Spring 2022

Water Intoxication: Current Developments In Hyponatremia

Allison C. Mosmiller
Gettysburg College

Water Intoxication: Current Developments In Hyponatremia

Abstract

This paper is a review of recent research on the subject of exercise-associated hyponatremia. Hyponatremia is notoriously difficult to diagnose and to treat due to its general symptoms and required specificity in diagnosis in order to assign appropriate treatment. If left untreated, Hyponatremia can result in the development of complications like cerebral edema, seizures, coma, and sometimes death. The pathogenesis of hyponatremia includes multiple proposed mechanisms, including overconsumption of hypotonic fluids, inappropriate release of antidiuretic hormone, inefficiency of fluid filtration by the kidneys, redirection of fluid into intestinal lumen, and activation of the renin-angiotensin-aldosterone system. Signs and symptoms of hyponatremia typically consist of dizziness, fatigue, irritability, generalized weakness, headache, nausea, and decreased urine output. More severe cases can result in presentation of excess thirst, general malaise, fatigue, headache, and vomiting. Timely treatment of hyponatremia is extremely important, and universal diagnosis techniques and treatment methods are still debated.

Keywords

Hyponatremia, exercise, water, sodium

Disciplines

Exercise Physiology | Medicine and Health Sciences | Physiology

Comments

Written for HS 319: Environmental Physiology

Water Intoxication: Current Developments in Hyponatremia

Allie Mosmiller

Dr. Drury HS 319

April 25, 2022

Introduction

Exercise-associated hyponatremia is a common electrolyte imbalance where plasma sodium levels drop below 135 mmol/L within or up to 48 hours after physical activity (Buck et al., 2021). The condition was first introduced in the 1980s and was associated with endurance athletes, but recently has been discovered in many physically demanding activities (Hew-Butler et al., 2017). In 2014, two football players died from low plasma sodium levels, bringing awareness to the dangers of hyponatremia in all athletes (McDermott et al., 2017). A study in 2017 stated that up to 20% of distance athletes had developed hyponatremia, but that is likely an underestimate when applied to the general population. It is anticipated that incidence reporting is inaccurate since diagnosis of hyponatremia is only possible with clinical urinalysis and blood testing. Asymptomatic individuals typically do not seek clinical assistance, often going undiagnosed. This indicates that hyponatremia is much more common than previously thought (Rosner, 2019). Differential diagnosis in pre-hospital settings is made increasingly difficult by mild to moderate symptoms being similar to those of heat related illnesses like heat exhaustion and heat stroke (Buck et al., 2021). Because of this difficulty, and the highly specific treatment dependent on diagnosis, hyponatremia has been thoroughly studied to determine how best to identify and treat it. Without treatment, hyponatremia can result in fatal physiological consequences such as cerebral edema, seizures, coma, and even death. It is important to understand the mechanisms behind the development of hyponatremia in order to enact appropriate prevention and treatment measures.

Etiology

At the Third International Exercise-Associated Hyponatremia Consensus Development Conference pathogenesis of exercise-associated hyponatremia was determined to be mainly

caused by the overconsumption of hypotonic fluids as well as the inappropriate release of anti-diuretic hormone (Hew-Butler et al., 2015). However, in a study observing participants in a New Zealand Ironman triathlon, five subjects developed hyponatremia with moderate water consumption, suggesting that there are other components involved in its development. Speedy et al. defines excessive fluid intake as more than 750 mL during prolonged exercise (2008). In short term exercise, fluid intake is often balanced by water loss. This includes sweating, gastrointestinal and respiratory (insensible) water loss, and urination. Excessive fluid intake is typically a result of lack of education on appropriate hydration practices as well as incorrect suggestions to have the highest intake of fluid possible in order to maintain hydration. This inappropriate consumption is often measured by weight gain after exercise (Rosner, 2019). With appropriate hydration, athletes should experience a consistent or slight decrease in weight from the beginning of exercise due to the balance of fluid gain with fluid loss. Cases where athletes show an increase in weight after exercise correlate with cases of hyponatremia. Endurance athletes are particularly susceptible to hyponatremic events due to their prolonged exertion times in which they are more likely to have excessive intake in fluids as well as diminished opportunities to relieve themselves, leading to increased water content in the body (Hew-Butler et al., 2017).

