Guideline 6: Electrolytes
Objectives

• Interpret the guideline recommendations and supporting evidence related to electrolytes.
• Discuss implementation strategies for best clinical practices.

Outline

• Context and general considerations
• Phosphorus
• Calcium
• Acid-Base
• Potassium
• Sodium
Disclosures

Carrero

- **Research funding**: Astellas, AstraZeneca, Viforpharma
- **Speaker Bureau**: Viforpharma, Abbott, Fresenius
- **Advisory boards**: Baxter, Bayer
- **Guideline making**: 2020 KDOQI/AND, ESPEN 2021
- **Educational activities within nutrition in CKD**: Co-director of TNT outreach program at ISRNM
  Chair of the European Renal Nutrition working group at ERA-EDTA

St-Jules

- **Research funding**: Relypsa

20 years since the last guideline!

1st face to face meeting,
AND offices, Chicago 2016
Steps in conducting an evidence-based clinical guideline

Step 1: Formulate Questions
- Define scope, develop the Questions
  Adults, CKD 1-5 Tx 1985-2018

Step 2: Literature review
- Gather and Classify the Research

Step 3: Appraise Articles
- Critically Appraise Each Article

Step 4: Summarize
- Summarize the evidence in an Overview Table and Evidence Summary

Step 5: Grade
- Develop Conclusion Statement and Grade the Strength of the Supporting Evidence

All online in the AND library
Dozens of meta-analyses
GRADE Methodology

Assigns separate grades for:

1) Evidence Quality
2) Strength of Recommendation
How do statements look like?

**KDOQI-AND (2020)**

- **Population:** "In adults with CKD 1-5D"...
- **Strength of evidence:** "we recommend...." or "we suggest...."
- **What about**
- **What for:** outcome (with **quality of evidence grading**)
Every patient is unique

Guidelines assist and inform decisions, but do not rule out clinical judgements

You will see many statements graded as OPINION
Guideline 6: Electrolytes

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You will probably have questions

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General Considerations

Electrolyte intake is the sum of:
- Natural sources from food / beverages
- Artificial sources
  - food additives
  - medication excipients, tap water, etc.

Conventional dietary assessment methods cannot adequately capture:
- Electrolyte intake from additives
- Electrolyte losses from cooking methods

Guidelines often avoided nutrient prescriptions (recommended ranges of intake)

- Dietary electrolytes often chemically, biochemically or therapeutically non-equivalent
- Diet therapy should be individualized and continuous; requires nutrition assessment
- No recommendation is permanent; circumstances change (e.g., disease progression)

General Considerations

- Serum electrolyte levels are regulated by homeostatic mechanisms
- Electrolyte disorders are multi-factorial; many potential dietary / non-dietary causal components affecting:

  External Balance
  Ins: Intake + Bioavailability
  Outs: Excretion (Kidney + GI) + sweat and insensible losses

  Internal Balance
  Osmotic changes (i.e. intra- to extracellular communications)
  Organ exchange (i.e. bone turnover)

Only dietary interventions and studies that addressed dietary electrolyte intake/output/balance were considered

Studies of serum levels and pharmacological interventions were not considered
Phosphorus

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).

When making decisions about phosphorus restriction treatment, consider the bioavailability of phosphorus sources (e.g. animal, vegetable, additives) (OPINION).

Main difference with other guidelines:
1. Does suggest specific dietary PO4 range (previously 800-1000 mg/d, RDA 700 mg/d, not accounting for added PO4). Restrict if/when needed
2. Individualize treatment based on patient needs, clinician judgment and availability/tolerance of adjunctive therapies (binders)
3. Need to account for dietary PO4 sources, as they have different bioavailability
Effects of dietary phosphorus restriction on serum phosphate
(Evidence 1B, derived from 10 RCTs)

- In non-dialysis CKD:
  Phosphate restriction regimens reduces serum phosphate and urinary phosphorus excretion

  Protein restriction regimens reduce serum phosphate
  Feiten 2005; Gameata 201; Malvy 1999; Mircescu 2007; Rosman 1989.

- In maintenance hemodialysis (no studies in peritoneal dialysis):
  Phosphate restriction regimens reduces serum phosphate
  Lou 2012; Sullivan 2009.

