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Incidence of Exercise-Associated Hyponatremia and Its Association With Nonosmotic Stimuli of Arginine Vasopressin in the GNW100s Ultra-endurance Marathon

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Objectives: (1) To examine the incidence of exercise-associated hyponatremia (EAH) during and after an ultramarathon and (2) to evaluate hypothesized nonosmotic stimuli [interleukin-6 (IL-6), hypoglycemia, ambient temperature] with arginine vasopressin (AVP) concentrations in hyponatremic versus normonatremic runners.

Design: Prospective cohort study.

Setting: The Great North Walk 100s ultramarathons.

Participants: Fifteen runners participated in either 103.7- or 173.7-km ultramarathons.

Main Outcome Measures: Serum sodium concentration ($[Na^+]$) and AVP concentration. Secondary outcome measures included IL-6, blood glucose, ambient temperature, weight change, fluid consumption, and use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Results: Postrace EAH incidence was 4 of 15 runners, whereas EAH incidence at any point during the race was in 10 of 15 runners. A significant positive correlation was noted between AVP and IL-6 ($r = 0.31$, $P < 0.05$) but not between AVP and blood glucose ($r = 0.09$, nonsignificant) or ambient temperature ($r = -0.12$, NS). Subgroup analysis revealed that the correlation between AVP and IL-6 was significant in hyponatremic ($r = 0.37$, $P < 0.05$) but not normonatremic runners ($r = 0.31$, NS). Hyponatremic runners lost less weight than normonatremic runners (2.5 vs 3.7 kg, $P < 0.05$, respectively) despite similar fluid consumption. Seven of 10 hyponatremic runners consumed NSAIDs versus 0 of 5 normonatremic runners.

Conclusions: Exercise-associated hyponatremia incidence midrace is higher than postrace, suggesting that 40% of runners are able to self-correct low serum $[Na^+]$ status during an ultramarathon. Interleukin-6 seems to be the main nonosmotic stimulus associated with AVP in hyponatremic runners. Nonsteroidal anti-inflammatory ingestion is more common in hyponatremic versus normonatremic runners.

Clinical Relevance: Exercise-associated hyponatremia associated with nonosmotic AVP secretion may be more common during ultramarathon races without discriminatory clinical symptomatology.

Key Words: hyponatremia, ultramarathon running, arginine vasopressin, interleukin-6

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INTRODUCTION

Exercise-associated hyponatremia (EAH) is a serious and potentially fatal condition that endurance athletes face. Knowledge of the symptoms, signs, pathophysiology, and treatment of EAH has improved considerably since the first case was reported in 1985.[1]

Exercise-associated hyponatremia is defined as "hyponatremia (serum or plasma sodium concentration ($[Na^+]$) < 135 mmol/L) occurring during or up to 24 hours after prolonged activity."[2]

The incidence of EAH has been reported to be as high as 30% in some endurance events; however, no study to date has performed intrarace blood tests.[3–12] Blood tests in these studies were collected postrace, meaning athletes who developed symptomatic EAH and did not complete the race would not be accounted for. It is possible that the reported incidence of EAH during an entire race is actually lower than expected if all athletes were tested or if samples were obtained during a race.

The pathophysiology of EAH is complex and not entirely understood. Essentially, EAH is a condition associated with consumption of fluid in excess of fluid loss, which results in a dilutional hyponatremia.[2] Dilution of the plasma results in a reduced osmolality, which triggers suppression of the antidiuretic hormone, arginine vasopressin (AVP). Arginine vasopressin suppression allows the renal system to excrete excess fluid, thus restoring a normal plasma osmolality. When $[Na^+]$ is less than 135 mmol/L, AVP should be undetectable.[13–15]

Cases of EAH have been associated with a detectable and therefore inappropriate concentration of AVP despite low plasma osmolality. In this setting, AVP prevents the diuresis of excess fluid and perpetuates the dilutional hyponatremia. This may be considered a variant of syndrome of inappropriate antidiuretic hormone secretion.[2,13–15] Given that there should be maximal osmotic suppression of AVP, its presence must require nonosmotic stimulation. A number of nonosmotic stimuli of AVP

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secretion have been identified, including hypoglycemia, hyperthermia, increased interleukin (IL-6), nausea, vomiting, and pain.[2,13–15] Use of nonsteroidal anti-inflammatory drugs (NSAIDs) has also been proposed to potentiate the effects of AVP.[2]

The aims of this study were to (1) evaluate the incidence of EAH both during and postrace and (2) assess the relationship of AVP concentrations versus potential nonosmotic stimuli commonly encountered during an ultra-endurance footrace.

