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A review in overhydration underlying Exercise-Associated Hyponatremia

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Abstract

Exercise-associated hyponatremia (EAH) is hyponatremia occurring during or up to 24 hours after prolonged physical activity. There is clear evidence that the primary cause of EAH is overconsumption of fluids relative to fluid losses. The electrolyte imbalance, in particular sodium triggered by overhydration is the aetiologic basis behind the illness. If untreated, hyponatremia causes cerebral and pulmonary edema resulting in seizures, coma and on occasion, death. Current understanding of overhydration underlying EAH is discussed. Aetiology, pathology, diagnosis, the role of sodium and preventive measures are key focal points in this review. The body of research spans more than two decades comprising of pioneering and up-to-date studies. Risk factors identified show strong correlation to hyponatremia. It is concluded that the underlying cause is more likely to be a combination of risk factors. Insufficient knowledge in the relationship between contributing risk factors has prompted the proposal of further study. EAH is a complex illness. With the health-conscious population expanding, incidence rates are rising. Educational strategies must be introduced to sport events and to individuals susceptible to EAH, promoting moderate fluid intake "*ad libitum*", thus benefiting the general population undertaking prolonged exercise. There is current controversy regarding sodium supplementation to prevent the onset of EAH with the literature supporting positions both for and against this supplement. Excessive sodium supplementation for ultra-endurance athletes may not be viable to counteract low sodium levels. In addition, the role of sodium depletion is not yet fully established, highlighting the necessity for further research in this field.

Introduction

Water is essential for life and maintaining optimal levels of hydration is important for humans to function well (Benelam and Wyness, 2010). Body fluid provides an enormous array of essential functions for human survival such as blood, saliva, synovial fluid, urine and sweat, containing specific concentration of solutes critical for the body to function correctly. The concentration of these solutes, known as osmolality are tightly controlled (Benelam and Wyness, 2010) where slight deviations in plasma osmolality under normal conditions stimulate mechanisms either to conserve or excrete water (Grandjean and Campbell, 2004) signifying that solute concentration, in particular sodium, is even more important than water alone for hydration. Disruption of sodium plasma homeostatic regulation associated with overhydration can be caused by various environmental and physiological processes such as exercise, sweat, temperature, diarrhoea, fever, fluid consumption and osmolality pathologies. Overhydration can dilute sodium plasma levels causing hyponatremia, leading to life-threatening symptoms. Sport events such as marathons and triathlons have been the primary focus on investigating exercise-associated hyponatremia (EAH). A condition first reported more than 2 decades ago, (Noakes *et al.,* 1985, Frizzell *et al.,* 1986) EAH has come to be recognised as arguably the most important, serious medical problem in endurance sport events (Hew-Butler *et al.,* 2008). With the population of health-conscious individuals undertaking more physical exercise increasing, EAH incidence rates are rising (Lau and Choi, 2009) highlighting the overall importance of establishing awareness of this preventable illness.

This review will focus on overhydration and the underlying aetiology and pathologies of EAH. Pioneering studies have revealed many risk factors with strong correlation to hyponatremia, where excessive fluid consumption is thought to be the primary cause. However, the identified risk factors may contribute collectively or individually, a debate which requires further investigation. Exercising in hot environments may complicate hyponatremia and, additionally, may have adverse effects on diagnosis, where signs and symptoms may resemble those of other heat-related illnesses. Using numerous case studies, the role of sodium in EAH will be reviewed in combination with certain “grey” areas such as whether sodium supplementation is beneficial for preventing EAH in ultra-endurance athletes. The review will highlight throughout the importance of awareness and educational strategies to overall decrease the incidence rate of EAH.