Effect of Phosphate-Specific Diet Therapy in patients on hemodialysis

- Reduced serum phosphate vs controls in all studies
  (although overall certainty of evidence was low, primarily due to randomization issues and deviations from protocol)
  -0.87 mg/dL
  Mean difference (95% CI -1.40, -0.33)

- Reduced serum phosphate in patients with persistent hyperphosphatemia for 4–6 months
  (without compromising nutrition status)

- Trials were too varied in design, setting, and approach to appropriately pool in meta-analysis and were too limited in number to evaluate the timing, dose, and strategy of phosphate-specific diet therapy

Conclusion
Low-quality evidence suggests that diet counseling by a dietician is safe and efficacious treatment for persistent hyperphosphatemia in patients on hemodialysis.

Due to a scarcity of data, the workgroup cannot make a recommendation regarding the effect of dietary phosphorus control on clinical outcomes (\textit{knowledge gap}).

- Dietary phosphorus does not fully determine serum phosphate.
- Although trials of pharmacological serum phosphate reduction show efficacy in lowering serum phosphate, the effect of this electrolyte reduction on health outcomes is mixed.

Supporting Evidence (II)

Implementation

Phosphorus from plant-based protein foods (nuts, seeds, legumes) is lower than animal-based protein foods (meat, eggs)

Vegetarian Compared with Meat Dietary Protein Source and Phosphorus Homeostasis in Chronic Kidney Disease

Cross-over trial in CKD G4 patients. 7 days of vegetarian vs meat diet with the same phosphorus content (800 mg/day).

In advanced CKD, plant-based diets resulted in lower serum phosphate, urinary phosphate excretion and serum FGF-23.

Advise preparing foods at home, using wet cooking methods such as boiling (and then discarding the water); may be particularly useful with meats and legumes.

Inorganic phosphorus has high bioavailability. Restricting processed foods can reduce phosphorus intake. Phosphorus additives add ~300-400 mg of highly bioavailable phosphorus / day; additive-free alternatives generally available, but more expensive.

Educating patients to avoid food additives reduces (modestly) hyperphosphatemia. About 50% reduction in phosphorus content when compared to additives.

*Based on ~2,150 kcal/d diet

279 patients with ESKD and hyperphosphatemia
Concerns of phosphorus restriction

Is it possible to control hyperphosphataemia with diet, without inducing protein malnutrition?
Margarita Rafino, Eduardo de Bonis, Marisa Martin\(^1\), Sagrario Rebollo, Basilio Martin, Rosa Miquel, Marián Cobo, Domingo Hernández, Armando Torres and Victor Lorenzo

Advice natural foods that have low amounts of organic phosphorus along with higher amounts of protein to ensure adequate protein intake

Example: 3 oz pork loin = 146 mg phos/22 mg protein.
3 oz ham = 239 mg phos/19 gm protein

- If serum phosphate levels are on range, restrictions can be less strict.
- In patients with protein-energy wasting, poor appetite, nausea or weight loss, phosphorus restriction may cause further decline in nutritional status.
- Nutritional strategies aimed at maintaining kidney function and delaying disease progression may include a lower (animal) protein diet. This will complement a lower phosphorus intake.

Phosphorus Knowledge by staff

- Familiarize yourself with the phosphorus content of common foods and food groups. USDA and other web resources are available. Be sure to use updated information.

- Phosphorus restrictions need to be individualized and based on:
  - CKD stage and/or residual renal function
  - Mineral and bone status
  - CVD risk
  - Diet
Final tips

• See what works to maintain phosphorus levels in the normal range with the least dietary restriction

• Leave healthy foods containing naturally occurring phosphorus in the diet as much as possible:

• Keep potassium content in mind when recommending nuts, seeds, legumes and dairy

Phosphate Binders

• Medications taken with meals and snacks that bind phosphorus in the gut and remove it via the bowels, so it is not absorbed.

• Can be recommended when dietary limitations do not bring the phosphorus level into the desired range and further diet restrictions may lead to malnutrition and or patient frustration.

• There are several choices for phosphate binders. Recommendations are usually based on patient tolerance, GI side affects, calcium content and cost.
Calcium balance; a concerted action

In CKD Ca levels tend to slightly decrease in moderate/advanced CKD

- Too little Ca can lead to secondary hyperparathyroidism
- Too much Ca can lead to extraosseous calcification and subsequent CVD/death
**KDOQI-AND (2020)**

- 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).