METHODS

Ethics Approval

Ethics approval was obtained from the Australian Institute of Sport Ethics Committee.

Recruitment

Participants were recruited from the 120 entrants to the Great North Walk (GNW) 100s ultra-endurance race. All athletes were contacted by email and provided with information on EAH and the research study. They received a questionnaire and an informed consent form, both of which were completed before acceptance into the study.

Inclusion Criteria

Event qualifiers who were available for 24 hours postrace blood tests were included in the study.

Exclusion Criteria

Athletes with diabetes, renal or cardiovascular disease, or use of prescription medications that interfere with renal function were excluded from the study.

Race Course

The GNW100s follow the "GNW" between Speers Point and Patonga, New South Wales. The race occurs annually in November. There are 2 side-by-side races of approximately 100 km (103.7 km) and 100 miles (173.7 km). Various stretches of the course expose the athletes to high temperatures and also to very cold temperatures. There are multiple steep ascents and descents within the race (Figure 1). The athletes must complete the 100-km race within 22 hours and the 100-mile race within 36 hours.

Venesection

Each athlete had either 4 (100 km entrants) or 5 (100 mile entrants) blood tests. These were performed at

- checkpoint 0 (within 60 minutes of the start),
- checkpoint 2 (52.6 km),
- checkpoint 4/100 km finish (103.7 km),
- checkpoint 7/100 mile finish (173.7 km), and
- 24 hours postrace.

Samples were collected as close to 24 hours postrace as possible (mean = 23.1 hours, range = 12.3-37.3 hours). The