Exercise-Associated Hyponatremia

It is widely accepted that EAH is the occurrence of hyponatremia during or up to 24 hours after prolonged physical activity (Almond *et al.,* 2005, Armstrong *et al.,* 1993, Clark and Gennari, 1993, Davis *et al.,* 2001, Frizzell *et al.,* 1986, Hew *et al.,* 2003, Hew-Butler *et al.,* 2008, Noakes *et al.,* 2004, Speedy *et al.,* 2000b) and is diagnosed when serum or plasma sodium concentration ($[Na^+]$) is below normal reference range of <135 mmol/L (Kratz *et al.,* 2002). Moderate EAH is defined as sodium between 130 to 121 mmol/L, and severe EAH is when the sodium is equal to or less than 120 mmol/L (Lau and Choi, 2009) with each stage presenting particular symptoms.

Signs and symptoms of EAH can develop when the sodium falls below 135 mmol/L (Hew *et al.,* 2003), however EAH is generally asymptomatic when sodium levels are between 130-134 mmol/L (Hiller *et al.,* 1987). Ayus *et al.,* (1992) state that early

symptoms of EAH including bloating, puffiness, nausea, vomiting, and headache are more likely to occur when there is a significant reduction in sodium, approaching a 7-10% decrease within a 24 hour period. These symptoms arise due to an increase of cell swelling and pressure, the consequence of excessive fluid intake compared to fluid losses result in low solute concentration outside of the cell relative to inside causing a fluid shift via osmosis (Moreau, 2004). If EAH is left untreated, hyponatremia can progress further. The lower the sodium the more severe the signs and symptoms become (Arieff *et al.,* 1976), advancing into potential life-threatening pathophysiological states such as cerebral edema (Clark and Gennari, 1993), altered mental status, confusion, disorientation, agitation and delirium (Davis *et al.,* 2001), seizures (Rothwell and Rosengren, 2008), respiratory distress (Luks *et al.,* 2007), coma and death (Garigan and Ristedt, 1999). This significant sodium decrease can be caused by several risk factors, primarily by continual increased fluid consumption in prolonged exercise (Hew-Butler *et al.,* 2008) and possibly through sodium depletion relative to sodium supplementation, as discussed later.

Risk factors for Exercise-Associated Hyponatremia

Early case studies have been at the forefront in establishing the underlying risk factors associated with EAH. The studies primarily focused on endurance events such as marathons (Davis *et al.,* 2001, Almond *et al.,* 2005) and triathlons (Speedy *et al.,* 1999) for the convenience of data collection such as; a large sample, set distance and an array of participants including age, sex, fitness and running experience. Davis *et al.,* (2001) completed a study at the 1998 and 1999 Suzuki Rock 'N' Roll Marathon® identifying risk factors for the development of EAH. A total of 26 participants from both 1998 and 1999 marathons were diagnosed as hyponatremic sodium<135 mmol/L including 15 with severe hyponatremia sodium<125 mmol/L. The group concluded that participants with greater risk factors were more likely to be female, have taken nonsteroidal anti-inflammatory drugs (NSAIDs) one week before the race, and have a slower finishing time (Davis *et al.,* 2001). A later comprehensive study was completed by Almond *et al.,* (2005) investigating hyponatremia among runners in the Boston marathon. Establishing similar aims to Davis *et al.,* (2001), Almond *et al.,* (2005) studied their cohort to estimate the incidence of hyponatremia and to identify the principal risk factors. Of 766 runners enrolled, 488 runners provided a usable blood sample at the finish line, 63 runners had hyponatremia (sodium<135 mmol/L) and three runners had severe hyponatremia (sodium<120 mmol/L). The risk factors identified by the group were; weight gain, >3 L fluid consumption during race, consumption of fluids every mile, slow race time >4:00 hours, female and low body-mass index. In addition, an array of studies all contributed to the well documented range of risk factors presented in Table 1. However, contrary to the well-established risk factors, a study by Hew-Butler *et al.,* (2008b) found experienced and well-trained male athletes perceived to be at no risk of EAH, were not immune to developing EAH if sustained fluid intake exceeded the capacity for fluid output. They concluded that risk factors are not necessarily the underlying causation of EAH (Hew-Butler *et al.,* 2008), however they do show a strong correlation with high incidence rates of EAH. Studies have identified that some individuals may be more predisposed to EAH than others, presenting a complex situation in aetiology requiring further investigation.