Acute hyponatremia can occur when the kidneys can no longer maintain water elimination and electrolyte reabsorption alongside high water intake, or due to unnecessary release of ADH (Kheetan et al., 2021). Sodium regulation in the body is highly affected by concentrations of the ion in different compartments. Hyponatremia is typically identified through low plasma sodium levels, and if these levels reach certain severity, it can lead to cell lysis, tissue damage, and sometimes death. In normal physiological ranges, sodium levels exist in

higher concentrations in the extracellular space, largely maintained by Na^+/K^+-ATPase, or the sodium potassium pump. Receptors that signal effectors of sodium balance are osmoreceptors located in the hypothalamic neurons (Sterns, 2015). When activated, these osmoreceptors trigger the release of arginine vasopressin, or anti-diuretic hormone (ADH) that increases reabsorption of fluid from the kidneys. Urine is maximally concentrated when sodium plasma levels decrease to 145 mmol per liter, however in normal osmoregulation, thirst signals from the hypothalamus and ADH secretion are inhibited once sodium plasma falls below 135 mmol per liter (Sterns, 2015). The maximum rate at which the kidneys can filter fluid is approximately 12-15 ml/min^{-1} (Kheetan et al., 2021). Once this rate has been reached, one theory of fluid redirection is accumulation of the unfiltered fluid within the intestine. This fluid buildup within the lumen of the intestine would cause an osmotic gradient of sodium ions, encouraging them to move from the extracellular fluid into the intestine, eventually resulting in hyponatremia. There has been some discrepancy in this theory in ultra-distance compared to ultra-marathon athletes in that the former was found to have elevated post-exercise plasma sodium levels, indicating that there was decreased movement of fluid out of the extracellular space (Kheetan et al., 2021).

In some cases, including non-exercise related hyponatremia, the inappropriate release of arginine vasopressin (AVP) or ADH plays a large role in severity and development of the condition. The normal pathway for AVP release is when arterial baroreceptors detect a decrease in blood volume, leading to release from the posterior pituitary and increased fluid retention from kidney distal tubules (Burst, 2019). This would typically also be accompanied by increased sodium reabsorption due to newly established osmotic gradients and aldosterone release, preventing the development of sodium imbalance. In exercise related cases, ADH is not suppressed as it typically is in the presence of low plasma osmolality due to non-specific stress

that typically accompanies exercise. These stressors can include exercise-associated activation of the sympathetic nervous system, nausea, vomiting, hypoglycemia, heat exposure, and medication use (Hew-Butler et al., 2017). Another theory for ADH release during exercise was evaluated in a study showing a correlation between inerleukin-6 (IL-6), an inflammatory cytokine that has been found to increase during exercise due to its function in mobilization of energy sources as well as muscle breakdown, and increased ADH levels (Hew-Butler et al., 2017).

Contributions to the development of hyponatremia through the loss of sodium via sweat and urine is currently under debate. While sweat does contribute to sodium loss to some extent, most studies are done on highly trained individuals who have developed efficient sweating with minimal sodium loss. This is indicative that in trained individuals, diluted sweat may help prevent hyponatremia by removing hypotonic fluid from the body and possibly equalizing sodium fluid balance (Sterns, 2015). This may indicate that untrained individuals are more susceptible to developing the condition due to higher sodium content in their sweat in addition to decreased knowledge of proper hydration methods. Recent research suggests that bones, skin, and cartilage may be utilized as a sodium reservoir during hyponatremic events. Studies have shown that bone density is directly proportional with changes in plasma sodium concentration throughout endurance exercise (Sterns, 2015). Cartilage has especially high concentrations in order to recruit high fluid pressures to facilitate cushioning during forceful movements and support anatomical structures (Sterns, 2015). In athletes that develop hyponatremia, it's predicted that there is a decreased ability to utilize these non-osmotically active stores, or that sodium is in fact moving into them, decreasing extracellular concentrations (Hew-Butler et al., 2017).

