Going the distance: food and fluid intake to optimize performance and minimize disease

Hyponatremia, Rhabdomyolysis and Renal Failure in Ultradistance Runners

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Hyponatremia
Rhabdomyolysis & Renal Failure
Fluid Intake
Sodium Intake
Recommendations
Exercise-associated hyponatremia (EAH) is the occurrence of hyponatremia in individuals engaged in prolonged physical activity and is defined by a serum or plasma sodium concentration below the normal reference range of the laboratory performing the test.
Incidence

Standard marathon:
- Asymptomatic: 0-13%
- Clinically symptomatic: 1%
- Deaths (confirmed): 5

Ultramarathon:
- Asymptomatic: 0-51%
- Clinically symptomatic: <1%

Ironman Triathlon:
- Asymptomatic: 0-18%
- Clinically Symptomatic: 12%
**PATHOPHYSIOLOGY**

**DILUTIONAL HYponatremia:**
Too much water (drinking too much)

**DEPLETIONAL HYponatremia:**
Losing too much salt (sweating)

**AUTOregulation**
EAH: etiologic possibilities

“pure” water retention from SIADH

mixed solute loss and water retention

“pure” solute depletion from sodium loss

\[ +\text{H}_2\text{O} \quad -\text{NaCl} \quad +\text{H}_2\text{O} \quad \text{?} \quad -\text{NaCl} \]

Exercise-induced antidiuretic hormone secretion?
Relationship between weight changes and post-race serum [Na+] in 2154 endurance athletes.

Noakes TD et al. PNAS 2005;102: 18550-18555
Measuring fluid losses during exercise:

Body weight ≠ Total Body Water
Body weight changes during exercise become less reliable indicators of fluid balance as race distance progresses.
EAH: signs and symptoms

- “pure” water retention from SIADH
- mixed solute loss and water retention
- “pure” solute depletion from sodium loss

**Diagram:**

- +H₂O
- -NaCl +H₂O → -NaCl

---

h/o overdrinking
bloating
vomiting
↔↑ BP
↑ body weight
↑↔↓ urination?

**“Dehydration”**
thirsty, dry mouth
skin tenting
orthostatic hypotension
↓ body weight
↓ urination

mixed
<table>
<thead>
<tr>
<th>EAH: diagnostic parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>“pure” water retention from SIADH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>+H₂O</th>
<th>-NaCl +H₂O</th>
<th>-NaCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Uosm</td>
<td>↑ Uosm</td>
<td>↑ Uosm</td>
</tr>
<tr>
<td>↑ pAVP</td>
<td>↑ pAVP</td>
<td>↑ pAVP</td>
</tr>
<tr>
<td>↑ weight</td>
<td>↔ weight</td>
<td>↓ weight</td>
</tr>
<tr>
<td>↓ BUN</td>
<td>↓ BUN</td>
<td>↓ BUN</td>
</tr>
<tr>
<td>↑ UNa⁺</td>
<td>↓ UNa⁺</td>
<td>↓ UNa⁺</td>
</tr>
</tbody>
</table>
Summary: Hyponatremia

EAH is a *life-threatening* fluid and sodium imbalance.

EAH can be diagnosed only by a *blood test*.

EAH is caused by a *combination* of excess fluid consumption and sweat sodium losses during ultraendurance running.
Hyponatremia
Rhabdomyolysis & Renal Failure
Fluid Intake
Sodium Intake
Recommendations
Skeletal Muscle

- 40% Body Weight
- 50% Total Body Water
- 70% Total Body K+

Extracellular Volume

- 35% Total Body Water
- 1-2% Total Body K+
Rhabdomyolysis

Dissolution of skeletal muscle

from direct or indirect injury

(ATP depletion, unregulated ↑ intracellular calcium)

Characterized by leakage of muscle cell contents into the circulation

(electrolytes, myoglobin, sarcoplasmic proteins)

Acute kidney injury is a dire complication of severe rhabdomyolysis from ↑ myoglobin

Bosch X et al NEJM, 2009
Figure 4.11  (a) An electron micrograph showing the normal arrangement of the actin and myosin filaments and Z disk configuration in the muscle of a runner before a marathon race. (b) A muscle sample taken immediately after a marathon race shows Z disk streaming caused by the eccentric actions of running. Reprinted from Hagerman et al. (1984).
Rhabdomyolysis

Diagnosed via creatine phosphokinase (CPK) levels measured in the blood

Normal range: between 60-400 IU/L

CPK is found in skeletal muscle, heart, brain

Enzyme which converts creatine to phosphocreatine

CPK is often used as surrogate measure to assess skeletal muscle damage

although myoglobin induces renal toxicity
WSER 2011

r = -0.22, p = 0.002

Fogard K et al ACSM 2012
Low incidence renal failure with exertional rhabdomyolysis