Table 1: A range of well-documented risk factors shown to increase the susceptibility of exercise-associated hyponatremia.

- **Low body weight** (Almond *et al.,* 2005, Stuempfle *et al.,* 2002, Speedy *et al.,* 2000b)
- **Female sex** (Almond *et al.,* 2005, Stuempfle *et al.,* 2002, Backer *et al.,* 1999, Davis *et al.,* 2001)
- **>4 hours of exercise** (Armstrong *et al.,* 1993, Clark and Gennari, 1993, Speedy *et al.,* 2000a)
- **Slow running or performance pace** (Almond *et al.,* 2005, Hew *et al.,* 2003, Noakes *et al.,* 1985)
- **Race inexperience** (Hew *et al.,* 2003, Shapiro *et al.,* 2006, Young *et al.,* 1987)
- **Excessive drinking behaviour** (Davis *et al.,* 2001, Reynolds *et al.,* 1998, Gardner, 2002, Hew *et al.,* 2003)
- **High availability of drinking fluids** (Hew *et al.,* 2003, Speedy *et al.*, 2000a)
- **Nonsteroidal anti-inflammatory agents** (Wharam *et al.,* 2006, Ayus *et al.,* 2000, Baker *et al.,* 2005)
- **Extremely hot or cold environmental conditions** (Flinn and Sherer, 2000, Reynolds *et al.,* 1998, Stuempfle *et al.,* 2002)

Investigating the Relationship between Risk Factors

During rest, maximal urine excretory rates are typically 800 to 1000 mL/hr (Ayus *et al.,* 2000), the consumption of fluids over the rate may lead to dilutional hyponatremia (Noakes *et al.,* 2001). Sweat is the primary mode of water and sodium loss during exercise, thus individuals exercising at low intensities would perhaps require less fluid than those at high intensities. The rise in metabolic heat production is smaller, consequently lowering total sweat amount required for thermoregulation. This might explain why females with low body weight, exercising at low intensities are more susceptible to overhydrating, perhaps due to a lower fluid requirement. To test this theory, a study investigating two female groups; selecting one high and one low body weight group could be undertaken to examine differences, if any, between rates of EAH relative to metabolic heat production and sweat rate. These important answers would help establish preventable measures such as fluid restriction for groups susceptible of EAH and may open up opportunities for further studies addressing the relationship between risk factors.

Overhydration Case Studies – Diagnosis Complications

Marathon running has become increasingly popular among athletes and non-athletes over recent decades. With the population of health-conscious individuals undertaking more physical exercise increasing, the incidence of EAH is expected to continue to rise in the future (Lau and Choi, 2009). The largest EAH studies have been conducted in the setting of mass participation sporting events, such as endurance triathlons (Speedy *et al.,* 1999) and marathons (Hew *et al.,* 2003, Almond *et al.,* 2005), as discussed earlier. Reports have emerged of serious illness and death from hyponatremia *(Ayus et al.,* 2000, Nearman, 2002) signifying the importance of broadening understanding of mechanisms involved in EAH to further improve awareness of the risks involved.

In addition to common sport event cohorts, EAH has been reported in hikers (Backer *et al.,* 1999) and trekkers (Basnyat *et al.,* 2000, Rothwell and Rosengren, 2008). EAH can be associated with a wide spectrum of exercise and must not be considered only for sport events such as marathons and triathlons, as prolonged low intensity exercise is identified as a risk factor associated with EAH, as discussed earlier. The case report from Rothwell and Rosengren (2008) showed a physically fit healthy 43-year old male with severe EAH trekking the Kokoda Trial, Papua New Guinea. The man collapsed the afternoon of the third day and had a generalised seizure, later diagnosed in hospital with a sodium level of 107 mmol/L. The evening before the collapse, fellow trekkers and guides encouraged him to drink large amounts of water, falsely diagnosing dehydration, further exacerbating the hyponatremia.

