.\textsuperscript{509} 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. As sodium is consumed largely from processed foods, the World Health Organization has initiatives for reducing sodium content in manufactured foods among the top priorities to combat non-communicable diseases.\textsuperscript{510} Consuming a low sodium diet generally requires education and skill development (cooking, label reading) and explicit choice to consume a low sodium diet. Therefore, a concerted and multi-faceted 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 availability of sodium in the food supply.\textsuperscript{510}

- 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.\textsuperscript{510} 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 demonstrate that achieving a reduced sodium intake is only apparent whilst receiving active intervention.\textsuperscript{494} 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:** 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 24hour collection, 2) sodium excretion is a direct reflection of intake. It is this latter assumption which has been recently challenged by Titze and colleagues, who have identified a sodium storage pool in the skin and a wide disparity between sodium intake and excretion day to day.\textsuperscript{511} 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 and can be time consuming to collect and require technical expertise in the analysis. A panel of methods is therefore recommended, as no one method is ideal to adequately assess adherence.\textsuperscript{510}

- **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.\textsuperscript{475} 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.\textsuperscript{512} In hypertensive adults, post-hoc analysis of clinical trials indicate sodium-to-potassium ratio may be more effective in lowering BP than lowering sodium or increasing potassium as single interventions.\textsuperscript{513} However, there are unknown safety aspects in CKD, particularly with the risk of hyperkalemia. Investigating the relative benefit of sodium reduction compared to potassium intake is beyond the scope of the current guidelines however warrants further research. Evidence for Potassium recommendations is addressed within these guidelines.
• Currently, there is too much uncertainty in the evidence to advice 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, utilizing 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, and provision of interventions which 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.
BIOPGRAPHIC AND DISCLOSURE INFORMATION

Jerrilyn D. Burrowes, PhD, RD, CDN, FNKF

Dr. Burrowes is Professor of Nutrition and Chair of the Department of Nutrition at Long Island University (LIU) Post in Brookville, NY. Dr. Burrowes has dozens of publications in refereed journals and she has been an invited speaker at numerous professional meetings and conferences on nutrition in kidney disease. She is the co-editor of the 1st and 2nd editions of the textbook entitled, Nutrition in Kidney Disease, and a 3rd edition is currently being planned. Dr. Burrowes has held many leadership and advisory roles in professional organizations and societies, and she has served on numerous association committees. She was recently elected Council Member to the ISRNRM for the 2018-2020 term. For the past eight years, Dr. Burrowes has served as the Editor-in-Chief for the Journal of Renal Nutrition (JRN). She received the Recognized Renal Dietitian Award and the Joel D. Kopple Award from the NKF Council on Renal Nutrition, and the Outstanding Service Award from the Renal Practice Group of the Academy of Nutrition & Dietetics. Dr. Burrowes has particular interest in the factors that influence appetite and their effect on health outcomes in dialysis patients; the influence of culture and ethnicity on dietary adherence in dialysis patients; and the use of complementary and alternative therapies for people with kidney failure. Dr. Burrowes earned her Bachelor’s degree in biology/pre-medicine from Fisk University in Nashville, TN; her M.S. degree in foods, nutrition and dietetics from New York University; and her Ph.D. in nutrition from New York University.

Financial Disclosure: Dr. Burrowes reports no relevant financial relationships.

Laura Byham-Gray, PhD, RDN, FNKF

Dr. Byham-Gray is a Professor and Vice Chair for Research in the Department of Nutritional Sciences, School of Health Professions at Rutgers University. She has received several extramural research grants from the federal agencies to investigate energy expenditure and protein-energy wasting in patients on renal replacement therapies. Dr. Byham-Gray has held numerous elected and appointed positions at the national, state, and local levels of National Guideline on Nutrition in CKD
Kidney Foundation, The American Society of Parenteral and Enteral Nutrition, and the
Academy of Nutrition & Dietetics. She has also served as the associate editor for the National
Kidney Foundation publication, the Journal of Renal Nutrition. Dr. Byham-Gray was the chief
editor for two books: Nutrition in Kidney Disease (Springer Publications, 2014), and the A
Clinical Guide to Nutrition Care in Kidney Disease (Academy of Nutrition and Dietetics,
2013) and has over 100 peer-reviewed articles and presentations to her credit.

