Regulation of electrolyte and fluid metabolism in multi-stage ultra-marathoners

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Regulation of electrolyte and fluid metabolism in multi-stage ultra-marathoners

Running title: Hyponatremia in multi-stage ultra-marathoners

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Abstract

The purposes were (i) to determine the prevalence of exercise-associated hyponatremia (EAH) in multi-stage ultra-marathoners and (ii) to gain more insight into fluid and electrolyte regulation during a multi-stage race. In 25 male ultra-marathoners in the ‘Swiss Jura Marathon’ 2008 with 11,000 m gain of altitude over seven stages covering 350 km, body mass, sodium concentration ([Na⁺]), potassium concentration ([K⁺]), creatinine, urea, specific gravity and osmolality in urine were measured before and after each stage. Before stage 1 and after stages 1, 3, 5 and 7, haemoglobin, haematocrit, creatinine, urea, [Na⁺], [K⁺], and osmolality were measured in plasma. Two athletes (8%) showed plasma [Na⁺] < 135 mmol/l. Body mass, plasma [Na⁺], and plasma [K⁺] remained unchanged (p > 0.05). Urine specific gravity (p < 0.001) and osmolality in both plasma (p < 0.01) and urine (p < 0.001) increased. Haematocrit (p < 0.0001), haemoglobin (p < 0.0001) and plasma albumin decreased (p < 0.001). Plasma volume (p < 0.01) and plasma urea (p < 0.001) increased. The K⁺/Na⁺-ratio in urine increased after each stage > 1.0 and returned to < 1.0 the morning of the next stage (p < 0.001). To summarize, more sodium than potassium was excreted during rest. The increased urinary sodium losses during rest are compatible with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or the cerebral salt-wasting syndrome (CSWS). Future studies need to determine the antidiuretic hormone (ADH) and both the atrial natriuretic peptide (ANP) and the brain natriuretic peptide (BNP) during multi-stage races.

Key words: fluid overload; dehydration; sodium; body mass; heat
**Introduction**

Exercise-associated hyponatremia (EAH) is a common finding in endurance athletes and defined as a serum sodium concentration ([Na⁺]) below 135 mmol/l [1]. In the scientific literature, EAH was first described in 1985 by Noakes et al. [2] as being caused by ‘water intoxication’. The ‘International Exercise-Associated Hyponatremia Consensus Development Conference’ defined EAH as hyponatremia occurring during or up to 24 h after prolonged physical activity [1]. Following Noakes et al. [3], three factors explain the occurrence of EAH in endurance athletes: (i) overdrinking due to biological or psychological factors; (ii) an inappropriate secretion of the antidiuretic hormone (ADH), in particular, the failure to suppress the secretion of ADH in the face of an increase in total body water; and (iii) a failure to mobilize sodium from the osmotically inactive sodium stores or alternatively inappropriate osmotic inactivation of circulating sodium.

The main reason for developing EAH is the behaviour of overdrinking during an endurance performance [3, 4]. To date, no study reported that drinking more than *ad libitum* during exercise produced any biological advantage, but it could cause EAH [5]. Studies have shown that athletes who were encouraged to limit their fluid intake by drinking only in response to thirst did not develop EAH [5-7]. Fluid overload leads to EAH [8], and a correlation between a change in body mass due to fluid overload and a change in serum [Na⁺] was described [3, 8, 9]. The primary cause of such weight gain can only be the overconsumption of fluids during exercise [8] either because of an exaggerated thirst drive during exercise or because of a behavioural conditioning [3, 10, 11].

The prevalence of EAH has been extensively investigated in different endurance sports disciplines such as running [8,12-17], swimming [18], cycling [19-22], and triathlon [23-26].
It seems that the prevalence of EAH varies depending upon the discipline and length of a performance [27]. The prevalence of EAH seemed to increase with the length of a race [18-30]. To date, no study investigated the prevalence of EAH in a multi-stage ultra-endurance performance such as a multi-stage ultra-marathon [31-35]. Literature for a single stage mountain ultra-marathon is rare [36, 37] and completely missing for a multi-stage mountain ultra-marathon. In a multi-stage ultra-marathon, athletes compete for one week [31] or longer [32-35] and complete more than a marathon per day [32, 33]. Ultra-marathoners run at a slow pace [32-35] and may be at an increased risk of fluid overload due to overdrinking.