Moreover, diagnosis may be further complicated in other circumstances such as exercise in hot environments where individuals wary of dehydration due to increased sweat rate may be advised to stay well hydrated, consequently becoming overhydrated. The Grand Canyon attracts around 400,000 visitors embarking on guided tours and hikes every year (Cothran *et al.,* 2005) where cases of EAH and other heat-related problems are common. EAH must be accurately identified as initial signs of hyponatremia are non-specific and may resemble heat-related illnesses like those of heat stroke, heat exhaustion and dehydration (Backer *et al.,* 1999). A study in the Grand Canyon by Shopes, (1997) found that heat exhaustion accounted for approximately 90 % of problems in hikers requiring emergency care; EAH may therefore be overlooked in heat-related scenarios. In addition, a previous study by Noakes *et al.,* 1990 reported around 1 in 10 individuals who collapsed in a hot environment had EAH, highlighting that overhydration must be recognised as the prevalence of EAH in these situations may be higher than first thought.

Inaccurate diagnosis of EAH in cases of suspected heat exhaustion may be treated with fluid replacement, consequently further diluting sodium, endangering the patient and causing severe symptoms such as those discussed earlier. Studies, including Rothwell and Rosengren (2008) support the common medical complication and false diagnosis of EAH, that excessive hypotonic consumption in conjunction with prolonged exercise significantly increases the susceptibility of the illness. Thus, prompt field diagnosis must be improved in situations when sufficient medical assistance is not possible, preventing EAH patients undergoing unnecessary and dangerous rehydration treatment.

The Role of Sodium in Exercise-Associated Hyponatremia – Depletion and Supplementation

In the majority of published cases, the primary aetiologic factor in EAH is excess fluid consumption over fluid losses (Hew-Butler *et al.,* 2008) predominantly caused by an increase in total body water relative to the amount of total body exchangeable sodium(Speedy *et al.,* 1999, Noakes *et al.,* 2004). Knowledge surrounding the aetiology of EAH is relatively well understood where disruption of renal homeostatic regulation is caused by various environmental and physiological processes, such as; fluid, exercise and temperature. However the role of sodium in EAH is of yet not fully established.

Excessive sodium loss has not been demonstrated to be a primary causative factor in the pathogenesis of EAH (Hew-Butler *et al.,* 2008), where sodium loss is no greater in individuals who develop EAH than in individuals who do not (Irving *et al.,* 1991). It is plausible to suggest that the loss of sodium may worsen the degree of hyponatremia, although not nearly as much as water retention through excessive hypotonic fluid consumption (Weschler, 2005). Montain *et al.,* (2006) mathematical model suggested that EAH may occur from excessive sodium depletion during ultra-endurance exercise, but the theory has not been documented in any laboratory or case study providing an opportunity for future research. In particular, a potential study could focus on athletes with increased sweat volume, greater than 3 % body mass loss and exercising over 12 hours in a hot environment. The study would investigate the importance of sodium loss in athletes who develop EAH, and whether sodium supplementation may prove to be beneficial in preventing the onset of EAH.

There are current "grey" areas in information regarding sodium supplementation in ultra-endurance events. Preliminary studies using drink supplements have shown conflicting evidence on the incidence of EAH and changes of sodium during prolonged exercise (Speedy *et al.,* 2002, Twerenbold *et al.,* 2003). According to Speedy *et al.,* (2002), no evidence was shown that sodium supplementation significantly influenced changes in sodium during an Ironman triathlon. Whereas Twerenbold *et al.,* (2003) stated the decrease in sodium over their prolonged trial was significantly ($p<0.001$) less in the trial where subjects consumed fluids with high sodium concentration, suggesting a decreased probability of developing EAH. Knowledge is currently deficient in this area possibly due to the difficult nature of data collection in ultra-endurance events and the limited availability of the studies on events such as Ironman. The conflicting evidence offers an opportunity to identify the relationship between sodium depletion and sodium supplementation during ultra-endurance events to broaden the current understanding and mechanisms of sodium in overhydration, underlying EAH.