Sympathetic nervous system activation and its initiation of the renin-angiotensin-aldosterone system (RAAS) during endurance exercise should also be considered as a contributor

to hyponatremia. This system is typically activated to increase blood volume via increasing water retention, and is consistent in the maintenance of blood volume during exercise (Hew-Butler et al., 2017). The increased water retention is mediated by angiotensin II and aldosterone, which increase water and sodium reabsorption in the proximal kidney tubule. If there are not sufficient plasma sodium levels prior to exercise, this increase in water retention could be a significant player in the development of hyponatremia. The RAAS system has multiple actions to increase blood volume, including signaling the hypothalamus to increase thirst. This activation may play a role in the increase in thirst experienced during exercise that leads to overhydration.

The greatest risk of hyponatremia that can result in death is cerebral edema. In more severe cases, hyponatremia symptoms often include confusion, delirium, weakness, altered mental status, or even seizures, which all indicate central nervous system dysfunction (Kheetan et al., 2021). What leaves the brain more susceptible to damage than other tissues is the anatomical difference of its capillaries, whose anatomical properties form the blood brain barrier, inhibiting easy diffusion of certain solutes (Kheetan et al., 2021). When extracellular levels of sodium drop below that of intracellular compartments, water moves along down its concentration gradient into cells, leading to swelling. The primary response to avoid brain swelling associated with hyponatremia is the shift of fluid from the brain to cerebrospinal fluid and eventually to peripheral vessels. If conditions do not improve, the body begins to decrease intracellular ion concentration to avoid cellular swelling (Kheetan et al., 2021). This ion decrease can lead to disruption of neuron function, contributing to the altered mental status that some patients experience. Brain cells also avoid cellular swelling through the rapid movement of electrolytes and the slower movement of organic osmolytes in order to maintain intracellular and extracellular osmolality (Sterns, 2018). Unfortunately, these response mechanisms only occur

after the system has reached a upper limit of tolerance or over long periods of time, giving time for edema to develop to concerning levels (Knechtle et al., 2019).

Signs and Symptoms of Hyponatremia

Hyponatremia is notoriously difficult to diagnose in the prehospital setting due to its general cognitive and physical symptoms. Primary care providers should consider exercise-associated hyponatremia as the origin of complaint in patients that present with symptoms during or within 24 to 48 hours of high intensity exercise, especially if the event lasted over 2 hours (Buck et al., 2021). In the past, exercise-associated hyponatremia was typically correlated with long duration activities like endurance running or triathlons, but more activities have been found to have risk of development of hyponatremia such as hiking, kayaking, climbing, and biking (Rosner, 2019). Mild symptoms include dizziness, fatigue, irritability, generalized weakness, headache, nausea, and decreased urine output. Initial symptoms like thirst, general malaise, fatigue, headache, and vomiting are identical to that of severe dehydration, making diagnosis more difficult. It is not until more severe symptoms develop that hyponatremia is able to be identified outside of the hospital setting (McDermott et al., 2017). Severe symptoms indicate a higher level of cognitive dysfunction and damage, including altered mental status, vomiting, dyspnea, pulmonary edema, unconsciousness, seizure, coma, or death (Armstrong, 2021). A differential diagnosis is aided by the lack of symptoms indicating dehydration, such as dry mucous membranes, orthostatic hypotension, and high core temperature (Rosner, 2019). Mild cases of hyponatremia can primarily present as asymptomatic, but signs such as slight hyperthermia, tachycardia, flushing of the skin, diaphoresis, and lethargy may be signs of low sodium levels. Providers should abstain from administering fluid until a comprehensive blood test can be performed (Buck et al., 2021).