During multi-stage races, a change in electrolyte and fluid metabolism across the stages has been described. Sodium retention [38-40] and an increase in both plasma volume [39] and total body water [32, 38-40] have been reported. The maintenance of plasma [Na⁺] was presumably due to an increased activity of aldosterone during performance. One study reported a significant increase in concentration of plasma aldosterone and a highly significant association between the change in aldosterone and the change in plasma [Na⁺] during a 5-day hill-walking [38]. Also in a 7-day hill-walking, the daily sodium-potassium-excretion ratio indicated sodium retention most probably due to an increased activity of aldosterone. In contrast, ADH was not affected during a multi-stage performance [39].

The aims of the present study were (i) to determine the prevalence EAH in multi-stage ultra-marathoners and (ii) to gain more insight into fluid and electrolyte regulation during the longest mountain ultra-marathon in Europe, the ‘Swiss Jura Marathon’. Based upon existing literature, we hypothesized that among these multi-stage ultra-marathoners EAH would occur more often as reported in previous investigations on marathoners.
Materials and Methods

Subjects
The organizer of the ‘Swiss Jura Marathon’ 2008 contacted all the participants six months before the start via a separate newsletter, and informed them about the planned investigation. The number of athletes was limited to 100 selected ultra-runners. Thirty-four male ultra-runners volunteered to participate in the study. Twenty-five of the 34 subjects finished the race successfully within the time limit. The study was approved by the Institutional Review Board for use of Human subjects of the Canton of St. Gallen, Switzerland. All athletes gave their informed written consent.

The Race
The 18th occurrence of the ‘Swiss Jura Marathon’ took place from 6th to 12th July 2008. This race is the longest multi-stage mountain ultra-marathon in Europe. The runners have to complete seven stages, covering a total distance of 350 km and a total gain of altitude of ~11,000 m, in the mountains of Jura (Switzerland), from Geneva (372 m above sea level) to Basel (244 m above sea level). The organizer provided accommodation and nutrition before, during and after each stage. During each stage, three refreshment points for food and drink, such as water, tea, hypotonic sports drinks, fresh fruit, dried fruits, energy bars and soup were offered. The athletes ingested fluids and solid nutrition ad libitum and recorded their fluid intake during the stages as well as during the rest periods. Before and after each stage, the researchers provided questionnaires to assess type and amount of fluids consumed.

Measurements and Calculations
Pre-race, the anthropometry of the subjects was assessed. Body mass was measured using a commercial scale (Beurer BF 15, Beurer GmbH, Ulm, Germany) to the nearest 0.1 kg. Body
height was determined using a stadiometer to the nearest 1 cm (Tanita HR 001 Portable Height Measure, Tanita Europe, Amsterdam, Netherlands). Percent body fat was estimated using the anthropometric method following Ball et al. [41]. Before and after each stage, body mass was measured and samples of urine were collected. Before stage 1 and after stages 1, 3, 5 and 7, venous blood samples were drawn. These procedures were performed before the start and directly after completing each stage. Standardization of the sitting position prior to blood collection was respected, since postural changes can influence blood volume and therefore haemoglobin concentration and haematocrit. Blood and urine samples were immediately transferred to the laboratory and were analysed within six hours.