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

**Katrina Campbell, PhD, RD**

Dr. Campbell is an Associate Professor at Bond University and Principal Research Fellow
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dietitian with a career spanning clinical practice, teaching and research, Katrina has been
dedicated to advancing the evidence base for the nutrition management in kidney disease. Her
work includes lifestyle interventions in CKD, investigating the role of dietary patterns in the
trajectory of CKD, nutrition status assessment and workforce issues, published in over 100
peer-reviewed papers. In an effort to translate evidence to practice, Dr Campbell has authored
numerous clinical guidelines and systematic reviews, 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.

Juan-Jesus Carrero, Pharm, PhD Pharm, PhD Med, MBA (section Chair)

Dr. Carrero is a Professor of Renal Epidemiology at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. Dr. Carrero is currently the co-director of education outreach program at the International Society of Renal Nutrition and Metabolism (ISRNM) and the chair of the European Renal Nutrition (ERN) working group at the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). In 2014 he received the Joel Kopple Award from the National Kidney Foundation for his work in Renal Nutrition Research. He has authored more than 350 peer-reviewed publications, and his research interests include chronic kidney disease epidemics, pharmacosafety and protein-energy wasting in chronic kidney disease, with special emphasis on the areas of body composition, diet quality and pro-catabolic endocrine disorders. He sits on the board of the Center for Gender Medicine at Karolinska Institutet and serves as associate editor for the Journal of Renal Nutrition, Journal of Nephrology and Nephrology-Dialysis and Transplantation.

Disclosures: Dr. Carrero reported no relevant financial disclosures.

Winnie Chan, PhD, RD, FNKF

Dr. Chan is a Specialist Renal Dietician, a Dietetic Research and Postgraduate Education Lead, and a Dietician Representative of Non-Medical Clinical Academic Research Group at Queen Elizabeth Hospital Birmingham, United Kingdom. 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 research grant from the British Renal Society. She has fostered particular clinical and research
interests in kidney transplantation. Her research work focused on investigating the role of nutritional factors and body composition on clinical and quality of life outcomes in kidney transplant recipients. In addition to publishing in well-respected journals, Dr Chan has authored the Practice-based Evidence in Nutrition (PEN) Knowledge Pathway in Intradialytic Parenteral Nutrition, The Global Resource for Nutrition Practice. She serves on the editorial board of Journal of Renal Nutrition. She has delivered numerous presentations and invited lectures in her areas of clinical and research expertise, including award-winning research at national and international conferences. She is an active research grant review panel member for Kidney Research UK and the British Renal Society. To date, she is serving as an Expert Advisor 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.

Lilian Cuppari, PhD (Chair)

Dr. Cuppari is a dietitian who completed a master’s degree in nutrition and PhD at Federal University of São Paulo, Brazil. She is currently affiliate professor in the Department of Medicine/ Division of Nephrology at Federal University of São Paulo, and a supervisor of nutrition in the renal unit of Oswaldo Ramos Foundation- Kidney Hospital in São Paulo serving as the leader of the research and clinical practice group on nutrition and kidney disease. She has published extensively in the field of nutrition and chronic kidney disease in the form of journal articles, books and book chapters. She is currently a member of the editorial board of Journal of Renal Nutrition.

Financial Disclosure: Dr. Lilian Cuppari reports no relevant financial relationships