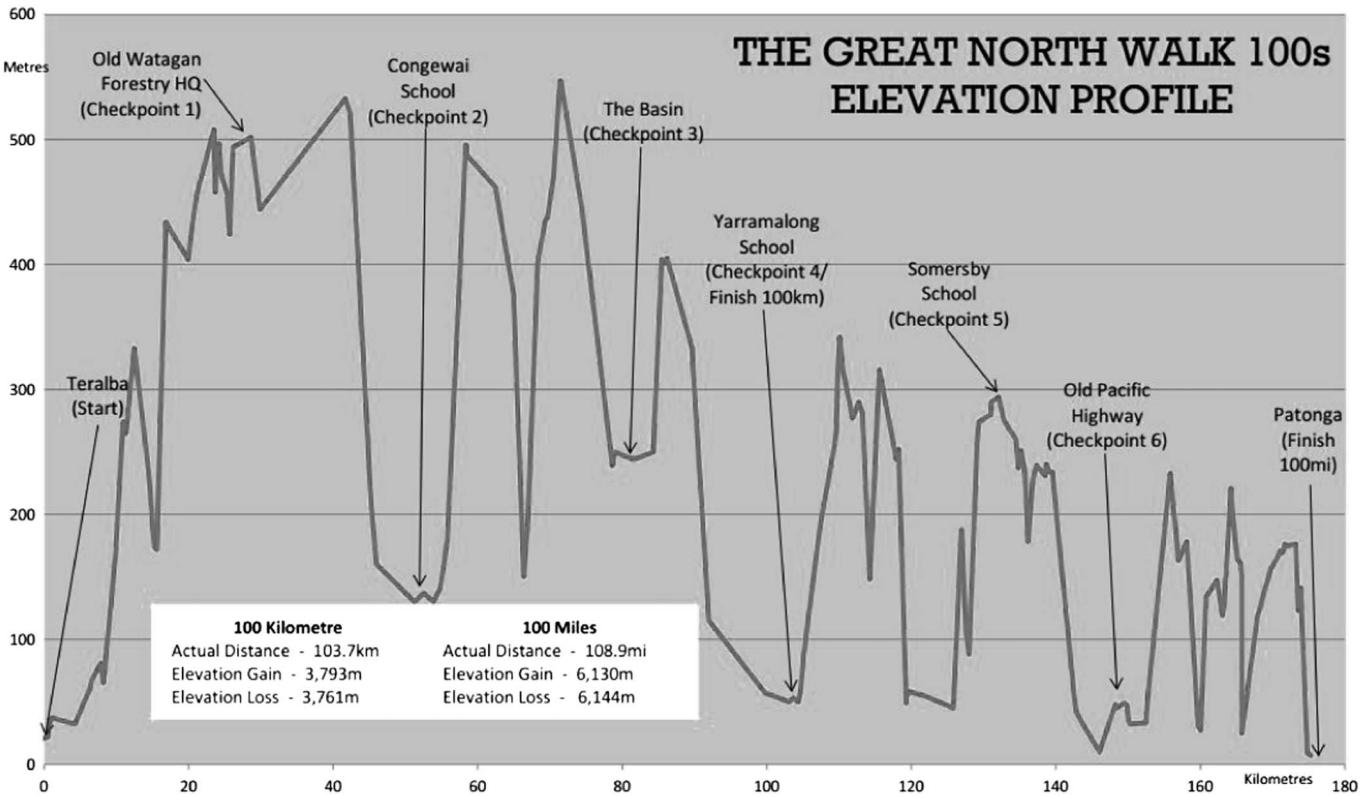

FIGURE 1. The GNW100s race profile and distances.

postrace sample was collected at the athlete's nearest Laverty Pathology Laboratory.

Venesection stations were set up within 30 meters of each checkpoint entrance. Athletes were immediately directed to the venesection station. Blood samples were obtained from the antecubital fossa in an upright seated position. Fifteen milliliters of venous blood was collected into one 5-mL EDTA plasma tube and two 5-mL serum clot activator tubes. The EDTA tube was centrifuged within 10 minutes of collection at 1500*g* for 10 minutes and then placed on dry ice. Clot activator tubes clotted for 30 to 60 minutes before being centrifuged at 1500*g* for 10 minutes and then placed on dry ice. All samples were kept on dry ice until they could be transferred to −80°C freezers.

Urine Collection

Urine samples were provided at the time of the prerace blood test and immediately postrace. The samples were kept on ice until they were transferred to clinical refrigerators.

Laboratory Measurements

Blood samples collected in serum clot activator tubes were analyzed for serum electrolytes, urea, creatinine, glucose, and IL-6. Serum electrolytes, urea, creatinine, glucose, and urinary sodium were measured using "Siemens Advia 2400" (Siemens Healthcare Diagnostics, Tarrytown, New York). Serum and urine electrolytes were measured using the Ion Selective Electrode method. Serum glucose was measured using the hexokinase assay principle. Urea was measured using the Roch-Ramel enzymatic reaction. Creatinine was assessed using the picric acid reaction method. Urine osmolality was measured on the "The Advanced Micro-Osmometer" (Advanced Instruments, Norwood, Massachusetts). Interleukin-6 was measured using a multiplex bead-array assay (Millipore Corporation, Bedford, Massachusetts) on the "Luminex 100" (Luminex Corporation, Austin, Texas).

Blood samples collected in the EDTA tubes were used to measure AVP using a manual double-antibody radioimmunoassay kit (Buhlmann Laboratories AG, Schonenbuch, Switzerland).

Questionnaires, Weight, and Temperature

Each athlete completed a prerace questionnaire and further questionnaires at each venesection station. The questionnaires inquired about any recent illnesses, injuries, medication use, symptoms of EAH, fluid and food consumption, and ratings of perceived exertion, heat stress, and thirst. Athletes were weighed without shoes and socks on scales that were placed on a hard flat surface. Ambient temperature and humidity were recorded using the Atech Scientific Measurement Limited (San Po Kong, Hong Kong) WS303-G-RC weather station.

Data Analysis

Data were analyzed combined (N = 15) and also grouped according to the presence of EAH. The main outcome (dependent) variables of the investigation were changes in serum sodium and AVP. Data have been analyzed via paired *t* tests and linear regression analyses, which were performed between the dependent and independent variables (temperature, blood glucose, IL-6). All other data, including demographic data, have been presented as mean ± SD. Statistical significance was defined as $P < 0.05$.