After venipuncture of an antecubital vein, two Sarstedt S-Monovettes (plasma gel, 7.5 ml) for chemical and one Sarstedt S-Monovette (EDTA, 2.7 ml) (Sarstedt, Nümbrecht) for haematological analysis were drawn. Monovettes for plasma were centrifuged at 3,000 g for 10 min at 4 °Celsius. Plasma was collected and stored on ice. In the venous blood samples, haemoglobin, haematocrit, [Na⁺], [K⁺], creatinine, urea, and osmolality were measured. Haematologic parameters were determined using ADVIA® 120 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Plasma parameters were measured using COBAS INTEGRA® 800 (Roche, Mannheim, Germany). Osmolality of plasma was determined using Fiske® Modell 210 Mikro-Osmometer (IG Instrumenten-Gesellschaft AG, Zurich, Switzerland). Urine was collected in Sarstedt monovettes for urine (10 ml). In the urine samples, creatinine, urea, [Na⁺], [K⁺], specific gravity and osmolality were determined. Osmolality was measured using Fiske® Modell 210 Mikro-Osmometer (IG Instrumenten-Gesellschaft AG, Zurich, Switzerland). Specific gravity was analysed using Clinitek Atlas® Automated Urine Chemistry Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Creatinine and urea were measured using COBAS INTEGRA® 800. Electrolytes were determined using ISE IL 943 Flame Photometer (GMI, Inc., Ramsey, MN, USA). Fractional
sodium excretion was calculated using the equation: Fractional excretion of sodium =
\[
\frac{(\text{Urine}\text{Sodium} \times \text{PlasmaCreatinine})}{(\text{PlasmaSodium} \times \text{UrineCreatinine})} \times 100
\]
according to Steiner [42]. Fractional urea excretion was calculated using the equation: Fractional urea excretion =
\[
\frac{(\text{Urine}\text{Urea} \times \text{PlasmaCreatinine})}{(\text{PlasmaUrea} \times \text{UrineCreatinine})} \times 100
\]
following Dole [43]. Transtubular potassium gradient was calculated using the equation: Transtubular potassium gradient =
\[
\frac{(\text{Urine}\text{potassium} \times \text{Plasmaosmolality})}{(\text{Plasmapotassium} \times \text{Urineosmolality})}
\]
according to West et al. [44]. Creatinine clearance was calculated following Gault et al. [45]. Glomerular filtration rate was calculated according to Levey et al. [46]. Percentage change in plasma volume was determined following Strauss et al. [47].

Before and after each stage, total body water was estimated using InBody 3.0 Body composition analyzer with a direct segmental multifrequency bioelectrical impedance method (InBody 3.0, Biospace, Seoul, Korea) following Bedogni et al. [48]. InBody 3.0 has a tetrapolar 8-point tactile electrode system and performs at each session 20 impedance measurements using four different frequencies (i.e. 5 kHz, 50 kHz, 250 kHz, 500 kHz) at each of the five segments right arm, left arm, trunk, right leg, and left leg. The subjects stood barefoot in an upright position on foot electrodes on the platform of the instrument, with the legs and thighs not touching and the arms not touching the torso. Four foot electrodes were used (i.e. two oval-shaped electrodes and two heel-shaped electrodes) and subjects were asked to grip the two palm-and-thumb electrodes (i.e. two thumb and two palm electrodes per athlete). The skin and electrodes were cleaned and dried before testing. Total body water was directly estimated.

During the stages, the athletes consumed food and drinks ad libitum and reported their intake of fluids and solid nutrition at each aid station. After each stage, they recorded their fluid intake up to the start of the next stage. At the aid stations, liquids and food were prepared in
standardized manner and were provided in same size portions. The composition of fluids and solid food, as reported by the athletes, was determined using a food table [49]. Also, the athletes were asked for symptoms of EAH such as weakness, dizziness, headache, nausea or vomiting after each stage [1].

Statistical Analysis
In order to increase the reliability of the data analyses, each set of data was tested for normal distribution as well as for homogeneity of variances in advance of statistical analyses. Normal distribution was tested using a D’Agostino and Pearson omnibus normality test and homogeneity of variances was tested using a Levene’s test in case of two groups and with a Bartlett’s test in case of more than two groups. Statistical analyses were performed using GraphPad Prism (Version 5, GraphPad Software, La Jolla, CA, USA), SPSS PASW (Version 18, SPSS Inc., Chicago, IL, USA) and Microsoft Excel (Version 14.0.6023.1000, Microsoft, Redmond, USA). Data are presented as mean values with 95% confidence intervals in the figures and tables and as mean values with standard deviation in the text. In case of a significant change during the race, Bonferroni-corrected paired t-tests were applied to detect a significant change from one time period to the other. Correlation analysis was used to check for associations between parameters with statistically significant changes. Statistical significance was accepted with $p < 0.05$ (two-sided for t-tests).
Results

Anthropometry, training and pre-race experience of the finishers are summarized in Table 1. Table 2 displays the stages, showing ascents and descents per stage, the general weather conditions and the running speed of the athletes. A total of 83 male athletes entered the race and 55 (66%) finished. Twenty-five runners (71%) of the 34 subjects finished within a mean race time of 44:37 (4:37) h:min. The winner took 31:17 h:min, and the participants finished within 143 (14) % of the winner’s time.