Denis Fouque, MD, PhD

Dr. Fouque is Professor of Nephrology at the University Claude Bernard Lyon1, and Chief of the Division of Nephrology at the Centre Hospitalier Lyon Sud in Lyon, France. He is the past Research Vice President (Health Affairs) at the Université Claude Bernard Lyon, the largest medical school in France (2012-2016). Dr Fouque has published 320 papers, including reviews, meta-analyses and 21 book chapters, among which 2 chapters in The Kidney, Brenner Guideline on Nutrition in CKD
and Rector, 2012 and 2015. His current h factor is 60. His research fields are in nutrition and metabolism in chronic kidney disease and dialysis. He is director of the adipocyte dysfunction research group in CARMEN at the University Claude Bernard Lyon1. Dr Fouque also got training in Evidence based Medicine by founding the Cochrane Collaboration Renal Group in 1997 and being the Co-ordinating Editor until 2001. Dr Fouque was President of the International Society for Renal Nutrition and Metabolism (2004–2006), co-editor-in-Chief of the Journal of Renal Nutrition (2003-2011), chairman of the ERA-EDTA Nutrition Guideline (2007) and vice-chairman of the European Renal Best Practice group of ERA-EDTA until 2017. He is the chairman of the European Nutrition working group of the ERA-EDTA, and the current Editor-in-chief of Nephrology Dialysis Transplantation journal.

Allon Friedman, MD
Dr. Friedman is Associate Professor of Medicine at Indiana University School of Medicine in Indianapolis and director of one of its affiliated dialysis units. Dr. Friedman trained at Tufts University and the USDA Human Nutrition Research Center in Boston prior to joining the Indiana University nephrology faculty. Dr. Friedman has published dozens of articles, editorials, and book chapters on topics related to the overlap between nutrition and kidney disease and has received grant funding from the NIH, National Kidney Foundation, and other institutions. One current area of research interest involves the impact and treatment of obesity-related kidney disease. He has played a leadership role at the American Society of Nephrology and the American Association of Kidney Patients and is currently a council member of the International Society of Renal Nutrition and Metabolism.

Financial Disclosure: Dr. Friedman reports no relevant financial relationships.

Sana Ghaddar, PhD, RDN
Dr. Ghaddar is a renal dietitian at DaVita Health Care. She has over 22 years of experience in the renal and clinical dietetics field. Dr. Ghaddar taught at two private universities for over 15 years and mentored several PhD students on their research studies. She served as a member of the K/DOQI Anemia Workgroup Expert Panel. She has several publications in well-respected Guideline on Nutrition in CKD
peer-reviewed journals, as well as editorials and book chapters. She has served as a member of
the editorial board for *Journal of Renal Nutrition and Archives of Clinical Nephrology*, and a
reviewer for several peer-reviewed journals. She presented at various national and international
conferences, as an invited speaker. Dr. Ghaddar has a special interest in nutrition in CKD, fluid
control and phosphorus balance, as well as in cognitive behavioral counseling to improve
patient outcomes.

**Financial Disclosure:** Dr. Ghaddar reports no relevant financial relationships.

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**D. Jordi Goldstein-Fuchs, DSc, APRN, NP-C, RD**

Dr. Goldstein-Fuchs is a nephrology nurse practitioner and kidney nutrition specialist with the
Pediatric Nephrology Division at Lucile Packard Hospital Stanford. She has worked with
adults within all stages of kidney disease and more recently has expanded her expertise to the
realm of pediatric nephrology. Dr. Goldstein-Fuchs has been engaged in both basic and clinical
research and has an active publication record pertaining to nutrition and metabolism in renal
disease. She is Editor Emeritus of the *Journal of Renal Nutrition*, having served as Co-Editor-
In Chief for 15 yrs. She has served on the Cardiovascular and Diabetes KDOQI Guideline
committees and is a Fellow of the National Kidney Foundation.

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

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**T. Alp Ikizler, MD (Chair)**

Dr. Ikizler is the Director of Division of Nephrology and Professor of Medicine at the
Vanderbilt University School of Medicine (VUSM) in Nashville, Tennessee. He also holds the
Catherine McLaughlin Hakim Chair in Vascular Biology. He is a member of American Society
of Clinical Investigation (ASCI), ASCI Advocacy Committee and FASEB Board of Directors
as the ASCI representative since 2017. Dr. Ikizler’s clinical interests and expertise are focused
on the care of the patients with CKD, end-stage renal disease on maintenance dialysis and
acute kidney injury. He has significant research and clinical interest in nutritional and
metabolic aspects of acute and chronic disease states. Dr. Ikizler was the Medical Director and
CEO of the Vanderbilt University Medical Center Outpatient Dialysis unit between 2000 and
2012. He is currently an Associate editor for Kidney International, and he was the Past