0% of 35 males developed acute renal failure in a retrospective study spanning 5 years
225,000 annual ER visits
(Sinert R et al Ann Emerg Med 1994)

Population-based analysis military base
22.2 cases per 100,000 per year
(Alpers JP Muscle and Nerve 2010)

Women have lower serum CK activities than men in response to same amount of exercise
(Noakes T, Sports Med 1987)
Myoglobin-induced acute kidney injury requires *nephrotoxic cofactors*

**Hypovolemicia**
- Intra-renal vasoconstriction concentrates myoglobin along renal tubules
- Renal tubular obstruction

**Aciduria**
- Myoglobin dissociates
- Precipitates with Tamm-Horsfall proteins to form casts
- Liberates ferrihemate which is nephrotoxic
Is there a link?
WSER 2011

Fogard K et al ACSM 2012

Creatine Kinase (U/L)

<table>
<thead>
<tr>
<th>Hyponatremic Runners</th>
<th>Normonatremic Runners</th>
</tr>
</thead>
<tbody>
<tr>
<td>133mEq/L, n=12(6%)</td>
<td>140mEq/L, n=195</td>
</tr>
</tbody>
</table>

*54,583

*p<0.05

30,335
CPK Values in the 100 km Race

Hypo\(\text{Na}^+\) at Checkpoint 2

- **Mean [CPK]** excluding severe EAH athlete
- **Severe EAH athlete**
CPK Values in the 100 Mile Race

HypoNa⁺ at Checkpoint 2 & 4

Mean [CPK] excluding severe EAH athlete

Severe EAH athlete

[CPK] U/L

Start 2 4 7 Post

Checkpoint
Hyponatremia + Rhabdomyolysis

Hyponatremia: *restrict fluid to decrease swelling*

**DILEMMA:**
save brain or kidney?

**SOLUTION:**
IV 3% Saline first
(↓cerebral edema
↓non-osmotic AVP)
Aggressive fluid next

Rhabdo: *increase fluid to prevent acute renal failure*
Summary: Rhabdomyolysis

Rhabdomyolysis is common after ultradistance races.

Acute renal failure is rare.

EAH, rhabdo and renal failure appears to be a unique problem in ultraendurance runners.
Hyponatremia

Rhabdomyolysis & Renal Failure

Fluid Intake

Sodium Intake

Recommendations
RUNNERS SWEAT

1° THERMOREGULATION

Exercise >40% VO₂ Max
92% water and 87% sodium losses derived from sweat

Average sweat [Na⁺]: ~35mEq/L
(range: 10-70)
hypotonic to plasma
WATER METABOLISM

REGULATED:

“need”
Fluids consumed
In response to thirst

Excess free water
Excretion (AVP)

UNREGULATED:

“need free”
moisture ingested foods
Palatability
Social
Habitual

Insensible losses
Obligate loss solutes
THIRST

"Thirst is one of the more powerful of the behavioral drives of the behavior.

When maximally stimulated in humans, the craving for water cannot be ignored and can become sufficiently intense to dominate all other thoughts and sensations."

Robertson GL, Kidney Int 1984
The physiological sensation of thirst is designed to protect plasma osmolality and volume — not total body water — within the normal physiological range.

Drinking to thirst will prevent both dysnatremias associated with exercise.

Prescribed drinking is appropriate under steady-state, controlled, conditions.
Thirst is stimulated in humans when the kidneys can no longer protect osmolality.

Independent of bodyweight change.