RESULTS

Race temperature ranged between 17.3°C and 29.6°C and relative humidity ranged between 48% and 95% on race day. Nineteen athletes were recruited to participate in this study. Of these, 2 athletes retired in-between checkpoints with grossly incomplete data sets and were excluded from analysis. Six athletes completed the 100-km race and 7 athletes completed the 100-mile race. Two other athletes dropped out between checkpoint 3 (81.6 km) and checkpoint 4 but were transported to checkpoint 4 and had blood tests taken within 30 minutes of dropping out and have been included in the 100-km group for analysis.

Data on Prospective Incidence of Exercise-Associated Hyponatremia

Incidence of EAH at the end of the race in the 100-km and 100-mile races was 2 of 8 athletes and 2 of 7 athletes, respectively. Furthermore, 2 of 3 female athletes had postrace EAH compared with 2 of 12 male athletes. The occurrence of EAH at any point during or postrace in the 100-km and 100-mile races was in 6 of 8 athletes and 4 of 7 athletes, respectively, with a total of 10 of 15 athletes having developed EAH at some stage during their races (Table 1). All female runners developed EAH at some point during the race. The range of $[Na^+]$ was 119 to 145 mmol/L.

There were significant differences in prerace to end of race serum $[Na^+]$, AVP, IL-6, blood glucose, urine $[Na^+]$, and urine osmolality. Subgroup analysis showed that these changes remained significant in the EAH group but only AVP, IL-6, and urine osmolality were significantly different in the group without EAH (Table 2). Despite no differences in mean urine $[Na^+]$ concentration prerace, mean urine $[Na^+]$ at the end of the race was lower in hyponatremic versus normonatremic athletes (Table 2).

Comparison of Characteristics of Hyponatremic Athletes to Normonatremic Athletes

None of the athletes displayed overt clinical symptoms or signs of severe EAH, such as persistent vomiting, puffiness, altered mental status, and pulmonary edema. Athletes in both groups (normonatremic and hyponatremic) reported similar incidences of nausea, occasional vomiting, transient mild confusion, and bloating (Table 3).

There was significantly less body weight loss (absolute and percentage) from the start of the race to the end of the race in the hyponatremic athletes compared with the normonatremic athletes (Table 3). There was no significant correlation of percent body weight change with serum $[Na^+]$ in our cohort ($r = 0.003$, $P = 0.69$). No normonatremic athletes used NSAIDs on race day or 24 hours before, compared with 7 of 10 hyponatremic athletes using NSAIDs. No significant differences were detected between the normonatremic and hyponatremic athletes for fluid consumed (total volume, milliliters

TABLE 1. Incidence of EAH at the GNW100s Ultra-endurance Race

Variable	100 km	100 mile	All
Athletes, n (male:female)	8 (6:2)	7 (6:1)	15 (12:3)
EAH at the end of race, n (%)	2 (25)	2 (28.6)	4 (26.7)
EAH at any point in race, n (%)	6 (75)	4 (57.1)	10 (66.7)
Males with EAH, n (%)	4 (66.7)	3 (50)	7 (58.3)
Females with EAH, n (%)	2 (100)	1 (100)	3 (100)

per hour and milliliters per hour·per kilogram), use of salt supplements, and hyponatremic symptoms (Table 3).

Assessment of Arginine Vasopressin in Exercise-Associated Hyponatremia and Its Relationship to Nonosmotic Stimuli

All readings of serum [Na^+] <135 mmol/L were associated with measurable AVP concentrations (mean = 13.4 pmol/L, SD = 12.6, range = 3.5-37.1).

Linear regression analyses were performed to assess the correlation of AVP versus hypothesized nonosmotic stimuli, such as IL-6, blood glucose, and ambient temperature. Blood glucose and ambient temperature correlations did not reach significance. However, IL-6 had a significant positive correlation with AVP (Figure 2).

Subgroup analyses of hyponatremic and normonatremic athletes were also performed. Results showed no correlation of AVP with ambient temperature. A positive correlation of blood glucose with AVP in the hyponatremic athletes approached statistical significance ($r = 0.30$, $P = 0.05$). Interleukin-6 showed no significant correlation to AVP in the normonatremic athletes, but there was a positive correlation in the hyponatremic athletes ($r = 0.37$, $P = 0.015$) (Table 4).