Guideline on Nutrition in CKD
President of International Society of Renal Nutrition and Metabolism 2010 – 2012, an Associate Editor of Journal of American Society of Nephrology 2006-2012, Director of the Master of Science in Clinical Investigation Program at VUSM 2005 - 2017 and member and Chair of American Board of Internal Medicine Nephrology Test Writing Committee 2008 - 2018. He is the recipient of National Kidney Foundation Joel Kopple Award, International Society of Renal Nutrition and Metabolism Thomas Addis Award and VUSM Excellence in Mentoring Translational Scientist Award. As a clinical investigator focused on mechanisms of disease and patient related outcomes, he is the principal investigator of a number of ongoing studies aimed at improving the outcomes and quality of life in patient populations ranging from early kidney disease, patients on maintenance dialysis and patients with acute kidney injury. He has published over 250 original articles, 50 editorial reviews and 20 book chapters. He is the co-editor of Handbook of Nutrition in Kidney Disease, 7th edition and Chronic Kidney Disease, Dialysis, and Transplantation, 4th edition.

George A. Kaysen, MD, PhD

Dr. Kaysen is an emeritus professor of Medicine and Biochemistry and Molecular Medicine at the University of California Davis School of Medicine. He was Chief of the Nephrology Division for 23 years at UC Davis and Acting Chair of Biochemistry and Molecular Medicine for 6 years. He is still actively engaged in research and in-patient care. His research interests are in the relationships between inflammation and nutrition and cardiovascular and infectious outcomes and regulation of lipoprotein structure and function in both patients and experimental animals with chronic kidney disease and/or proteinuria as well as regulation of albumin metabolism both in patients with CKD and with nephrotic range proteinuria. He received his MD and Ph.D at the Albert Einstein College of Medicine in the Bronx NY

Joel D. Kopple, MD

Dr. Kopple is a nephrologist who is Professor Emeritus of Medicine and Public Health at the David Geffen UCLA School of Medicine and UCLA Fielding School of Public Health. He served from 1982 to 2007 as the chief of the Division of Nephrology and Hypertension Guideline on Nutrition in CKD
at Harbor-UCLA Medical Center. Kopple's research focus has been on amino acid and protein metabolism and nutritional and metabolic disorders and their management in kidney disease and kidney failure. He has authored or coauthored many hundreds of peer-reviewed manuscripts, invited papers and chapters. He is an editor of many proceedings and symposia and an editor of the textbook entitled, Nutritional Management of Renal Disease. He founded the International Society of Renal Nutrition and Metabolism, the International Federation of Kidney Foundations, and World Kidney Day, served a central role in founding other institutions, and served as president of the National Kidney Foundation, the American Society of Parenteral and Enteral Nutrition, and other professional and scientific societies. Dr. Kopple is a Fellow of the American Society for Nutrition, the American Society of Nephrology and the National Kidney Foundation. He has received many awards including the David M. Hume Memorial Award by the National Kidney Foundation, the Robert H. Herman Memorial Award and the E.V. McCollum Award from the American Society for Nutrition, and the Belding Scribner Award of the American Society of Nephrology. Dr. Kopple has received honorary doctorate degrees from the University of Pavol Jozef Šafárik, the University of Szeged, and the University d'Auvergne. The National Kidney Foundation and its Council on Renal Nutrition designated the 'Joel D Kopple Award' in Renal Nutrition, which is annually granted to a distinguished individual for his/her efforts to advance the field of renal nutrition. The International Federation of Kidney Foundations has created a separate Joel D. Kopple Award which is given to a person or group that has made a major contribution to the health or well-being of people with or at risk for kidney disease.