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

- **Insufficient data to define optimal dietary calcium intake in adult patients on maintenance dialysis or with kidney Tx (knowledge gap)**

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**Supporting Evidence**

**A dietary calcium intake of approximately 800-1,000 mg/d maintains calcium balance in patients with CKD stages 3-4 who are not receiving active vitamin D analogs, at least in the short term.**

Similar to estimated average requirement (EAR-800-1000 mg/d) and recommended dietary allowance (RDA- 1000-1200 mg/d) for healthy individuals (IOM)

3 small trials in non-dialysis CKD:

- Martinez 1997. non-randomized clinical trial. Early CKD patients with a low protein (40g/d) and low phosphorus (600 mg/d) diet with versus without 0.5 g/d of calcium for 10 days. **High calcium led to reduced iPTh. Calcium, phosphate and calcitriol did not change.**

- Spiegel 2012. crossover balance study. 6 patients with CKD 3-4 and 6 controls consumed high (2,000 mg/d) versus low (800 mg/d) calcium diets for 9 days. **High calcium led to reduced iPTh and 1,25-dihydroxivitamin D decreased. Calcium and phosphate did not change.**

- Hill 2013. Randomized cross-over balance study. 8 patients with CKD stages 3-4 consumed a calcium diet of 2457 mg/day (1,500 mg of calcium from calcium carbonate + 957 mg/day of dietary calcium) versus placebo (957 mg/day of dietary calcium) for 3 weeks. **Serum calcium, phosphorus and iPTh did not change.**
Sources of calcium and absorption

- Elemental Calcium in foods 800-1000mg (similar to RDA)
- Dietary supplements + calcium-based binders (per 1000mg)
  - Calcium carbonate 400 mg
  - Calcium acetate 250 mg
  - Calcium citrate 200 mg

Vitamin D supplements + calcimimetics increase calcium absorption in the body
- D2 ergocalciferol, inactive vitamin D
- D3 cholecalciferol, inactive vitamin D
- calcitriol, active vitamin D
- cinacalcet, etelcalcetide

Implementation:

- **Hypercalcemia** is relatively common in patients receiving maintenance dialysis.
- **Observational evidence** links higher serum calcium concentrations to increased nonfatal cardiovascular events and mortality.
- **In the event of hypercalcemia**, the following adjustments are recommended:
  - If taking calcium-based phosphate binders: reduce dose or switch to a noncalcium phosphate binder.
  - If taking active vitamin D analogues: reduce dose or therapy discontinued until serum concentrations of calcium return to normal.
  - If hypercalcemia persists: consider using a low dialysate calcium concentration (1.5-2.0 mEq/L). Proceed with caution because observational studies have linked this approach with increased risk for arrhythmia and heart failure.
  - If the above does not work, consider restricting dietary calcium intake
Food Sources of Calcium (besides that supplements and fortified foods)

**Fruits + vegetables** – Green vegetables (most low bioavailability)

*Dairy* – milk, yogurt, some cheeses (high bioavailability)

**Fortified foods** – fortified cereals, juice, milk alternatives (soy, almond, rice), tofu

**Other foods** – Bones (e.g., canned finfish), almonds (low bioavailability)

*Also high phosphorus content*
Statements on Acid Load

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 1-4</td>
<td>Increase fruit and vegetable intake to reduce NEAP to reduce the rate of decline of residual renal function</td>
<td>2C</td>
</tr>
<tr>
<td>CKD Stage 3-5D</td>
<td>Bicarbonate or citric acid/sodium citrate supplementation to reduce NEAP to reduce the rate of decline of residual renal function</td>
<td>1C</td>
</tr>
<tr>
<td>CKD Stage 3-5D</td>
<td>Maintain serum bicarbonate levels at 24-26 mmol/L</td>
<td>Opinion</td>
</tr>
<tr>
<td>CKD Stage 3-5D</td>
<td>Oral bicarbonate improved nutrition status</td>
<td>Statement</td>
</tr>
</tbody>
</table>

Supporting Evidence: eGFR Decline

Population
- Stage 3 CKD, urine ACR >200 mg/g
- Non-malignant hypertension, no diabetes
- Metabolic Acidosis (Total CO₂ >22 and <24 mmol/L)
  n=108 (36 per group) matched on age, sex, race/ethnicity, eGFR and urine albumin

