Sodium and Potassium Intake and Cardiovascular and Bone Health: How Important is the Ratio?

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Disclosures

Boards/Scientific Advisory Committees –
  ILSI
  Showalter
  Pharmavite

Grants –
  NIH
  Alliance Potato Research and Education
  ILSI - NA
Questions being Addressed

• How do Na and K affect heart and bone?

• Is the Na:K ratio more (or equally as) as important as individual nutrients? What is the strength of the evidence?

• How can recommendations be achieved?
  – Increasing K some and reducing Na some
  – Should recommended intakes be tied to energy?
K and Na Biological Functions

• $K^+$ = major intracellular cation.
• $Na^+$ = extracellular cation.
• Resting cellular-membrane potential and the propagation of action potentials in neuronal, muscular, and cardiac tissue.
• Fluid balance and electrolyte regulation.
• Acid-base balance.
• Enzyme activities.
Role of Salt

Affects Heart and Bone

Is it the cation or anion?
K and CVD-Related Deaths

RCT in 1981 in elderly men

59% reduction in CVD morality

Chang et al, AJCN 83:1289-96, 2006
### HR (95% CI) for Highest vs Lowest Quartile of Na/K Intake

<table>
<thead>
<tr>
<th></th>
<th>US (NHANES III)</th>
<th>NIPPONDATA 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortalities</td>
<td>1.46 (1.27-1.67)</td>
<td>1.16 (1.06-1.27)</td>
</tr>
<tr>
<td>CVD</td>
<td>1.46 (1.11-1.92)</td>
<td>1.39 (1.20-1.61)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2.15 (1.4-3.12)</td>
<td>1.43 (1.17-1.76)</td>
</tr>
</tbody>
</table>

HRs for Na/K were higher than for either alone

Mineral Intakes and BP in US Adults

The Data

n = 4382 women and 4395 men

Weaver et al., Under review.
Aim

Predict blood pressure from sodium, potassium, calcium and magnesium intake and their ratios from food and supplements
Factors Predicting Blood Pressure

• Models were developed for predicting systolic blood pressure (SBP) and diastolic blood pressure (DBP).

• Age, race/ethnicity explained 29% SBP and 11% DBP in women compared to 15% for SBP and 15% for DBP in men.

• Diet explained ~1% of the variation.
Mineral Ratio Intake Distributions in US Adults

Female

Na/K

Normal Probability Density

Log Na/K Ratio

Male

Na/Ca

Normal Probability Density

Log Na/Ca Ratio

Shaded area = % below recommended ratios
Na:K intake predicted (P<0.01) SBP in females and males but not Na or K alone
Adolescents (12-14 y)
NHANES 1999-2014

Hypertension greater at Na:K ratios >2.5
Much Less Known on Na/K and Bone

Relationship between Na/K and bone must be through Ca metabolism.
Renal Calcium Reabsorption

**PCT: 60-70%**
- Paracellular.
- Competes with Na for reabsorption.

**TAL: 25%**
- Paracellular.
- Dependent on Na reabsorption and K secretion.

**DCT-PCT: 8-10%**
- Transcellular, hormone dependent (PTH, Vit D.).
- Some activity facilitated by Na reabsorption.

Average urinary Ca loss = 1mmol (40mg) Ca/100mmol (2290mg) Na.

Moor and Bonny, Am J Physiol Renal Physiol, 310:1337-1350, 2016
Sodium Retention in Black and White Female Adolescents in Response to Salt Intake
Dietary salt varied

Low Na diet → 1.3 g/d
High Na diet → 4 g/d
Traditional Theory

• Sodium intake and excretion are in balance within one day after drastic shifts

• Total body Na+ content is maintained constant within narrow limits
Urinary sodium excretion
(Mean ± SEM)


* Significantly different from whites at p<0.05
Effects of Salt intake on Calcium Excretion and Balance in Black and White Adolescents

Urinary calcium excretion
(Mean ± SEM)

Calcium retention
(Mean ± SEM)

Na and Ca share same transporters in kidney.

Wigertz et al., AJCN 81:845-50, 2005
Urinary Na from 1 Black Girl and 1 White Girl on Controlled High Na Diet

**Black Girl**

**White Girl**

Weaver et al., J Hyperten 34:1290-1297, 2016
Distribution of 24 h Urinary Na on Controlled High Na Diet

16% misclassified as low Na intake

Weaver et al., J Hyperten 34:1290-1297, 2016
Effect of K citrate supplementation after 6 months in older men and women on net acid excretion and calcium retention.