No correlations were noted between expected osmotically regulated variables (serum [Na^+], AVP, urine [Na^+], and urine osmolality) except for postrace serum [Na^+] correlating significantly with postrace urine [Na^+] (Table 5). Subgroup analysis showed no significant correlations (data not shown).

DISCUSSION

Our results have important clinical implications. In our cohort, the incidence of EAH at any stage during the race was much higher than previously reported incidences of EAH. This emphasizes the necessity for medical care providers to consider EAH high on their differential diagnosis both during and after an ultramarathon. Our results reinforce recommendations to have point of care serum [Na^+] testing available at all endurance races and that administration of intravenous fluids should be avoided unless their necessity has been established.[2]

The most important finding was 10 of 15 athletes developed EAH at some point during the race, which is much higher than the postrace incidence of 4 of 15 athletes. This suggests that EAH may "self-correct" during a race and that EAH symptoms may be more common than previously thought but are ascribed to other common ailments (runner's cramp, heat exhaustion). All athletes with symptoms or signs of EAH were given further safety advice about safe drinking habits (drink to thirst only).[16] Furthermore, all these athletes were experienced and would be expected to have developed appropriate hydration regimens. Given this, we suspect that the incidence of EAH may have been even higher (including symptomatic cases) without this close monitoring/intervention.

Exercise-Associated Hyponatremia Risk Factors

Multiple risk factors for developing EAH have been identified, including excessive drinking, weight gain during exercise, low body weight, female sex, slow running performance, event inexperience, and use of NSAIDs.[2]

In our cohort, there was no statistically significant difference in fluid consumption between hyponatremic and normonatremic athletes. However, there was significantly more weight lost by normonatremic than hyponatremic athletes (Table 3), suggesting overhydration may not exclusively reflect the total amount of fluid consumed.[17] Other factors are likely to influence the volume of fluid being excreted, such as inappropriate AVP secretion, to explain this difference in weight despite similar fluid consumption rates.

Robust research has demonstrated that in cool environments and with race durations of less than 18 hours, EAH is strongly associated with weight gain.[17] However, recent research has demonstrated that in warmer running conditions in longer duration events, EAH is seen more frequently with weight loss than it is with weight gain.[12] This may be explained by increased sweat sodium losses in longer duration

TABLE 2. Differences in Serum and Urine Sodium, AVP, and Nonosmotic Stimuli in GNW100s Athletes From Prerace to Finish

	All Athletes (N = 15)		EAH (n = 10)		Non-EAH (n = 5)	
	Prerace	Finish	Prerace	Finish	Prerace	Finish
Serum [Na^+], mmol/L	139.3 (3.1)	136.7 (3.4)*	138.7 (3.7)	135 (1.7)*	140.6 (0.6)	140.2 (3.4)*
AVP, pmol/L	5.2 (2.5)	15.4 (12.8)*	5.0 (2.7)	13.8 (12.8)*	5.6 (2.3)	18.6 (13.7)*
IL-6, pg/mL	0.3 (0.3)	9.8 (5.2)*	0.1 (0.2)	10.6 (6.1)*	0.5 (0.4)	8.4 (2.8)*
Blood glucose, mmol/L	5.0 (1.2)	5.7 (1.3)*	5.0 (0.6)	5.9 (1.0)*	4.9 (2.0)	5.2 (1.8)
Urine [Na^+], mmol/L†	89.0 (56.6)	48.4 (55.2)*	80.4 (31.7)	25.8 (15.0)*	104.4 (89.1)	89.2 (79.0)
Urine osmolality†, mmol/kg	499.6 (258.6)	883.6 (268.1)*	512.4 (236.9)	784.4 (284.0)*	476.6 (322.6)	1062.0 (101.9)*

Continuous variables are expressed as mean (SD) unless specified.
*Significant difference between prerace and postrace values ($P < 0.05$).
†n = 14, EAH = 9, non-EAH = 5.