Intervention
1. Usual care (UC)
2. UC + 0.3 mEq/kg/d sodium bicarbonate (HCO₃⁻)
   (25.2 mEq/d)
3. UC + Fruit and vegetables (F+V) to reduce PRAL 50%
   (2-4 cups/d)

PRAL = (Pro (23%) + P (29%))
- (K (37%) + Mg (5%) + Ca (6%))
PRAL percentages derived from estimates from HD and controls (Kalantar-Zadeh et al., 2002)

HCO₃⁻: p <0.001 vs UC
F+V: p <0.001 vs UC

Mean (SD) presented; Graph developed using data from Goraya et al., 2020
Supporting Evidence: Nutritional Status

Population
- 6 non-dialyzed CKD (eGFR 3-19 mL/min/1.73m²)

Intervention (crossover)
- 3-day inpatient N-balance studies
- 0.7-1.2 mEq/kg/d NaCl and NaHCO₃⁻

Supporting Evidence: Nutritional Status

Protein Intake (g/kg/d)

MAMC (cm)

Albumin (g/L)

Graphs adapted from de Brito-Ashurst et al., 2009
Implementation Considerations

Potential Renal Acid Load (PRAL)
Acidic: Pro + P
Alkaline: K + Ca + Mg

Alkaline: F+V
Neutral: Milk/yogurt, nuts/seeds, legumes
Acidic: Cheese, grains, MPF, eggs

Considerations
1. ↑ fruit & vegetables
2. Substitute animal-based proteins for plant-based proteins or dairy
Statements on Potassium

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 3-5D &amp; Post-TX</td>
<td>Adjust dietary potassium intake to maintain serum potassium in the normal range</td>
<td>Opinion</td>
</tr>
<tr>
<td>CKD Stage 3-5D &amp; Post-TX</td>
<td>In patients with hypo- or hyper-kalemia, adjust dietary or supplemental potassium intake on patient’s individual needs and clinical judgment</td>
<td>Opinion</td>
</tr>
</tbody>
</table>

Note: No target value or range of recommended potassium intake

Supporting Evidence: Potassium

**Population**
- 8 non-diabetic HD, 8 controls
- Matched in age and sex

**Intervention**
1. 0.25 mg K/kg KCl
2. 0.25 mg K/kg KCl + 50 g Glucose

70-kg = 684 mg K+ (banana ≈ 450 mg K)

- Patients with CKD stages G3b-5D have impaired dietary potassium tolerance
- Transient postprandial hyperkalemia from large potassium bolus
Implementation Considerations

- Overall health goals of the patient
- Other causes of hyperkalemia (dietary and non-dietary): Medications, kidney function, hydration status, glycemic control, adrenal function, catabolic state, or gastrointestinal problems
- If hyperkalemia cannot be reversed, identify key sources of dietary potassium
- Recommend fruit, vegetables, and other low-potassium foods (food list)
- Demineralization using wet-cooking methods

Potassium Content of Foods

- Widely distributed in foods
- Possible to maintain dietary balance and quality while restricting dietary potassium
- Depends on the portion size (e.g., peanuts)

Figure from St-Jules & Shah, unpublished
Effect of Demineralization on Potassium

Ranges presented; graph developing using data from Jones, 2001

Restricting Dietary Potassium Intake

- Issues with dietary balance and variety
- Processed foods with potassium additives
- Demineralization
- Control portions of potassium dense foods
  - Beverages: coffee, tea, juice, milk
  - F+V: root vegetables, bananas, tomatoes (soups/ sauces), avocado, cooked greens, melons, kiwi
  - Protein Foods: nuts/seeds
## Statements on Sodium

<table>
<thead>
<tr>
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<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 3-5D &amp; Post-TX</td>
<td>Limit dietary sodium intake to 2,300 mg/d to lower BP and improve volume control</td>
<td>1B-1C</td>
</tr>
<tr>
<td>CKD Stage 3-5</td>
<td>Limit dietary sodium intake to 2,300 mg/d to reduce proteinuria</td>
<td>2A</td>
</tr>
<tr>
<td>CKD Stage 3-5D</td>
<td>Reduce dietary sodium intake to improve volume control and a more desirable body weight</td>
<td>2B</td>
</tr>
</tbody>
</table>
Supporting Evidence: Sodium

16 studies
4 cohort studies (He 2015; Mc Causland 2012; Mills 2016, Dong 2010).