No athlete complained of symptoms indicating EAH. Nine of the 34 participants (26%) dropped out due to overuse injuries of the lower limbs. No non-finisher showed any signs of EAH. Plasma [Na⁺] of < 135 mmol/l was found in two athletes who finished the competition. In the first one, it occurred after stage 5 (134 mmol/l) and stage 7 (133 mmol/l), in the second one after stage 1 (134 mmol/l) and stage 7 (133 mmol/l). The estimated prevalence of EAH was 8%.

The athletes were running at a mean speed of 7.9 (0.8) km/h with no change in speed across the stages (p > 0.05). Body mass remained unchanged (p > 0.05) (Figure 1 Panel A). Body mass was significantly lower after the stages and returned to pre-race values before each stage. Urine specific gravity increased after stage 1 above baseline and remained increased (p < 0.001 (Figure 1 Panel B). Urine osmolality increased after stage 2 and remained increased (p < 0.001) (Figure 1 Panel C). Plasma osmolality increased after stage 5 and remained increased (p < 0.01) (Figure 1 Panel D).

Haematocrit and haemoglobin decreased significantly (Table 3) (p < 0.0001). Plasma volume (Figure 2 Panel A) increased after stage 1 and remained increased (p < 0.001). Plasma
albumin concentration (Figure 2 Panel B) decreased after stage 3 and remained decreased \((p < 0.001)\). Plasma \([\text{Na}^+]\) (Figure 3) and plasma \([\text{K}^+]\) (Table 3) remained unchanged \((p > 0.05)\). Plasma urea concentration increased (Table 3) \((p < 0.0001)\). Post-race plasma volume was significantly and negatively related to post-race plasma albumin concentration (Figure 4 Panel A). The mean post-stage plasma urea concentration correlated significantly and positively to the mean values of post-stage plasma osmolality (Figure 4 Panel B).

Urine \([\text{K}^+]\) increased after each stage and returned to base line values \((p < 0.001)\) (Figure 5 Panel A). Also, urine \([\text{K}^+]\) was significantly higher post-stage compared to pre-stage. Urine \([\text{Na}^+]\) remained unchanged (Figure 5 Panel B) \((p > 0.05)\). The \([\text{K}^+] / [\text{Na}^+]\)-ratio in urine increased after each stage and returned to baseline the morning of the next stage (Figure 5 Panel C) \((p < 0.001)\). The transtubular potassium gradient increased after stage 1 and remained increased (Figure 5 Panel D) \((p < 0.001)\). Fractional sodium excretion remained unchanged across the race \((p > 0.05)\). Fractional urea excretion, creatinine clearance and glomerular filtration rate decreased \((p < 0.0001)\) (Table 3).

The athletes consumed more fluids during the stages than during rest periods (Figure 6 Panel A). Fluid intake showed no correlation with plasma \([\text{Na}^+]\) \((p > 0.05)\). Intake of both sodium (Figure 6 Panel B) and potassium (Figure 6 Panel C) with fluids was higher during stages than during rest.

Total body water remained unchanged \((p > 0.05)\) (Figure 7 Panel A) \((p > 0.05)\). Post-race plasma volume was significantly and positively related to the change in post-race total body water (Figure 7 Panel B).
Discussion

The most important finding of our study was that *ad libitum* drinking was sufficient to maintain fluid and electrolyte balance during a multi-stage ultra-endurance race. This finding is consistent with recent studies of Nolte *et al.* [50-52] reporting that *ad libitum* fluid replacement was appropriate to maintain total body water, plasma osmolality, urine specific gravity, urine osmolality and serum [Na⁺] despite a loss in body mass [50, 51]. In addition, *ad libitum* fluid intake prevented EAH.