TABLE 3. Comparison of Characteristics of Athletes With and Without EAH

Variable	All Athletes	Normonatremic	Hyponatremic
Athletes (n)	15	5	10
Age, y	43.7 (9.8)	43.8 (8.0)	43.7 (11.0)
Weight change, kg	−2.9 (1.1)	−3.7 (0.9)	−2.5 (0.9)*
Weight change, %	−4.2 (1.4)	−5.2 (0.9)	−3.6 (1.4)*
100 km race time, h†	18.5 (3.2)	14.8 (1.8)	19.7 (3.5)
100 mile race time, h‡	33.2 (3.6)	30.5 (4.0)	35.2 (1.5)
100 km total fluid consumed, mL†	10 840 (3239)	13 400 (3818)	9987 (2876)
100 mile total fluid consumed, mL‡	16 000 (3829)	14 278 (2182)	17 293 (4577)
Fluid consumption, mL/h	547 (182)	641 (250)	501 (128)
Fluid consumption, $mL \cdot kg^{-1} \cdot h^{-1}$	7.72 (2.14)	8.85 (2.83)	7.15 (1.6)
Reported EAH symptoms	11/15	4/5	7/10
Use of NSAIDs	7/15	0/5	7/10
Use of salt supplements	10/15	4/5	6/10

Continuous variables are expressed as mean (SD) unless specified.
*$P < 0.05$ comparing the normonatremic and hyponatremic groups.
†All athletes (n = 8), normonatremic (n = 2), hyponatremic (n = 6).
‡All athletes (n = 7), normonatremic (n = 3), hyponatremic (n = 4).

events, impaired mobilization of osmotically inactive sodium stores, and/or inappropriate inactivation of osmotically active sodium.[12] This may explain why none of the hyponatremic athletes in our results gained weight as the race was of longer duration and performed in warm conditions. However, these factors were not assessed in this study.

Although the number of athletes studied was small, every female athlete developed EAH during the event compared with 7 of 12 male athletes. In both the 100-km and 100-mile races, EAH athletes finished the race on average 5 hours later than normonatremic athletes. In the 100-km group, this difference approached significance ($P = 0.06$). This supports a trend toward slower pace being associated with EAH.

Use of NSAIDs has been associated with EAH because of its ability to potentiate the effects of AVP.[18,19] All 7 athletes who used NSAIDs (during the race or within 24 hours of the race) developed EAH. Six of the 7 athletes ingested NSAIDs before developing EAH. These findings suggest that NSAIDs played a role in the pathogenesis of EAH in these ultramarathoners, perhaps by potentiating the effect of AVP on the renal system thus lowering the threshold for developing EAH.

Our results also suggest that the use of salt supplements is not protective against EAH given that 6 of 10 athletes with hyponatremia used salt supplements.

Nonosmotic Stimuli

Several studies have demonstrated an increase in AVP after induction of hypoglycemia.[20–23] Our data did not show any significant correlation of AVP concentration with blood glucose levels although a positive correlation in the hyponatremic subgroup approached significance (Table 4, Figure 2).