**General considerations**
- Trials of short duration and small sample size.
- Focus on clinical endpoints (BP, inflammation, body weight, fluid and proteinuria).
- Hard outcomes (death, progression) rely upon observational evidence.
- In the vast majority of trials, the target sodium restriction was 2,000-2,300 mg/day
- Lack of consensus as to what constitutes a high sodium intake, which was either based on usual intake, or providing supplemental sodium to ensure high sodium intake, around 4,000 mg sodium/day = Limited applicability for implementation purposes.

### Population
- Stages 3-4 CKD
- HTN (SBP/DBP 130-169 / >70 mmHg)
  - 3.2 ± 1.1 anti-HTN meds
- N = 538 → n = 25 (randomized) → n = 20

### Intervention
**Phase I:** 2-wk crossover (1-wk run-in, 1-wk WO)
1. Low-Na diet (1,380 mg/d) + placebo
2. Low-Na diet + 2,760 mg Na (NaCl)
   - Weekly tailored education (diet history; in-person during visits and phone)
   - Handouts + daily checklists
   - Low-Na foods (1 frozen meal/day, snacks, breakfast cereal, cheese, bread)

**Phase II:** Maintenance
- Monthly education (phone, up to 6-mo)

### Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>BL</th>
<th>Low</th>
<th>High</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECV (L)</td>
<td>19.2 ± 3.7</td>
<td>20.0 ± 3.7</td>
<td>0.8 [0.4-1.2]</td>
<td></td>
</tr>
<tr>
<td>uAlb/Cr (g/mol)</td>
<td>21 (2-65)</td>
<td>9 (2-82)</td>
<td>27 (5-127)</td>
<td></td>
</tr>
<tr>
<td>uNa (g/24h)</td>
<td>2.9 (1.8-4.3)</td>
<td>1.7 (1.3-2.6)</td>
<td>3.8 (2.9-5.0)</td>
<td>2.1 (2.0-2.5)</td>
</tr>
</tbody>
</table>

BP (+1.3/1.2), ECF and uAlb values maintained at 6-mo (p >0.05)

McMahon et al., 2013a; McMahon et al., 2013b; Campbell et al., 2014
Implementation Considerations

• ~12% of dietary sodium from foods
  – 7-day dietary records
• 24-hour dietary recalls vs 24-hour urine
  – Men: r = 0.32
  – Women: r = 0.30

Mattes & Donnelly, 1991
Rhodes et al., 2013

Systematic Review of Urine Na⁺ in the U.S. (n = 38)

Bernstein & Willett 2010;92:1172-1180
Encouraging the Choice for Low Sodium

**Ideal**
- Preparing meals at home
- Limiting intake of processed foods

**Less Bad**
- Substitutions (compare similar products)
- Better choices when eating/ordering out
- Demineralization

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### Implementation Considerations (II)

**Graph developed using data from Vollmer et al., 2001**

Values presented as mean (95% CI)

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**DASH-Sodium Study (n=168)**
- HTN: 140-159 / 90-95 mmHg
- No CKD, anti-HTN medications

**Intervention**
- Controlled feeding study (30 days/tx)
- Control (Western diet) vs DASH
- 1,150 mg and 3,450 mg sodium per 2,100 kcal
- Non-additive interaction between dietary factors (e.g., potassium) and sodium on blood pressure
Implementation Considerations (III)

- Chemical analysis of meat and poultry products with nutrient content claims for reduced sodium, and matched non-sodium reduced counterparts
- +184 mg sodium (95% CI 90, 279 → +44 ± 43%)

Graph developed using data from Parpia et al., 2018; Values presented as mean (range)
Additional Resources

- A Clinical Guide to Nutrition Care in Kidney Disease (Academy)
- National Kidney Diet (Academy)
- Pocket Guide to Nutrition Assessment of the Patient with Kidney Disease (NKF)
- Renal Dietitian Certificate of Training (Academy)
- Standards of Practice and Standards of Professional Performance for Renal Dietitians (Academy)
- Strategies I: Essentials of Nutrition Practice for Chronic Kidney Disease (NKF SCM)
- Strategies II: Advanced Practice in Renal Nutrition (NKF SCM)
- Webinar Series: Nutrition in CKD Guideline Update (NKF & Academy)

NKF: www.kidney.org
Academy: www.eatright.org

Thank You!