Diagnosis and Treatment

Diagnosis and treatment for acute hyponatremia has developed to defined pre-hospital and clinical procedures. Historically, there have been risks in the treatment of hyponatremia involved in misdiagnosis and administration of hypotonic saline, which further decreases plasma sodium concentration, as well as rapid treatment resulting in the complication of osmotic demyelination syndrome (Sterns, 2018). These risks make accurate diagnosis crucial in determining appropriate treatment.

Prehospital Diagnosis and Treatment

It is important to recognize symptoms in the pre-hospital setting in order to avoid the administration of hypotonic saline, which will aggravate symptoms and significantly increase the progression of the condition. Since symptoms of mild hyponatremia are subtle and can often be mistaken for other conditions like heat exhaustion or dehydration, it is important to obtain a thorough initial assessment. Proper hydration allows the body to optimally thermoregulate, allowing temperature to be used as a diagnostic tool (McDermott et al., 2017). While a rectal temperature achieves the most accurate measurement of core temperature, it is often uncomfortable for the patient in the prehospital setting, so an oral or axillary temperature should be obtained to differentiate hyponatremia from heat illnesses like heat exhaustion and heatstroke (Buck et al., 2021). If within the scope of care, a 100 mL bolus of hypertonic saline should be administered orally or intravenously if there is a presence of neurological symptoms which indicate severe hyponatremia. If hypertonic saline is unavailable, clinical medical attention is temporarily unavailable, and the patient is neurologically stable, it's recommended the patient consume food or fluid with high sodium concentration until onset of urination (Rosner, 2019).

Clinical Diagnosis and Treatment

In hospital settings, adequate testing is required to determine the level of severity of hyponatremia in order to prescribe the correct treatment. New classifications of hyponatremia subtypes have been developed by major organizations in the US in Europe. Moderate hyponatremia is defined as 125-129 mmol/L of serum sodium, and severe hyponatremia is defined as less than 125 mmol/L (Hoorn & Zietse, 2017). Initial testing should determine whether the patient has hypotonic or non-hypotonic hyponatremia. Exercise associated hyponatremia typically falls under hypotonic hyponatremia, whereas non-hypotonic hyponatremia can be caused by hyperglycemia, administration of mannitol, or hypertonic radiocontrast (Hoorn & Zietse, 2017). Hypotonic hyponatremia has been further divided into hypovolemic, euvolemic, and hypervolemic hyponatremia. Hypovolemic and euvolemic are difficult to distinguish from each other upon physical examination, whereas hypervolemic hyponatremia is often accompanied by symptoms such as edema or ascites depending on the severity (Hoorn & Zietse, 2017). Testing should include urine osmolality, urine sodium levels, urine output, fractional uric acid excretion, and plasma copeptin concentration. Copeptin is an ADH prohormone that can be measured easily to indicate levels of ADH release, and may bring light to the inappropriate release of the hormone (Hoorn & Zietse, 2017). Priority in testing should be taken by urine osmolality and urine sodium due to evidence showing better diagnostic performance when considering these variables over volume status (Hoorn & Zietse, 2017). Differentiation of hypovolemic hyponatremia and hypervolemic hyponatremia can be found in evaluation of urine sodium levels since the kidneys will react to changes in blood volume. A urine sodium value of 30 mmol/L or below can be defined as hypovolemic hyponatremia.