Angela Yee-Moon Wang, MD, PhD, FRCP

Dr. Wang was graduated from the University of New South Wales, Australia and is Honorary Associate Professor, Associate Consultant at the University of Hong Kong, Queen Mary Hospital. She was the recipients of the NKF Joel D. Kopple Award 2018, John Maher Award of the ISPD 2006, and Travelling Lecturer Award of Asian and Pacific Federation of Clinical Biochemistry 2012. She is currently the President of the International Society of Renal Nutrition and Metabolism (ISRNM) and a Council member of the ISPD. She is a North and
East Asia Regional Board member of the International Society of Nephrology (ISN), Committee Member of the ISN-Advancing Clinical Trial Core Group, and Executive Committee member of the Standardized Outcomes in Nephrology (SONG) Initiative, workgroup member of the SONG-PD and SONG-HD CVD. She was also an Executive Committee Member of KDIGO (Jan 2015 - Dec 2017). She is a workgroup member of the NKF KDOQI Nutrition Guidelines in CKD and the ISPD PD Adequacy Guideline update (2017-2019). She chaired the ISPD Adult Cardiovascular and Metabolic Guidelines (2012 – 2015) and is a Subcommittee Chair of the ISPD PDOPPS. She was also a Core workgroup member of the first KDIGO – CKD-MBD guidelines (2007 – 2009). She also co-chaired the first KDIGO CKD-MBD Guideline Implementation Summit in Asia in 2018.

She is currently serving on the editorial board of JASN, CJASN, NDT (Editor of Cardiovascular Section), Am J Nephrol, Nephron Clin Pract (Associate Editor), European Medical Journal (EMJ)-Nephrology (Editor-in-Chief), Renal Replacement Therapy (Associate Editor), Nephrology (Subject Editor), J Ren Nutr, J Diabetes, Blood Purification, Biomedicine Hub, etc. She was previously an Associate Editor of AJKD and an International Editor of CJASN. Her main research interests are in CKD and dialysis complications, especially in the areas of cardiovascular disease, renal nutrition and metabolism.

**Disclosures:** Dr Wang reported no relevant financial disclosures.

**Evidence Review Team**

**Mary Rozga, PhD, RDN** is a Nutrition Researcher for the Evidence Analysis Center at the Academy of Nutrition and Dietetics. In this role, she works as a systematic review and guideline methodologist and works with expert practitioners, researchers and patient advocates on a wide variety of nutrition topics to create evidence-based information for dietitians. Prior to this position, Dr. Rozga worked in the academic setting with a focus on breastfeeding research, including providing peer-counseling breastfeeding support to low income women in the community setting. She has served as an Assistant Professor at Bowling Green State University, where she created a master’s course on Environmental Nutrition. Dr. Rozga has
published both primary and secondary research in peer-reviewed journals such as *The Journal of the Academy of Nutrition and Dietetics*, *Public Health Nutrition*, and the *Maternal & Child Health Journal*. Dr. Rozga received the 2015 Editorial Review Board Choice Research Article of the Year from the *Journal of Human Lactation*. Dr. Rozga earned a Bachelor’s degree in Dietetics from Central Michigan University, a Master’s degree in Nutrition Research from Bastyr University, and a PhD in Human Nutrition from Michigan State University, where she also completed her dietetic internship.

Financial Disclosure: Dr. Rozga reports no relevant financial relationships.

**Deepa Handu, PhD**, serves as a Senior Scientific Director for the Academy of Nutrition and Dietetics Evidence Analysis Library. She has methodological expertise in conducting systematic reviews and quantitative analysis in the field of nutrition. In her position at the Academy, she has led the development of a number of systematic reviews and clinical practice guidelines, and conducted research to improve evidence-based methods for the EAL. Dr. Handu previously has served as the Dietetic Internship Director at Edward Hines Jr. VA Hospital, Director of the Master of Science in Nutrition and Wellness program at Benedictine University, and Assistant Clinical Professor at Loyola University. Dr. Handu’s research interests lie in the areas of evidence-based methods/research methodology, public health nutrition, youth overweight prevalence and obesity risk, and diabetes. Her work has been published in refereed journals, she has published a book on Research Methodology, and she has delivered numerous professional presentations at the local, state, and national level. Dr. Handu earned her Ph.D. in Human Nutrition from Michigan State University.

Financial Disclosure: Dr. Handu reports no relevant financial relationships.


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