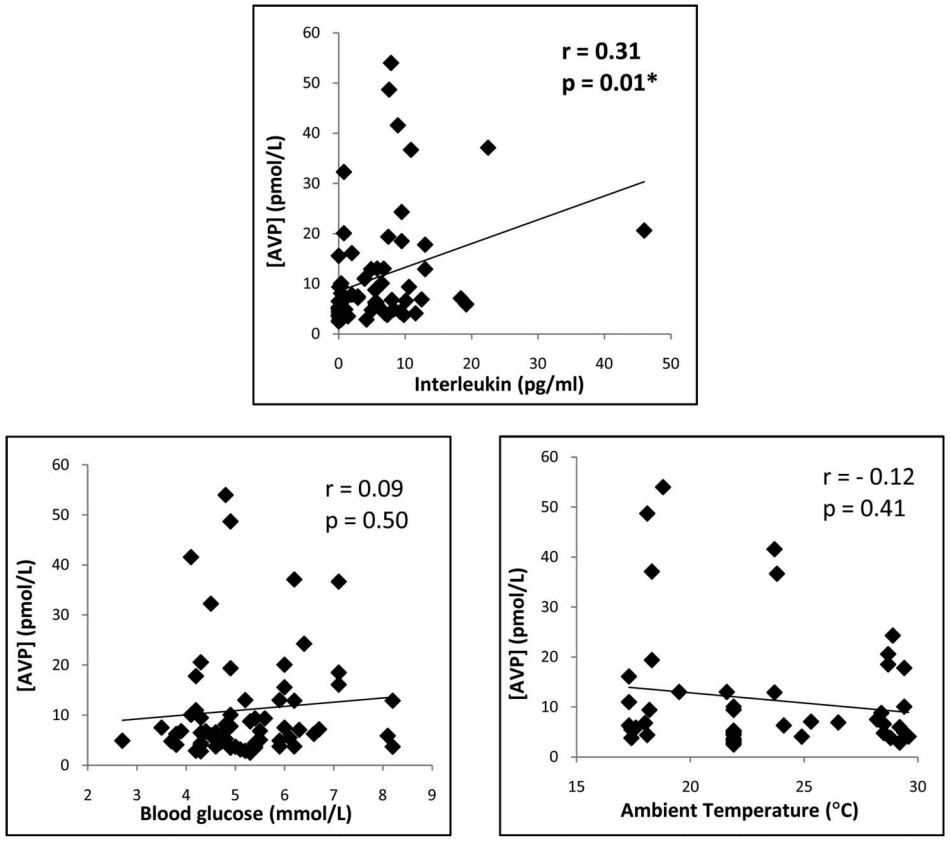

FIGURE 2. Linear relationships between AVP concentration and the nonosmotic stimuli of blood glucose, ambient temperature, and IL-6.

TABLE 4. Regression Analyses Comparing AVP With Nonosmotic Stimuli

	IL-6			Blood Glucose			Ambient Temperature		
	All Athletes (N = 15)	Non-EAH (n = 5)	EAH (n = 10)	All Athletes (n = 15)	Non-EAH (n = 5)	EAH (n = 10)	All Athletes (n = 15)	Non-EAH (n = 5)	EAH (n = 10)
AVP data points	65	23	42	66	23	43	52	18	34
r Value	0.31*	0.31	0.37*	0.09	0.12	0.30	0.12	0.23	0.11

*Significant correlations with $P < 0.05$.

Animal studies indicate that AVP may be an endogenous antipyretic.[24,25] Other studies suggest exercise itself is pyrogenic.[26] Therefore, it is hypothesized that AVP concentration may increase in exercise to maintain body temperature homeostasis.[15] Our data did not demonstrate any correlation of ambient temperature with AVP. Moreover, our data suggested an opposite relationship with lower ambient temperatures associated with higher AVP concentrations during the course of the race (temporal data not shown). As such, our data set does not rule out any association between hypoglycemia or hypothermia and AVP but could not detect any such relationships because of the lack of "extreme" values (significant hypoglycemia or excessively hot ambient temperatures) in our cohort.

Increased IL-6 levels have been hypothesized as a nonosmotic stimulus of AVP.[15,27] Research has demonstrated a positive correlation between IL-6 and AVP, with one study identifying IL-6 as a direct secretagogue for AVP.[28,29] Interleukin-6 levels increase dramatically in exercising humans with IL-6 being produced from exercising muscle rather than from circulating inflammatory cells.[30,31] Endurance athletes have had elevations of IL-6 concentrations up to 8000 times the prerace level.[14,32,33] Interleukin-6 may be important during exercise to mobilize energy stores,[34–36] demonstrated by a reduced exercise capacity in IL-6–deficient mice.[37] The increased IL-6 production is possibly because of muscle contraction and/or release of calcium from the sarcoplasmic reticulum, which activates myocyte IL-6 transcription factors.[36] However, local muscular inflammation from muscle fiber breakdown also causes increased IL-6 concentrations, suggesting rhabdomyolysis could be related to the development of EAH.[27,38]

There is evidence to support that endurance exercise stimulates IL-6 production, which in turn stimulates nonosmotic secretion of AVP which may result in EAH, especially in athletes who drink ahead of thirst. Previous ultramarathon research has identified increased IL-6 from prerace to postrace but found a negative nonsignificant correlation of IL-6 to AVP.[14] However, our results contradict this study. We identified a statistically significant positive correlation of IL-6 to AVP, and when subgroup analysis was performed, there was no correlation of IL-6 to AVP in normonatremic athletes but a significant correlation was present in the hyponatremic athletes. As yet, this is the strongest evidence identified that IL-6 may stimulate secretion of AVP during exercise, precipitating EAH.