Those with lower sodium levels around 120 mEq/L or less of serum sodium concentrations upon hospitalization are at lower risk of rapid correction complications (Sterns,

2018). Presentation of less severe hyponatremia in patients is indicative of higher risk for developing osmotic demyelination syndrome. Osmotic demyelination is often found in patients with serum sodium concentrations equaling <115 mEq/L, and results from overcorrection of hyponatremia (Tandukar et al., 2021). Osmotic demyelination occurs when the brain has responded to low levels of sodium by the movement of organic osmolytes into the extracellular space to avoid cellular swelling and lysis. The movement of these osmolytes out of the cell disrupts their function in production, function, and maintenance of oligodendrocytes, which produce the neuron's myelin sheaths. These myelin sheaths allow for increased action potential velocity and high efficiency of neuroglial communication, neuronal excitability, and neurotransmission. When the function of the oligodendrocytes is disrupted, destruction of the oligodendrocytes and myelin sheaths occurs, resulting in presentation of neurological symptoms associated with osmotic demyelination syndrome (Tandukar et al., 2021). While patients who have more severe hyponatremia are at less of a risk of developing complications due to overcorrection, compared to mild hyponatremia, more severe versions of the condition are correlated to higher mortality rates (Turkmen et al., 2021). It is important to determine how much treatment is appropriate due to the high sensitivity of cerebral tissues to changes in osmolality. Some case studies suggest that rapid correction of 4-6 mEq/L prevents the development of hyponatremic seizures, and administration of hypertonic saline to raise serum sodium concentrations by 5 mEq/L has been used to prevent cerebral edema by increasing extracellular osmolality (Sterns, 2018). To avoid osmotic demyelination, relowering sodium plasma levels within physiologically normal ranges within 12 hours of rapid treatment should be considered. Physicians should be wary of symptoms appearing 1-7 days after treatment including seizures, behavioral disturbances, swallowing disfunction, paralysis, or movement disorders

(Sterns, 2018). In hospital treatment should include a bolus of 100 mL of 3% NaCl hypertonic saline either intravenously or orally with the goal to raise serum sodium concentrations by 4-5 mm/L or until neurological symptoms are resolved (Buck et al., 2021). In severe cases, it is not uncommon for a second bolus of hypertonic saline to be administered, however this significantly increases the risk of overcorrection complications. New suggestions include careful monitoring of symptoms and serum sodium levels with high caution during administration of a second bolus, as well as a possible decrease in bolus volume (Chifu et al., 2021).

Prevention

Individuals who are at higher risk of developing hyponatremia should take extra precautions before physical activity. The prevalence of hyponatremia has always been higher in women than in men (Knechtle et al., 2019). One case describes a 42-year-old ironman participant who presented post-race with headache, nausea, and confusion. She gradually developed more severe symptoms, including seizures, cerebral edema, and a plasma sodium concentration of 123 mmol/L. She had to be intubated, forced to urinate, and after 16 hours of treatment her plasma sodium levels returned to normal levels. She was extubated two days later and after 6 months was able to return to work (Knechtle et al., 2019). While some studies have shown that women have a higher incidence of exercise-associated hyponatremia, when adjusted for duration of the activity and body-mass index (BMI), sex difference was not statistically significant (Rosner, 2019). The discrepancy often found between sexes is likely due to low body weight, which is associated with decreased speed and increased likelihood of exercise weight gain. Other risk factors include short stature, low body weight, low BMI, slow running pace, low competition experience, use of non-steroidal anti-inflammatory drugs (NSAIDs), duration of the event being four hours or longer, extreme heat, and extreme cold (Knechtle et al., 2019).

The most straightforward prevention method to reduce the risk of developing hyponatremia is strategic hydration. The danger of endurance activities is the prior impression to drink as much as possible in order to avoid dehydration (López de Lara et al., 2021). Overconsumption of fluids is one of the main causes of hyponatremia, making appropriate hydration during exercise extremely important. In one study, ad libitum drinking, or drinking as much and as often as desired, was encouraged. Out of 28 participants, only one developed a mild form of hyponatremia that was asymptomatic (Nolte et al., 2019). In a study where endurance athletes were educated on hydration strategies before a race, only 1.6% of athletes developed hyponatremia after the event, which was very mild (134 mmol/L) (López de Lara et al., 2021). These results show that by educating athletes prior to endurance events on proper hydration strategies and the importance of only drinking upon thirst, most cases of hyponatremia can be prevented. According to the National Athletic Trainer's association, individuals participating in strenuous physical activity should monitor their weight before and after exercise to ensure that there is no excess fluid intake that exceeds the weight that is lost during activity (McDermott et al., 2017). On an individual level, hydration status can be evaluated through personal cues such as thirst sensation, urination frequency, and urine color. These factors should be investigated before strenuous physical activity to inform the individual on their hydration status to avoid hypohydration or hyperhydration. (McDermott et al., 2017). Because fluid loss during exercise is highly variable between individuals, developing a personal hydration plan is important in prevention of hyponatremia (Rosner, 2019)

