Serum chloride is a mortality risk predictor in type 2 diabetes mellitus – analysis of 91,159 patients in the West of Scotland

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Background

- Chloride is the principal extracellular anion in the body

- Chloride functions
  - Maintenance of osmotic pressure
  - Acid-base balance
  - Muscular activity
  - Movement of water between fluid compartments

- >85% of chloride is consumed as sodium chloride (salt)

- Sodium chloride (salt) is known to increase blood pressure and CV risk

- Evidence that the chloride component of NaCl may have a specific role in salt sensitivity
Outcome studies

Belgian Inter-university Research on Nutrition and Health (BIRNH)
- General population, 10 year follow up
- 9106 participants,

Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM)
- Heart failure population
- 2679 participants with bloods, post-hoc analysis
- Each SD increase in chloride associated with reduction in all-cause mortality

Outcome studies

Glasgow Blood Pressure Clinic (GBPC)

- 12,968 treated hypertensive patients, 35 year follow up
- Serum chloride <100 was associated with 20% higher all cause mortality, CV and non-CV mortality

Outcome studies

Renal Failure

- 923 pre-dialysis CKD patients, median follow up 33 months
- Increased risk of primary outcome (death or CV event) in Q1 ($\text{Cl}^- < 103.9 \text{mEq/L}$) and Q4 ($\text{Cl}^- > 108.1 \text{mEq/L}$)

Aim

- To determine if serum chloride is associated with mortality risk in adults with type 2 diabetes mellitus
Methods

Study population
- Data from NHSGGC SafeHaven
- 91,159 adults with T2DM
- Patients stratified into 2 groups: serum
  - Serum chloride <100 mmol/L and ≥ 100 mmol/L
- 10 years follow up

Survival analysis
- Cox-PH model used to study the association between serum chloride and mortality
- Adjusted for age, sex, serum sodium
Outcomes

Primary
- All-cause mortality

Secondary cardiovascular outcomes
- Cardiovascular death
- Death from MI
- Death from heart failure
- Death from stroke
- Death from cancer
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>All N= 91,159</th>
<th>CI- &lt;100 mmol/L N=13,459</th>
<th>CI- ≥100 mmol/L N=77,757</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years (SD)</strong></td>
<td>60.0 (15.7)</td>
<td>60.6 (16.9)</td>
<td>59.9 (15.5)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Female, N (%)</strong></td>
<td>42774 (47%)</td>
<td>6270 (47%)</td>
<td>36504 (47%)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Serum chloride, mmol/L (SD)</strong></td>
<td>102.9 (3.6)</td>
<td>96.7 (3.0)</td>
<td>103.9 (2.5)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Serum sodium, mmol/L (SD)</strong></td>
<td>138.6 (3.1)</td>
<td>135.3 (3.8)</td>
<td>139.2 (2.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
All-cause mortality

n at risk 91159. n events 20304

p < 0.001
HR 1.44
CV and MI death

vascular death. n.events = 6232
p < 0.001
HR = 1.41

MI. n.events = 1986
p < 0.001
HR = 1.41
Heart failure and stroke death

heart failure. n.events = 200
p = 0.09
HR = 1.38

heart failure. n.events = 1590
p = 0.003
HR = 1.24
Cancer death

heart failure. n.events = 5577
p = 0.003
HR = 1.12
Conclusions

- Serum chloride <100 mmol/L was associated with increased risk of death in adults with type 2 diabetes mellitus.

- Findings in keeping with studies in other populations.

- Mechanism by which low serum chloride is associated with mortality is unknown.

- Further study is warranted.