In case of an excessive fluid intake with fluid overload, we would expect a decrease in plasma [Na⁺] and a stable or increased body mass [4, 29]. However, plasma [Na⁺] remained unchanged. The determination of changes in body mass is a useful objective measure of intake [12] and retention [53] of fluids. In the present athletes, however, body mass decreased after each stage but, by the next morning, the athletes had returned to their pre-race body mass values. During endurance performance, the body aims at maintaining [Na⁺] and osmolality in plasma, but not body mass [54]. The fact that thirst was appropriate to return body mass each day after a stage to pre-race values displays that thirst obviously is an accurate mechanism to insure appropriate fluid intake [50-52, 54].

Plasma [Na⁺] remained unchanged as has already been reported for multi-stage races [38, 40]. Asymptomatic EAH was found in two athletes; in one finisher after stage 5 and stage 7, and in the other finisher after stage 1 and stage 7. Considering overdrinking as the main risk factor for EAH [3, 4], the athletes showed an increased fluid intake towards the end of the race, mainly due to the increasing ambient temperatures.
Sodium and potassium concentrations and osmolality in plasma and urine are indirect markers for the activity of aldosterone and ADH-secretion. An inappropriate ADH-secretion (SIADH) is considered as a potential mechanism to develop EAH [3]. One of the most important roles of ADH is the regulation of the body's retention of water. ADH causes the kidneys to conserve water and reduces urine volume [55]. The most important variable regulating ADH-secretion is plasma osmolality or the concentration of solutes in the plasma and other sodium regulating hormones. In the present subjects, plasma osmolality increased significantly. Regarding other solutes in plasma, plasma urea concentration increased significantly and the increase in plasma osmolality was related to the increase in plasma urea concentration. Also, plasma albumin concentration decreased and the decrease in plasma albumin concentration was associated with the increase in plasma volume.

The decrease in haematocrit, haemoglobin and albumin concentration, and the increase in total body water showed that these athletes became more and more diluted during the race. The progressive haemodilution might be due to Na\(^+\)-retention and K\(^+\)-secretion as an effect of an increased activity of aldosterone [56] as well as due to an increase in ADH with fluid conservation [57]. Wade et al. [34] reported chronically elevated aldosterone levels in multi-stage ultra-marathoners in a 20-day 500-km race with a decreased urine excretion rate. In the present athletes, however, plasma osmolality was probably protected as plasma [Na\(^+\)] remained unchanged and urea concentration increased. We assume that the increase in plasma urea concentration across the race induced the increase in plasma osmolality. The increase in plasma urea concentration was most probably due to an augmented protein catabolism during the race due to a myofibrillar breakdown [58].

Another important finding was that the K\(^+\)/Na\(^+\)-ratio in urine was < 1.0 before a stage and increased to > 1.0 after a stage, as has already been shown in 100-km ultra-marathoners [59,
and multi-stage ultra-triathletes [61]. This finding suggests that during the stages more potassium than sodium was excreted, and a positive ratio for K⁺/Na⁺ in urine suggests an increased activity of aldosterone. Transtubular potassium gradient increased throughout the race reaching a value of > 10, indicating an increased activity of aldosterone [44, 62]. The biological action of aldosterone is to increase the retention of sodium and water and to increase the excretion of potassium by the kidneys [55]. An increase in aldosterone seems to be a physiological reaction in multi-stage ultra-marathoners [34, 35]. In a 20-day 500-km race, urinary aldosterone excretion increased during the race on days 5, 8 and 20. Plasma [Na⁺] increased on days 2 and 13, but decreased on day 20 [34]. While aldosterone secretion was increased, sodium excretion was reduced.