Non-hydration related strategies for hyponatremia prevention are minimal but can be useful for individuals when preparing for endurance activities. Recent studies have examined effect of sodium intake during endurance exercise to see if supplementation can prevent the

development of hyponatremia. Sodium supplementation has become a common practice among endurance athletes in an attempt to prevent muscle cramping, dehydration, and reduce nausea (Hoffman & Stuempfle, 2015). Unfortunately, sodium intake during exercise is not correlated with reduction of nausea or prevention of muscle cramping, dehydration, and hyponatremia (Hoffman et al., 2015). Glycerol is another commonly consumed supplement before exercise to aid in prolonging exercise that would otherwise be shortened by dehydration. Glycerol increases water retention and plasma volume, ultimately leading to a decrease in plasma osmolality. This can worsen the effects of overhydration if combined with excessive water intake, and should be used with caution to avoid hyponatremia (Armstrong, 2021).

Conclusion

Hyponatremia is the most common exercise-associated electrolyte imbalance that is life-threatening, yet highly preventable (Hew-Butler et al., 2008). While the condition is associated with a complicated etiology, the largest contributor to exercise-associate hyponatremia is overhydration (Rosner, 2019). Education of athletes, coaches, first responders, and physicians on appropriate prevention techniques and treatment options are important moving forward. This should include information about the consequences of dehydration and fluid overload, hydration-monitoring strategies including pre- and post-exercise weight measurements, scheduling to allow for optimal hydration, and environmental influences on fluid intake (McDermott et al., 2017). Those who present with mild to moderate symptoms of hyponatremia should seek the advice of their physician regarding treatment, and severe symptoms should be treated with one or more boluses of hypertonic saline in a clinical setting (Hew-Butler et al., 2017). Adjustment to guidelines for prevention measures and treatment may improve incidence and mortality rates associated with hyponatremia (Hew-Butler et al., 2017).

References

Armstrong, L. (2021). *Rehydration during Endurance Exercise: Challenges, Research, Options, Methods*. *13*(3). https://doi.org/10.3390/nu13030887

Buck, E., Miles, R., & Schroeder, J. (2021). Exercise-Associated Hyponatremia. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK572128/

Burst, V. (2019). *Etiology and Epidemiology of Hyponatremia*. *52*, 24–35.

Chifu, I., Gerstl, A., Lengenfelder, B., Schmitt, D., Nagler, N., Fassnacht, M., & Weismann, D. (2021). *Treatment of symptomatic hyponatremia with hypertonic saline: A real-life observational study*. *184*(5), 647–655. https://doi.org/10.1530/EJE-20-1207

Hew-Butler, T., Jordaan, E., Stuempfle, K., Speedy, D., Siegel, A., Noakes, T., Soldin, S., & Verbalis, J. (2008). *Osmotic and nonosmotic regulation of arginine vasopressin during prolonged endurance exercise*. *93*(6), 2072–2078. https://doi.org/10.1210/jc.2007-2336

Hew-Butler, T., Loi, V., Pani, A., & Rosner, M. (2017). *Exercise-Associated Hyponatremia: 2017 Update*. *4*, 21. https://doi.org/10.3389/fmed.2017.00021

