Salt Intake and Cardiovascular Risk

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Outline

• Evidence linking salt and blood pressure

• Evidence linking salt and cardiovascular disease

• Challenges studying salt and cardiovascular disease

• Salt, CKD, and cardiovascular disease
Modern Western Diet

High sodium intake
- Lack of renal adaptation and other defects in sodium excretion
  - Retention of sodium by the kidneys
  - Excess of sodium in the body
    - Extracellular fluid volume expansion
      - Excess of cellular sodium
        - Release of digitalis-like factor
          - Na⁺/K⁺-TPase
            - Vascular smooth-muscle cell contraction
              - Deficit of cellular potassium
                - Increased peripheral vascular resistance

Low potassium intake
- Ineffective potassium conservation
  - Excessive renal and fecal potassium loss
  - Deficit of potassium in the body

↑BP with age associated with higher salt intake (INTERSALT) – 52 communities worldwide, n=10,079

Increase in SBP with Age (mmHg per yr)

R = 0.566
P = <0.001

↑6 gm/day (100 mmol sodium) over 30 years → ↑SBP 9mmHg

Adapted Intersalt, BMJ 1988;297:319-32
The Effect on Systolic and Diastolic Blood Pressure of Reduced Sodium Intake and the DASH Diet

- 412 participants with prehypertension or Stage 1 hypertension
- High Sodium 140-150 mmol
- Intermediate 100-110 mmol
- Low Sodium 60-70 mmol

The Effect on Systolic Blood Pressure of Dietary Sodium Intake, According to Subgroup

Relation between the net change in 24-hour urinary sodium excretion and blood pressure in the meta-analysis

He, F. J. et al. Hypertension 2003;42:1093-1099
Outline

• Evidence linking salt and blood pressure

• Evidence linking salt and cardiovascular disease
Direct evidence for salt and CVD

Possibly independent of blood pressure
- Endothelial damage, direct effect on LVH, vascular reactivity
- Adverse effects of sympathetic, RAAS activation

Observational studies of CVD:
- Meta-analysis (Strazulloo, BMJ 2009) per 6 gm salt
  - Stroke: RR=1.23 (95% CI=1.06-1.43), p=0.007
  - CVD: RR=1.14 (95% CI=0.99-1.32), p=0.07
Chang (AJCN 2006)

- Five kitchens of veterans’ home in Taiwan
  - 1981 veterans
  - 40% were hypertensive

- Kitchens cluster-randomized to potassium-enriched (lower Na) or regular salt (‘95-’99)

- Significant reduction in CVD mortality
  - RR = 0.59 (95% CI = 0.37-0.95)

- Experimental group lived longer (0.3-0.9 yrs)
  - Spent less ($426/yr) on inpatient care for CVD
Cumulative hazard ratios (HRs) of cardiovascular disease-related deaths for the treatment and control groups

TOHP I and II Trials of Blood Pressure

• TOHP I (1987-1990)
  – DBP 80-89, aged 30-54 years, 18-month fu, 10 sites
  – 2,182 randomized participants, 744 in sodium arm

• TOHP II (1990-1995)
  – DBP 83-89, aged 30-54 years, overweight, 3-4 year fu
  – 2,382 randomized participants

• TOHP Follow-up
  – Observational follow-up 10-15 and 5-10 yrs after I and II
  – 4,526 participants
  – Medical records/death linkage
  – Intent to treat
TOTAL CVD by Randomized Sodium Intervention in TOHP Follow-up Study

<table>
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<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
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<tbody>
<tr>
<td>Adjusted for Demographics</td>
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<tr>
<td>Overall</td>
<td>0.75</td>
<td>0.57-0.99</td>
<td>0.044</td>
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<tr>
<td>Adjusted for Demographics, BS Wt and Na</td>
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<tr>
<td>Overall</td>
<td>0.70</td>
<td>0.53-0.94</td>
<td>0.018</td>
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<tr>
<td>Phase I</td>
<td>0.48</td>
<td>0.25-0.92</td>
<td>0.027</td>
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<tr>
<td>Phase II</td>
<td>0.79</td>
<td>0.57-1.09</td>
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</table>
Cumulative Incidence of CVD Adjusted for Clinic, Age and Sex