While the K⁺/Na⁺-ratio in urine was < 1.0 before a stage, sodium might be lost during the night, most probably due to decreased activity of aldosterone. This mechanism might lead to hyponatremia. Sodium loss during rest might, however, also be due to cerebral salt-wasting syndrome (CSWS), defined by the development of extracellular volume depletion due to a renal sodium transport abnormality in patients with intracranial disease and normal adrenal and thyroid function [63]. The injured brain may release natriuretic proteins acting directly on the kidneys [64]. CSWS is considered a definite clinical entity and may be more common than perceived. In addition, it should also be considered in situations without cerebral disease [65]. The exact mechanism for CSWS remains still unclear. In the setting of a cerebral injury, one hypothesis is an exaggerated renal pressure–natriuresis response caused by an increased activity of the sympathetic nervous system and dopamine release is responsible for an increased urinary sodium loss. Another hypothesis involves the release of natriuretic factors, possibly including brain natriuretic peptide (BNP) or urodilatin by the injured brain [66]. Differentiation of this disorder from SIADH can be difficult because both disorders can present with both hyponatremia and concentrated urine with increased natriuresis.
Some limitations of our study have to be acknowledged. First of all, we were not able to report the volume of excreted urine. This might have been helpful to clarify if the observed findings are caused by over-hydration or more likely by ADH-secretion. ADH reduces renal free water excretion and is responsible for water retention in the kidney [67, 68]. In the state of hyponatremia and/or hypervolemia, ADH should be suppressed [67]. In case ADH is inadequately secreted, water retention could lead to both fluid overload and EAH. A further limitation is that we did not record the use of non-steroidal anti-inflammatory drugs (NSAID). The use of NSAIDs is common in endurance athletes [37] and is a risk factor for both hyponatremia and altered renal function [30]. In Ironman triathletes, the use of NSAID was related to the incidence of EAH [30]. Furthermore, we only recorded sodium and potassium intake in fluids but not in solid food. A high sodium intake in salted solid food might have had an effect on plasma [Na⁺]. However, Hew-Butler et al. [69] showed that ad libitum sodium supplementation was not necessary to preserve serum [Na⁺] in athletes competing for ~12 hours in an Ironman triathlon.

Regarding the two athletes developing EAH, it has to be acknowledged that EAH was very mild without any clinical implications - hence it is purely a biochemical diagnosis with no real clinical implications. Nevertheless, the reasons remain unclear. It is most likely that the two affected cases might show a mild abnormality that could lead to symptomatic EAH if, for example, there was inappropriate ADH-secretion as well. An inadequate aldosterone response could be associated with an impaired mobilization of osmotically-inactive sodium into the expanded blood volume. This would be one mechanism explaining a reduced serum [Na⁺] concentration in the absence of clear evidence for overdrinking and fluid retention.

To summarize, 8% of these multi-stage mountain ultra-marathoners developed asymptomatic EAH where EAH occurred mainly at the end of the race in stages 5 and 7. The increased
Urinary sodium losses during rest are compatible with the syndrome of inappropriate secretion of antidiuretic hormone or the cerebral salt-wasting syndrome. Future studies need to determine the antidiuretic hormone (ADH) and both the atrial natriuretic peptide (ANP) and the brain natriuretic peptide (BNP) during multi-stage races.
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Figure captions

**Figure 1:** Timeline of changes in body mass (Panel A), urine specific gravity (Panel B), urine osmolality (Panel C) and plasma osmolality (Panel D). B = before stage, A = after stage. * = significantly different from previous value, § = significantly different from baseline. P-value = change in data during time (B1 vs. A7).

**Figure 2:** Timeline of changes in plasma volume (Panel A) and plasma albumin (Panel B). B = before stage, A = after stage. * = significantly different from previous value, § = significantly different from baseline. P-value = change in data during time (B1 vs. A7).

**Figure 3:** Timeline of changes in plasma [Na⁺]. B = before stage, A = after stage. * = significantly different from previous value. P-value = change in data during time (B1 vs. A7).

**Figure 4:** Post-race plasma volume was significantly and negatively related to post-race plasma albumin (Panel A). The mean values of post-stage plasma urea correlated significantly and positively to the mean values of post-stage plasma osmolality (Panel B).

**Figure 5:** Timeline of changes in urine potassium (Panel A), urine sodium (Panel B), the potassium-to-sodium-ratio (Panel C) and the transtubular potassium gradient (Panel D). B = before stage, A = after stage. * = significantly different from previous value, § = significantly different from baseline. P-value = change in data during time (B1 vs. A7).

**Figure 6:** Timeline of fluid (Panel A), sodium (Panel B) and potassium (Panel C) intake. S = stage, R = rest, * = significantly different from previous value.

**Figure 7:** Timeline of changes in total body water (Panel A). * = significantly different from previous value. Post-race plasma volume was significantly and positively related to post-race total body water (Panel B).