Hew-Butler, T., Rosner, M., Fowkes-Godek, S., Dugas, J., Hoffman, M., Lewis, D., Maughan, R., Miller, K., Montain, S., Rehrer, N., Roberts, Wi., Rogers, I., Siegel, A., Stuempfle, K., Winger, J., & Verbalis, J. (2015). *Statement of the Third International Exercise-Associated Hyponatremia Consensus Development Conference, Carlsbad, California, 2015*. *25*(4), 303–320. https://doi.org/10.1097/JSM.0000000000000221

Hoffman, M., & Stuempfle, K. (2015). *Sodium Supplementation and Exercise-Associated Hyponatremia during Prolonged Exercise*. *47*(9), 1781–1787. https://doi.org/10.1249/MSS.0000000000000599

Hoffman, M., Stuempfle, K., & Valentino, T. (2015). *Sodium Intake During an Ultramarathon Does Not Prevent Muscle Cramping, Dehydration, Hyponatremia, or Nausea*. *1*(1), 39. https://doi.org/10.1186/s40798-015-0040-x

Hoorn, E., & Zietse, R. (2017). *Diagnosis and Treatment of Hyponatremia: Compilation of the Guidelines*. *28*(5), 1340–1349. https://doi.org/10.1681/ASN.2016101139

Kheetan, M., Ogu, I., Shapiro, J., & Khitan. (2021). *Acute and Chronic Hyponatremia*. *6*. https://doi.org/10.3389/fmed.2021.693738

Knechtle, B., Chlíbková, D., Papadopoulou, S., Mantzorou, M., Rosemann, T., & Nikolaidis, P. (2019). *Exercise-Associated Hyponatremia in Endurance and Ultra-Endurance Performance—Aspects of Sex, Race Location, Ambient Temperature, Sports Discipline, and Length of Performance: A Narrative Review*. *55*(9), 537. https://doi.org/10.3390/medicina55090537

López de Lara, D., Ruiz-Sánchez, J. G., Cuesta, M., Seara, G., Calle-Pascual, A. L., Rubio Herrera, M. Á., Runkle, I., & Verbalis, J. G. (2021). *Exercise-Induced Hyponatremia: An Assessment of the International Hydration Recommendations Followed During the Gran Trail De Peñalara and Vitoria-Gasteiz Ironman Competitions*. *8*. https://doi.org/10.3389/fnut.2021.781229

McDermott, B., Anderson, S., Armstrong, L., Casa, D., Cheuvront, S., Cooper, L., Kenney, L., O'Connor, F., & Roberts, W. (2017). *National Athletic Trainer's Association Position Statement: Fluid Replacement for the Physically Active*. *52*(9), 877–895. https://doi.org/10.4085/1062-6050-52.9.02

Nolte, H., Nolte, K., & Hew-Butler, T. (2019). *Ad libitum water consumption prevents exercise-associated hyponatremia and protects agains dehydration in soldiers performing a 40-km route-march*. *6*. https://doi.org/10.1186/s40779-019-0192-y

Rosner, M. (2019). *EXERCISE-ASSOCIATED HYPONATREMIA*. *130*, 76–87.

Speedy, D., Noakes, T., & Schneider, C. (2008). *Exercise-associated hyponatremia: A review*. *13*(1), 17–27. https://doi.org/10.1046/j.1442-2026.2001.00173.x

Sterns, R. (2015). *Disorders of Plasma Sodium—Causes, Consequences, and Correction*. *372*(1), 55–65. https://doi.org/10.1056/NEJMral404489

Sterns, R. (2018). *Treatment of Severe Hyponatremia*. *13*(4), 641–649. https://doi.org/10.2215/CJN.10440917

Tandukar, S., Sterns, R., & Rondon-Berrios, H. (2021). *Osmotic Demyelination Syndrome following Correction of Hyponatremia by ≤10 mEq/L per Day*. *2*(9), 1415–1423. https://doi.org/10.34067/KID.0004402021

Turkmen, E., Karatas, A., & Altindal, M. (2021). *Factors affecting prognosis of the patients with severe hyponatremia*. *42*(2), 113–222. https://doi.org/10.1016/j.nefro.2021.03.007.