TOHP I

Cumulative Incidence of CVD or Death

Follow-up Years

Cumulative Incidence of CVD or Death

Na Control
Active Na
Cumulative Incidence of CVD Adjusted for Clinic, Age and Sex

TOHP II

Cumulative Incidence of CVD or Death

Follow-up Years

Na Control
Active Na
Outline

• Evidence linking salt and blood pressure

• Evidence linking salt and cardiovascular disease

• Challenges studying salt and cardiovascular disease
Salt intake in the United States

• Recommended daily salt intake:
  – < 5.8gm/day (<100 mmol sodium or 2300 mg)
    • 1 gm salt = approx 17 mmol or 400 mg sodium

• WHO recommendations
  – <5 gm/day (<85 mmol sodium or 2000 mg)

• Current daily intake in US:
  – 9.4 gm/day (3700 mg sodium)
Average daily salt intake in male and female Americans, as ascertained from 24-hour dietary recall, 2005-2006

Mean (95% CI) 24-h urinary sodium excretion (mg/24 h) by study year (US studies)

Where is the salt?

80% in processed or pre-prepared foods

Sources: Mattes et al.
## Table 1a. Mean Intake of Sodium, Mean Intake of Energy, and Percentage Sodium Contribution of Various Foods Among US Population, by Age, NHANES 2005–06

<table>
<thead>
<tr>
<th>Rank</th>
<th>Food Group</th>
<th>All Persons</th>
<th>2-18</th>
<th>2-3</th>
<th>4-8</th>
<th>9-13</th>
<th>14-18</th>
<th>19+</th>
<th>19-30</th>
<th>31-50</th>
<th>51-70</th>
<th>71+</th>
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<td>Yeast breads</td>
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<td>Chicken and chicken mixed dishes</td>
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<td>3</td>
<td>Pizza</td>
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<td>Pasta and pasta dishes</td>
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<td>5</td>
<td>Cold cuts</td>
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<td>Condiments</td>
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<td>Mexican mixed dishes</td>
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<td>8</td>
<td>Sausage, frankfurts, bacon, and ribs</td>
<td>4.1</td>
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<td>Regular cheese</td>
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<td>Grain-based desserts</td>
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<td>12</td>
<td>Beef and beef mixed dishes</td>
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<td>2.9</td>
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<td>Rice and rice mixed dishes</td>
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<td>14</td>
<td>Eggs and egg mixed dishes</td>
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<td>1.9</td>
<td>2.4</td>
<td>2.7</td>
<td>2.4</td>
<td>2.7</td>
<td>3.0</td>
<td>2.9</td>
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</tbody>
</table>
Sources of salt in our grocery bags

- 35% from cereal & cereal products
  - breads, cereals, pastries
- 26% from meat & meat products
- 8% from milk & milk products
  - milk, cheese

Source: http://www.actiononsalt.org.uk
Why do food manufacturers use so much salt?

- Preservative
- Weight of food

Taste
- Inexpensive way to add flavor
- Habituated to very salty food
- Can be unlearned
  - (6 wk down regulation of salt taste receptors)
Less sodium intake when adding salt at the table

Beauchamp et al. JAMA 1987
Salt intake (g/day by 24 hr urine)

Diastolic BP (mmHg)

Stroke mortality (1/100000)

Experience around the world

• Japan
  – Educational efforts in the 60’s resulted in measurable decreases in salt intake, blood pressure, and stroke
  – Targeted individual education because most intake from salt added during cooking and on table.