(Modified from Moseley et al., JBMR 28:497-504, 2013)
2 yr RCT of 2400 mg/d K-citrate in 201 men and women >65 y

Femoral Neck BMD

Spine, total hip ~

Jehle JCEM doi: 10.1210/jC.2012-3099
Interaction of Na:Ca inspiration for a Na:K trial

Predictions of Ca x Na on bone loss in postmenopausal women from 2-y longitudinal study

Devine et al., AJCN 62:470, 1995

Predicts no loss of total hip bone density by ↑891 mg Ca or halving Na intake.
# IDEAL Na/K Ratio?

No currently accepted ratio.

<table>
<thead>
<tr>
<th>Molar Ratio</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on DRI AIs</td>
<td>I 0.83</td>
</tr>
<tr>
<td>Pre-agriculture revolution estimate</td>
<td>&lt;0.3</td>
</tr>
</tbody>
</table>

**Intersalt:**
- Yanomamo, Brazil 0.01
- Western 3
- Asian 5
- Tianjin, China 7.58
- X of 32 countries 3.24

**Recommended targets**
- WHO 1.0
- TOHP follow-up 1-2
- Interim goal* 2

Can Recommendations be Achieved? Nutrients in the USDA Food Pattern at Each Energy Level

It takes 3000 kcal to meet current dietary recommendations for potassium intake on American diets. At 1800 kcal and above, 1500mg sodium goal is no longer attained.

<table>
<thead>
<tr>
<th>Energy Level (kcal)</th>
<th>1000</th>
<th>1200</th>
<th>1400</th>
<th>1600</th>
<th>1800</th>
<th>2000</th>
<th>2200</th>
<th>2400</th>
<th>2600</th>
<th>2800</th>
<th>3000</th>
<th>3200</th>
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<tbody>
<tr>
<td>Nutrient</td>
<td>Units</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Energy</td>
<td>kcal</td>
<td>992</td>
<td>1200</td>
<td>1389</td>
<td>1602</td>
<td>1797</td>
<td>1997</td>
<td>2190</td>
<td>2384</td>
<td>2583</td>
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<td>2985</td>
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<tr>
<td>Protein</td>
<td>g</td>
<td>44</td>
<td>55</td>
<td>65</td>
<td>83</td>
<td>87</td>
<td>91</td>
<td>100</td>
<td>106</td>
<td>111</td>
<td>118</td>
<td>120</td>
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<tr>
<td>Carbohydrate</td>
<td>g</td>
<td>128</td>
<td>155</td>
<td>184</td>
<td>203</td>
<td>234</td>
<td>260</td>
<td>287</td>
<td>312</td>
<td>343</td>
<td>376</td>
<td>396</td>
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<tr>
<td>Fiber, total dietary</td>
<td>g</td>
<td>14</td>
<td>17</td>
<td>21</td>
<td>25</td>
<td>28</td>
<td>30</td>
<td>34</td>
<td>37</td>
<td>41</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Total lipid (fat)</td>
<td>g</td>
<td>36</td>
<td>43</td>
<td>47</td>
<td>55</td>
<td>61</td>
<td>71</td>
<td>77</td>
<td>86</td>
<td>92</td>
<td>99</td>
<td>111</td>
</tr>
<tr>
<td>Sat. Fat</td>
<td>g</td>
<td>9.7</td>
<td>11.2</td>
<td>12.3</td>
<td>14.0</td>
<td>15.8</td>
<td>18.7</td>
<td>20.1</td>
<td>22.5</td>
<td>24.0</td>
<td>25.7</td>
<td>28.4</td>
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<tr>
<td>Mono. Fat</td>
<td>g</td>
<td>13.1</td>
<td>15.7</td>
<td>17.3</td>
<td>20.0</td>
<td>22.4</td>
<td>26.1</td>
<td>28.4</td>
<td>31.4</td>
<td>33.8</td>
<td>36.2</td>
<td>40.7</td>
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<tr>
<td>Poly. Fat</td>
<td>g</td>
<td>10.9</td>
<td>12.8</td>
<td>13.7</td>
<td>16.4</td>
<td>18.2</td>
<td>20.9</td>
<td>22.8</td>
<td>25.0</td>
<td>27.2</td>
<td>29.1</td>
<td>33.5</td>
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<tr>
<td>Calcium</td>
<td>mg</td>
<td>751</td>
<td>803</td>
<td>849</td>
<td>1184</td>
<td>1221</td>
<td>1235</td>
<td>1290</td>
<td>1323</td>
<td>1374</td>
<td>1416</td>
<td>1434</td>
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<tr>
<td>Iron</td>
<td>mg</td>
<td>8</td>
<td>10</td>
<td>13</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>20</td>
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<td>26</td>
<td>26</td>
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<tr>
<td>Magnesium</td>
<td>mg</td>
<td>169</td>
<td>212</td>
<td>250</td>
<td>310</td>
<td>336</td>
<td>351</td>
<td>394</td>
<td>418</td>
<td>457</td>
<td>491</td>
<td>509</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>mg</td>
<td>886</td>
<td>1052</td>
<td>1195</td>
<td>1562</td>
<td>1643</td>
<td>1690</td>
<td>1836</td>
<td>1932</td>
<td>2046</td>
<td>2156</td>
<td>2203</td>
</tr>
<tr>
<td>Potassium</td>
<td>mg</td>
<td>1667</td>
<td>2059</td>
<td>2374</td>
<td>2971</td>
<td>3272</td>
<td>3478</td>
<td>3836</td>
<td>3945</td>
<td>4275</td>
<td>4544</td>
<td>4780</td>
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<tr>
<td>Sodium</td>
<td>mg</td>
<td>885</td>
<td>1088</td>
<td>1265</td>
<td>1527</td>
<td>1666</td>
<td>1722</td>
<td>1883</td>
<td>2028</td>
<td>2153</td>
<td>2296</td>
<td>2329</td>
</tr>
</tbody>
</table>