Robertson GL, Recent Prog Horm Res 1977
# Field Study Data: Replacing bodyweight

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Race (km)</th>
<th>Na+ pre (mmol/L)</th>
<th>Na+ post (mmol/L)</th>
<th>Na+ change</th>
<th>% BW loss</th>
<th>Time (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Twerenbold</td>
<td>41 Run</td>
<td>137±1</td>
<td>133±2</td>
<td>-4</td>
<td>+2</td>
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<tr>
<td>2002</td>
<td>Glace</td>
<td>160 Run</td>
<td>144</td>
<td>140</td>
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<td>2002</td>
<td>Gerth</td>
<td>100 Run</td>
<td>137±5</td>
<td>131±2</td>
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<td>-1</td>
<td>14</td>
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<tr>
<td>2005</td>
<td>Hew-Butler</td>
<td>109 Bike</td>
<td>139±3</td>
<td>138±3</td>
<td>-1</td>
<td>-2</td>
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<td>2003</td>
<td>Stuempfle</td>
<td>161 Snow</td>
<td>141±1</td>
<td>138±2</td>
<td>-3</td>
<td>-2</td>
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<tr>
<td>1989</td>
<td>Nelson</td>
<td>42 Run</td>
<td>139±0</td>
<td>142±0</td>
<td>3</td>
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<td>4</td>
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<td>1973</td>
<td>Refsum</td>
<td>90 Ski</td>
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<td>141</td>
<td>-1</td>
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<tr>
<td>1978</td>
<td>Cohen</td>
<td>42 Run</td>
<td>139±2</td>
<td>142±2</td>
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<td>-3</td>
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<tr>
<td>1977</td>
<td>Kavanagh et al.</td>
<td>42 Run</td>
<td>146±2</td>
<td>148±2</td>
<td>3</td>
<td>-3</td>
<td>4</td>
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<tr>
<td>1976</td>
<td>Noakes</td>
<td>160 Run</td>
<td>144±1</td>
<td>140±3</td>
<td>-4</td>
<td>-3</td>
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<td>2005</td>
<td>Hew-Butler</td>
<td>56 Run</td>
<td>139±3</td>
<td>138±3</td>
<td>-1</td>
<td>-4</td>
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<tr>
<td>2006</td>
<td>Hew-Butler</td>
<td>226 Tri</td>
<td>141±2</td>
<td>141±3</td>
<td>0</td>
<td>-4</td>
<td>12</td>
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<td>1975</td>
<td>Maron</td>
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<td>141±1</td>
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<td>-4</td>
<td>3</td>
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<tr>
<td>1989</td>
<td>Rocker et al.</td>
<td>42 Run</td>
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<td>149</td>
<td>5</td>
<td>-5</td>
<td>3</td>
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<tr>
<td>1954</td>
<td>Beckner</td>
<td>42 Run</td>
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<td>156</td>
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<td>-5</td>
<td></td>
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<tr>
<td>1964</td>
<td>Astrand</td>
<td>85 Ski</td>
<td>144</td>
<td>152</td>
<td>8</td>
<td>-6</td>
<td>9</td>
</tr>
</tbody>
</table>

*Hew-Butler et al, CJS 2006*
Summary: Fluid Intake

Water intake is highly regulated, governed cooperatively by osmotically-driven thirst stimulation and anti-diuretic hormone secretion (arginine vasopressin; AVP).
Hyponatremia

Rhabdomyolysis & Renal Failure

Fluid Intake

Sodium Intake

Recommendations
Sodium supplementation has been shown to be beneficial:

*High intensity work in hot ambient temperatures*

*Exercisers un-acclimatized to heat*

*Long duration (<24) exercise*
Longer distance + hotter temperature = ↑ contribution sweat [Na+] losses
The IOM in 2004 set the adequate index for daily sodium intake at **1.5g (60mmol)** for sufficient for physically active people.

*The mean dietary intake in the USA is 3.1-4.7g (135-204mmol) for males and 2.3 – 3.1g (100-135mmol) for females.*

*thus, for those ingesting a western diet, sodium supplementation seems unnecessary during exercise <24 hours in temperate climates.*
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>24-hour Pre-race (N = 18)</th>
<th>During Race (N = 18)</th>
<th>24-hour Post-race (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Volume (liters)</td>
<td>3.3 ± 1.7 (0.9 – 6.2)</td>
<td>0.3 ± 0.3 (0.03 – 1.6)</td>
<td>1.7 ± 1.7 (0.5 – 5.6)</td>
</tr>
<tr>
<td>Specific Gravity</td>
<td>1.009 ± 0.00 (1.003 – 1.019)</td>
<td>1.017 ± 0.01 (1.003 – 1.030)</td>
<td>1.021 ± 0.00 (1.005 – 1.029)</td>
</tr>
<tr>
<td>Total Na+ (mEq)</td>
<td>195.0 ± 79.6 (40.4 – 322.5)</td>
<td>8.8 ± 5.9 (0.3 – 26.2)</td>
<td>44.5 ± 39.5 (11.1 – 118.1)</td>
</tr>
<tr>
<td>Total K+ (mEq)</td>
<td>83.5 ± 33.5 (32.4 – 135.0)</td>
<td>25.4 ± 17.5 (2.2 – 74.9)</td>
<td>55.7 ± 33.7 (15.4 – 104.0)</td>
</tr>
</tbody>
</table>

* Unpublished data *
Is sweat sodium regulated?

sweat [Na+] vs. AVP; r=0.70; p<0.05

adapted from Brown MB et al
AJP Regul Integr Comp Physiol 2011
SODIUM APPETITE: Does it exist in humans?