• UK
  – Mostly salt from processed/prepared foods. Set standards, efforts directly with food manufacturers, 10% over the first 3 years

• Other countries with sodium reduction efforts
Percent change in incident CHD with 3 gm/day reduction in dietary salt

Comparing salt reduction to other preventive measures (deaths 2010-2019)
Reducing salt ➔ reducing costs

- WHO estimates $1 per person to reduce salt through regulatory means, public campaigns, monitoring.
  - More cost effective than treating all hypertensives
  - Actually cost savings even if only modest reductions in salt achieved.

- Gradual reduction over the decade to 1 gm/day reduction ➔ 7 dollars saved in healthcare for 1 dollar spent.
Outline

• Evidence linking salt and blood pressure
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• Challenges studying salt and cardiovascular disease
• Salt, CKD, and cardiovascular disease
Salt, CKD, and cardiovascular disease


• **Night-time “non-dipping” in CKD may contribute to CVD risk**
  – Nocturnal hypertension compensates for diminished daytime natriuresis - enhances pressure natriuresis at night. Kimura, Dohi, Fukuda, Hypertension Research 33, 515-520 (June 2010)

Sodium restriction in ESRD

2 site dialysis unit comparison (Kayikcioglu...Ok, Nephrol. Dial. Transplant. (2009) 24 (3): 956-962)

- Site A - Salt <5 gm, intensive ultrafiltration to maintain predialysis BP <140/90 without meds
- Site B – Medications to control blood pressure

- Comparison of patients at each center at least one year.
- Age and dialysis duration distribution similar between centers.
<table>
<thead>
<tr>
<th></th>
<th>Centre A (n = 190)</th>
<th>Centre B (n = 204)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Use of antihypertensive medication (n = %)</td>
<td>13 (7%)</td>
<td>86 (42%)</td>
<td>0.001</td>
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<tr>
<td>ACE-/I or ARB</td>
<td>8</td>
<td>27</td>
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<td>Calcium channel blocker</td>
<td>1</td>
<td>43</td>
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<tr>
<td>Beta blocker</td>
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<td>3</td>
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<tr>
<td>Furosemide</td>
<td>1</td>
<td>1</td>
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<td>Combination of two medications</td>
<td>1</td>
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<td>Interdialytic weight gain (kg)</td>
<td>2.29 ± 0.83</td>
<td>3.31 ± 1.12</td>
<td>0.0001</td>
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<td>Interdialytic weight gain (kg for 70 kg man)</td>
<td>2.61 ± 0.98</td>
<td>4.05 ± 1.52</td>
<td>0.0001</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>126 ± 15</td>
<td>126 ± 21</td>
<td>ns</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>75 ± 12</td>
<td>76 ± 11</td>
<td>ns</td>
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<td>Pulse pressure (mmHg)</td>
<td>51 ± 9</td>
<td>50 ± 12</td>
<td>ns</td>
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<td>Systolic BP ≥140 (%)</td>
<td>18</td>
<td>37</td>
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<td>Diastolic BP ≥90 (%)</td>
<td>12</td>
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<td>Patients with systolic BP ≥140 and/or diastolic BP ≥90</td>
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<tr>
<td>At the time of starting the HD programme</td>
<td>78</td>
<td>83</td>
<td>ns</td>
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<tr>
<td>Current situation</td>
<td>19</td>
<td>37</td>
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<td>Intradialytic hypotension (number of episode per 100 HD sessions)</td>
<td>11</td>
<td>27</td>
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<td>Centre-A (n = 190)</td>
<td>Centre-B (n = 204)</td>
<td>P-value</td>
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<td><strong>LA indices</strong></td>
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<td>LA index (cm/m^2)</td>
<td>2.40 ± 0.34</td>
<td>2.74 ± 0.53</td>
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<td>LA volume index (mL/m^2)</td>
<td>29.5 ± 10.0</td>
<td>36.7 ± 21.7</td>
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<td><strong>LV measurements and indices</strong></td>
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<td>LV diastolic index (cm/m^2)</td>
<td>2.61 ± 0.33</td>
<td>2.97 ± 0.64</td>
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<td>LV end-systolic index (cm/m^2)</td>
<td>1.60 ± 0.29</td>
<td>1.96 ± 0.47</td>
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<td>Interventricular septal index (cm/m^2)</td>
<td>0.79 ± 0.13</td>
<td>0.83 ± 0.14</td>
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<td>Posterior wall index (cm/m^2)</td>
<td>0.76 ± 0.11</td>
<td>0.83 ± 0.11</td>
<td>0.0001</td>
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<td>LV ejection fraction (%)</td>
<td>68 ± 10</td>
<td>63 ± 09</td>
<td>0.0001</td>
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<tr>
<td>LV fractional shortening (%)</td>
<td>39 ± 8</td>
<td>35 ± 6</td>
<td>0.0001</td>
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<td>LV mass indexed to height^{2.7} (g/m^{2.7})</td>
<td>59 ± 16</td>
<td>74 ± 27</td>
<td>0.0001</td>
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<tr>
<td>LV hypertrophy (%)\textsuperscript{a}</td>
<td>124 (74%)</td>
<td>171 (88%)</td>
<td>0.001</td>
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<td><strong>Pulsed Doppler parameters</strong></td>
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<tr>
<td>Mitral-inflow E (cm/s)</td>
<td>73 ± 22</td>
<td>76 ± 27</td>
<td>ns</td>
</tr>
<tr>
<td>Mitral-inflow A (cm/s)</td>
<td>83 ± 18</td>
<td>82 ± 25</td>
<td>ns</td>
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<tr>
<td>Deceleration time (min/s)</td>
<td>0.23 ± 0.06</td>
<td>0.28 ± 0.07</td>
<td>0.0001</td>
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<td>Isovolumic relaxation time (min/s)</td>
<td>0.08 ± 0.01</td>
<td>0.12 ± 0.02</td>
<td>0.0001</td>
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<td>Mitral-inflow A-wave duration (min/s)</td>
<td>0.14 ± 0.02</td>
<td>0.16 ± 0.03</td>
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<td>E/A ratio</td>
<td>0.90 ± 0.31</td>
<td>0.96 ± 0.33</td>
<td>0.076</td>
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<tr>
<td>Mitral valve lateral annulus Ee/Ae (min/s)</td>
<td>0.99 ± 0.43</td>
<td>0.89 ± 0.41</td>
<td>0.034</td>
</tr>
</tbody>
</table>
Sodium restriction in heart failure