Diet in American Children Falls Short of Guidelines

DASH Accordance Scores in 9793 US aged 8-18y from NHANES 2003-2012

Score range 0-9

Total fat
Saturated fat
Protein
Cholesterol
Fiber
Calcium
Magnesium
Potassium
Sodium

Range mean scores 1.48-2.14

All Low!

Cohen et al. JAND 2017; 117:1437-1444
Should DRIs for Na:K be energy adjusted?

High correlation between Na and Energy in foods: $r=0.81$  
K and Energy in foods: $r=0.72$


For sodium target of 0.75 mg/Kcal:

<table>
<thead>
<tr>
<th>Energy (Kcal/d)</th>
<th>Na (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1600</td>
<td>1200</td>
</tr>
<tr>
<td>2000</td>
<td>1500</td>
</tr>
<tr>
<td>2400</td>
<td>1800</td>
</tr>
<tr>
<td>2800</td>
<td>2100</td>
</tr>
<tr>
<td>3200</td>
<td>2400</td>
</tr>
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# Status of Evidence for Dietary Na, K, Na:K and Cardiovascular Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na Adults:</td>
<td>Strong dose-response, generalizable for BP</td>
<td>Weak ability to assess diet, weak chronic disease outcome evidence</td>
</tr>
<tr>
<td>K Adults:</td>
<td>Moderate lack dose-response</td>
<td>Moderate-lack controlled feeding studies</td>
</tr>
<tr>
<td>Na:K ratio Effect may be stronger but less studied</td>
<td>RCT data lacking; only observational evidence</td>
<td>Children: None</td>
</tr>
</tbody>
</table>
### Status of Evidence for Dietary Na, K, Na:K and Bone Outcomes

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>No RCTs with strong disease measures</td>
</tr>
<tr>
<td>Some evidence in adults and children with biomarkers</td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>Scanty and only adults</td>
</tr>
<tr>
<td>1 dose-response-Ca balance</td>
<td></td>
</tr>
<tr>
<td>1 RCT and BMD</td>
<td></td>
</tr>
<tr>
<td>Na:K ratio</td>
<td>Non-existent</td>
</tr>
</tbody>
</table>
Sodium: How do you set an EAR for a nutrient to limit?

The purpose of the RDA/EAR is to prevent deficiency

“Under conditions of maximal adaptation and without sweating, the minimal amount of sodium required to replace losses is estimated to be no more than 0.18 (8 mmol)/day.”—IOM, 2005

“The AI for sodium is set for young adults at 1.5 g (65 mmol)/day to ensure the overall diet provides an adequate intake of other important nutrients…”—IOM, 2005

Is there evidence for sodium deficiency in normal, acclimatized individuals at intakes below 1500 mg/d?
Sodium: How do you set an EAR for a nutrient to limit?

The purpose of the UL is to prevent toxicity

“The adverse effects of higher levels of sodium intake on blood pressure provide the scientific rationale for setting the Tolerable Upper Intake Level (UL).”—IOM, 2005

“It is well-recognized that the current intake of sodium for most individuals in the United States and Canada greatly exceeds both the AI and UL.”—IOM, 2005

If excess sodium intake is problematic (and there’s little evidence of deficiency in normal individuals) should we focus on revising the UL?
Research Gaps

• Scant data in children using controlled feeding studies for heart and bone outcomes. For Na – limited generalizability and dose-response. For K – no data.

• The Na:K ratio requires more study – fixing one and varying other so dose and ratio effects are understood.