Isotonic sport drinks containing electrolytes cannot prevent the development of EAH in athletes who drink to excess (Speedy *et al.,* 2001, Almond *et al.,* 2005) as these drinks have sodium levels of <135 mmol/L, further diluting sodium if substantial water is consumed during exercise. In theory, a hypertonic sodium supplementation may maintain body osmolality, reducing the risk of EAH by increasing sodium levels, however risks of excessive sodium supplementation in combination with overhydration have been documented (Luks *et al.,* 2007). The report by Luks *et al.,* (2007) described a study of an ultra-cyclist with pulmonary edema during the Bicycle Race Across America. The 38-year old was hospitalised weighing 2.7 kg greater than his pre-race weight and it was hypothesised that his daily sodium intake was 23-25 g (1000-1100 mEq). It was suggested that this amount led to an expanded extracellular volume and increased hydrostatic pressure resulting in acute pulmonary edema. The study presents an extreme example of pushing the limits of physiological homeostasis where current knowledge is deficient; in addition the case reveals that over supplementation may not be viable to counteract EAH signifying that excessive sodium may have a detrimental effect on health in ultra-endurance events.

Preventive measures

Current prevention is relatively established under normal EAH. Excessive fluid intake is the main cause of EAH so for individuals participating in endurance exercise and particularly those at increased risk for EAH should avoid over consumption of fluids before, during and after exercise (Speedy *et al.,* 2000a, Reid and King, 2007). Continual education in the aetiology and prevention of EAH are fundamental to reduce the medical risk in prolonged exercise, avoiding serious illness and on occasion, death. Introducing educational material at race events would be a useful method to advise participants of such risk factors, promoting moderate fluid intake "*ad libitum*" (Rogers and Hew-Butler, 2009). Fluid requirement must be characterised individually and be primarily dependent on risk factor circumstances. Therefore, universal guidelines with specific volumes have proven difficult to develop due to different environments, duration, and intensity of exercise and individual variation in sweat rates and renal water excretion (Sawka *et al.,* 2007). With multiple variables to consider the importance of implementing the correct educational strategy for coaches and athletes to recognise risk factors and to seek medical attention when signs and symptoms arise are essential. With rising numbers of non-athletes undertaking endurance events (Lau and Choi, 2009), the need of ongoing education is vital for participants whom might be at higher risk of EAH. A study advising athletes to limit fluid availability reduced the incidence of EAH without deleterious effects (Sharwood et al., 2004) demonstrating that EAH can be easily prevented by measures such as fluid restriction.

Conclusion

This review has discussed the main cause of EAH to be overconsumption of fluids relative to fluid losses. Overhydration causes sodium dilution and is the potential risk factor for EAH during prolonged exercise. However, it must be considered alongside a combination of factors such as length of exercise, intensity, gender and temperature. The proposed study investigating fluid requirement between female body weights relative to exercise intensity would provide a greater insight into the risk factor relationships contributing to EAH. The emphasis on hydration during prolonged exercise such as hiking can contribute towards increased fluid consumption, especially in a hot environment. Signs and symptoms of EAH resemble those of heat-related illnesses making diagnosis difficult, further awareness is required.

Sodium depletion, an inferior contributor to EAH can only be considered in extreme cases where physical activity is >12 hours. Due to the nature and limited availability of ultra-endurance studies such as those using Ironman events, data on sodium depletion and supplementation are rare. Thus, there are still many unanswered questions and gaps in a range of research areas for EAH. Further research is required investigating the role of sodium in EAH and whether different forms of sodium supplementation (e.g. liquid or solid) can significantly decrease the incidence rate of EAH in individuals predisposed to sodium depletion.

There are no universal guidelines for fluid intake due to multiple variables. Moderate fluid intake or perceived need "*ad libitum*" are key preventive measures. Life-threatening complications could be avoided by promoting awareness. Thus, educational strategies must be introduced to large sport events and to individuals at greater risk of EAH. The gaps highlighted are the basis of novel investigations

aiming to dive deeper into the complex role of overhydration underlying EAH. These studies will continue to reveal new questions building upon current knowledge, subsequently, aiding to reduce incidence rates for this preventable illness.

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