Hospitalization (IV Class)
Hypertonic Saline solution → i.v. furosemide (250-500 mg bid)
120 mmol Na →
Compensated state (II Class)
120 mmol Na → oral furosemide (250-500 mg bid)
Discharge (II Class)
120 mmol Na → oral furosemide (250-500 mg bid)
30 days after Compensated Patients (II Class) (232 patients)
Randomization
80 mmol Na (114 patients) (oral 250-500 mg bid furosemide)
120 mmol Na (118 patients) (oral 250-500 mg bid furosemide)
Follow-up (180 days)
Readmissions (30 pts)
Mortality (15 pts)
Readmissions (9 pts)
Mortality (6 pts)
Outcomes at 180 days

In normal sodium arm vs. low at 180 days:

• Greater diuresis
• Lower body weight
• Lower creatinine
  • (2.1 vs. 1.4 mg/ml)
• Lower BUN
• Lower BNP

In low sodium arm

• Increased aldosterone
• Increased PRA
Conclusions

• Lower dietary salt lowers blood pressure
  – May be particularly beneficial in CKD as a salt-sensitive state

• Lower dietary salt lowers CVD risk.
  – Via blood pressure lowering, possibly other direct mechanisms
Conclusions

• Both clinical management and research are complicated by high salt food environment.
  – Most of our patients are consuming well above guideline targets, cannot comply with recommendations without substantial personal or environment changes.

• Only few studies examining salt reduction in CKD or ESRD and CVD outcomes
  – Have the potential for high yield results