15–20% Addisonian patients relate true salt cravings

Perinatal sodium loss increases salt appetite

Sodium Palatability increases with:

- Exercise with sweat loss
- Hemodialysis
- Experimental sodium depletion
Palatability Rating
% of full scale

Palatability rating
to 1 M NaCl solution
as a function of [Na\(^+\)]_p

Takamata A et al, Appl Physiol 1994
Sweat $[\text{Na}^+]$ accounted for 21% of variance in sodium palatability (55% placebo)

The “saltier” the sweat, the more the subject “craved” salty beverages (increased palatability)
Hew-Butler T et al HMR (in press)

\[ r = 0.99; \ p < 0.0001 \]

\[ \Delta \text{Total BMC} \quad (g) \]

\[ \Delta \text{Plasma [Na}^+\text{]} \quad (\text{mEq/L}) \]
$r = 0.93; p < 0.01$
CONFLICTING DATA
SODIUM
SUPPLEMENTATION
Benefits vs. Detriments
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>FINISHERS (n=6)</th>
<th>NON-FINISHERS (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories/h</td>
<td>*308 ± 100</td>
<td>185 ± 91</td>
</tr>
<tr>
<td>Liters fluid/h</td>
<td>0.7 ± 0.3</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>mEq Na+/h</td>
<td>*29 ± 17</td>
<td>16 ± 8</td>
</tr>
<tr>
<td>mEq Na+/L fluid</td>
<td>*44 ± 24</td>
<td>28 ± 12</td>
</tr>
<tr>
<td>% CHO</td>
<td>82 ± 11</td>
<td>88 ± 10</td>
</tr>
<tr>
<td>% Fat</td>
<td>12 ± 8</td>
<td>6 ± 6</td>
</tr>
<tr>
<td>% Protein</td>
<td>7 ± 4</td>
<td>5 ± 6</td>
</tr>
</tbody>
</table>
38yo male participating in RAAm consumed 23-25g of sodium/day (1000-1100mmol) developed pulmonary edema during day 3 with 2.7kg weight gain and BP of 170/100mmHg

Luks et al MSSE 2007

In humans, an increase in dietary sodium from 10-150 mmol is accompanied by a 2kg weight gain reflecting a 2L expansion of the extracellular fluid.
Salt Supplementation:

↑ weight gain
↑ Tc
↑ Heart rate

hypervolemic effects on respiration?
performance?

hypervolemic normonatremia?

Can sodium supplements prevent EAH?

Hew-Butler T et al BJSM 2006

Speedy DB et al CJSM 2002

- Sodium supplementation ($r^2 = 0.29; p<0.0001$)
- Placebo supplementation ($r^2 = 0.38; p<0.0001$)
- No supplementation ($r^2 = 0.17; p<0.0001$)

Triathlete with hyponatremic encephalopathy who gained 3.8 kg
13 females running 3 hours ingesting 1L/h of high (680mg/L), low (410mg/L) or no sodium beverages

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>HIGH</th>
<th>LOW</th>
<th>WATER</th>
</tr>
</thead>
</table>
| Pre-run [Na+]\(_p\)  
  (mmol/L)                | 137.3 (1.2)| 137.2 (1.2)| 137.5 (1.6)|
| Post-run [Na+]\(_p\)  
  (mmol/L)                | **134.8 (2.5)** | **132.8 (1.7)** | **131.3 (1.7)*** |
| Δ [Na+]\(_p\)  
  (mmol/L)                | -2.5 (2.5)  | -4.4 (2.5)  | -6.2 (2.1)*  |
| Δ Body weight  
  (kg)                    | 2.1 (1)    | 1.8 (1.2)   | 1.9 (1.9)    |
| Performance  
  (km)                   | 39.9 (4.3) | 42.0 (4.8)  | 40.6 (5.2)  |

*adapted from Twerenbold R et al, BJSM 2003
Sweat sodium losses appear to be regulated during exercise.

Electrolyte beverages may *attenuate* blood \([\text{Na}^+]\) decline when fluid intake matches or exceeds body mass losses.

Hot weather and long duration exercise increases the need for sodium.
Hyponatremia

Rhabdomyolysis & Renal Failure

Fluid Intake

Sodium Intake

Recommendations
Fluid and sodium balance are highly regulated through redundant, evolutionarily conserved, physiological mechanisms aimed to protect plasma sodium/osmolality during and after exercise.
Recommendations

Use body weight as a *guide* not a rule

Drink to thirst

Salt to taste

particularly in hot weather and un-acclimatized salt may attenuate development of EAH but does *NOT PREVENT IT*

Listen to your body
CONCLUSION

EAH, rhabdomyolysis and acute renal failure are more common in ultrarunners.

Although life-threatening consequences are rare (<1%), the ↑risk for ultrarunners underscores the importance of maintaining water and sodium homeostasis during exercise by abiding rather than outsmarting the body’s regulatory mechanisms.
Thank you
Good luck
Enjoy the race