The presence of IL-6 may be physiological rather than pathological, and therefore, strategies to combat EAH should not be aimed at reducing IL-6. Instead, we must recognize that AVP concentrations may be higher than expected, thereby increasing an athlete's vulnerability to develop EAH, especially if they ignore their thirst regulation and drink ahead of thirst. Interleukin-6 may be present in a pathological state too. This is most likely when inflammation is present secondary to illness or exertional rhabdomyolysis. This might explain why athletes with recent illness, interrupted training, or lacking event experience are considered to be at high risk for EAH. Therefore, appropriate training to allow adequate athlete preparation and not competing while unwell may reduce the incidence of EAH. This advice is consistent with current guidelines.

Limitations

Our study was limited by having only 15 subjects making statistical significance difficult to achieve without very strong correlations. Two athletes had blood tests within 15 to 30 minutes of finishing the race instead of immediately. This could not be avoided as the athletes pulled out of the race

TABLE 5. Regression Analyses Assessing the Relationship Between Osmotic Parameters in GNW100s Athletes

	AVP—Serum [Na^+] (Entire Race)		AVP—Urine [Na^+] (Race Finish)		AVP—Urine Osmolality (Race Finish)		Serum [Na^+]—Urine [Na^+] (Race Finish)		Serum [Na^+]—Urine Osmolality (Race Finish)	
	AVP	Serum [Na^+]	AVP	Urine [Na^+]	AVP	Urine Osmolality	Serum [Na^+]	Urine [Na^+]	Serum [Na^+]	Urine Osmolality
Mean	11.1	137.7	13.9	48.4	13.9	883.6	136.9	48.4	136.9	883.6
SD	11.2	4.8	11.7	55.2	11.7	268.1	3.5	55.2	3.5	268.1
Range minimum	2.5	119.0	3.8	11.0	3.8	392.0	132.0	11.0	132.0	392.0
Range maximum	54.0	145.0	41.6	199.0	41.6	1264.0	145.0	199.0	145.0	1264.0
Data points	66		14		14		14		14	
r Value	0.03		0.11		0.48		0.55*		0.23	

*Significant correlations with $P < 0.05$.

at points distant to a venesection station. Further studies are recommended on larger athlete populations to verify our findings.

Additionally, we did not measure hematocrit or hemoglobin concentration in our cohort of athletes to critically assess changes in blood or plasma volume. Such changes could potentially influence serum sodium concentrations, via increasing or decreasing hydrostatic forces, which have previously been shown to modify blood sodium concentrations.[39] Therefore, the contribution of plasma volume contraction or expansion could not be assessed (or corrected for) with regard to any of our chosen blood parameters.

We also did not measure core body temperature to accurately assess heat load or cold stress in individuals in response to changes in ambient temperature. Ambient temperature measurements were recorded at each checkpoint, but these were separated by at least 50 km. This means it was not possible to accurately measure overall heat/cold stress experienced by the athletes. Unfortunately, there were no weather stations in close vicinity to the race to gain larger volumes of temperature data to allow for improved correlations of ambient temperature with changes in AVP and/or serum [Na^+].

Finally, our duty of care to the athletes may have affected our results too. All participants were provided with EAH information and were advised before race about the dangers of drinking ahead of thirst. If athletes were within 2% of their original starting weight at any of the checkpoints, we advised that they were drinking too much fluid and reinforced the need to drink to thirst only. Therefore, our evidence-based medical advice may have further reduced the incidence and severity of EAH as seen in our convenience sample.

CONCLUSIONS

The incidence of EAH may be as high as 67% in ultramarathons, which is much higher than previous reports. Given the potential severe consequences of EAH, this highlights the need for improved dissemination of information and education for endurance athletes and medical care providers on fluid consumption strategies to minimize the risk of developing EAH.

We have been able to further confirm the inappropriate secretion of AVP in the presence of low sodium and showed that although hyponatremic athletes lost weight, they lost less weight than normonatremic athletes. Exercise-associated hyponatremia incidence was higher in female than in male athletes, which is consistent with previous studies.

Six out of 7 athletes who used NSAIDs later developed EAH, suggesting NSAIDs may potentiate AVP's effect, thus increasing an athlete's susceptibility to EAH.

Interleukin-6 may be the main nonosmotic stimulus to AVP during prolonged endurance running with no significant relationships detected between AVP and either glycemic status or ambient temperature.

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