TOPICS IN EXERCISE SCIENCE AND KINESIOLOGY

*Review Article*

# The onset of Exercise-Associated Hyponatremia and Individual Differences in Inappropriate Arginine Vasopressin Excretion: A Review of Proposed Mechanisms

MICHELLE E. STEHMAN†, and STEPHEN A. MARIS‡

Department of Exercise Science and Athletic Training, Springfield College, Springfield, MA USA

†Denotes graduate student author, ‡Denotes professional author

## ABSTRACT

***Topics in Exercise Science and Kinesiology Volume 2: Issue 1, Article 10, 2021.*** Exercise-associated hyponatremia (EAH) has been reported to develop during endurance events such as triathlons and marathons. As these events become more popular, the incidence of developing EAH also increases. The development of EAH is commonly associated with the overconsumption of hypotonic fluids such as water and tends to be more prevalent in females. There is also evidence to suggest the inappropriate secretion of arginine vasopressin (AVP) leading to water retention may predispose an individual for developing EAH, especially when coupled with the overconsumption of fluids. Recent research suggests females are associated with more risk factors such as slower pace times and compliance with hydration. Females may also be more at risk because they have a lower total body water percentage and should not be consuming as much fluid as male athletes. Other individual differences that could influence EAH onset is the presence of genetic polymorphisms associated with the onset of EAH, the AVP and Oxytocin Receptor (OXTR) gene. The purpose of this review is to summarize the complicated factors underlying EAH in relation to inappropriate AVP secretion and water retention, and individual differences based on sex and genetics. In an effort to reduce the risk of developing EAH, we identified a series of biomarkers and possible genetic polymorphisms that could be used in the creation of an entrée of testing procedures to identify those at greatest risk for developing EAH.

KEY WORDS: Exercise, Endurance, EAH, Genetics, Fluid balance

## INTRODUCTION

Exercise-associated hyponatremia (EAH) can develop during or after physical activity and can be fatal if left untreated or improperly managed (24). EAH is defined as having a blood sodium level less than 135 mmol/L (24). Furthermore, EAH can occur with or without the presence of symptoms and can lead to further complications such as seizures, altered mental status, and exercise-associated hyponatremic encephalopathy (EAHE) (43). The normal range for blood

sodium concentration is 135-145 mmol/L, with severe EAH developing around a concentration <125 mmol/L (23). Knowledge of EAH was minimal until a runner from Durban, South Africa was diagnosed with EAH in 1981 (31). Prior to this, athletes viewed fluid consumption during exercise as weakness and were even advised to refrain from consumption, resulting in cases of hypernatremia (33). In the beginning of the 1980s, athletes were encouraged to consume as much fluid as possible before and during physical activity in order to prevent dehydration and heat-related illnesses (34). Incidence of EAH has since been on the rise around the world especially in the United States possibly due to both increased awareness and increased research surrounding the potentially fatal condition (23).

EAH was originally only reported in scenarios of the upper limit of human endurance such as ultramarathons and ironman triathlons (24). In recent years, EAH has been reported in events such as marathons (2,45-46), hiking (35), military personnel (37-38), football players (6, 52), yoga (41), and bicycling (56). This in turn, could be of concern in habitual exercisers who may not be aware of the dangers and importance of proper hydration (47). The dangers of EAH in marathon runners was first generalized as public knowledge in 2003 when two female charity runners died due to EAH related cerebral edema (45). Past investigations indicate that the incidence of EAH after a marathon run was confirmed in 13-18% of the participants, with one reported death during the 2002 Boston Marathon due to possible EAH complications (2, 46). Between 2008 and 2014, it was reported that three high school football players within the United States during pre-season practice lost their lives due to EAH complications (6, 53). Trends indicate that EAH is still prevalent as in recent years, EAH negatively affected a college football player from Utah in March 2019 (45). Thus, EAH is a concern not only in advanced endurance athletes, but in recreational and advanced sporting events (24).

As reported by others, the single most contributable risk factor for the development of EAH is the overconsumption of hypotonic fluid in volumes greater than fluid losses (24). Other risk factors include weight gain during exercise, slow running or performance time, exercise duration greater than 4 hours, inadequate training, and availability of fluids during events (23). In the majority of symptomatic EAH cases, individuals either maintained or gained weight during the physical activity (23). Specifically, a meta-analysis by Noakes et al., found athletes who gained more than 4% body weight during an exercise event had an increased risk of developing severe EAH (34). This gain in weight was confirmed by Speedy et al., whose results indicated a positive correlation between weight gain and EAH as 73% of the participants who developed severe EAH had either gained or maintained their initial body weight (46).

The development of EAH is usually a result of a defect in the renal and hormonal control mechanisms or due to the excessive ingestion of fluid overwhelming these systems (40). The main pathophysiology of EAH is dilutional hyponatremia due to the overconsumption of hypotonic fluids (24). Specifically, body water expansion in relation to the total body amount of exchangeable sodium (34). In majority of the athletes who develop EAH, there is an increase in total body water relative to total body exchangeable sodium which seems to be a result of the overconsumption of hypotonic fluids greater than fluid losses (24). This indicated there may be

other factors contributing to the development of EAH in these athletes (34). Some of these other factors that could lead to the development of EAH could be associated with inappropriate AVP secretion, differences between sexes, and possible genetic polymorphisms underlying fluid homeostasis. Thus, the purpose of this review is to summarize the proposed mechanisms underlying EAH in relation to inappropriate arginine vasopressin (AVP) secretion, differences in sex, and genetic effects during exercise.

## METHODS

Sixty-four articles were initially screened for this review. After reviewing each article, forty-two articles were selected to be included in this review. Articles chosen for this review were retrieved via online database searching such as PubMed, MEDLINE, SPORT-discus, and Google Scholar. Keywords used to find articles were exercise-associated hyponatremia, arginine vasopressin, sex, gender, and performance. The articles chosen were published in English, and were published within the last 20 years, with exceptions for landmark papers and guidelines. The subject demographics were athletes ages 18-65 years old, participating in endurance exercise or team sports. Articles were selected with outcomes such as weight gain during exercise, the overconsumption of fluids, the development of exercise-associated hyponatremia, AVP secretion, and endurance exercise performance. For the review of possible genetic mechanisms underlying individual differences, we included animal and human research participants. Articles were identified using the NCBI's Gene database using the following keywords to identify genes of interest; <AVP gene>, <OXTR gene>, <EAH>, and <AVP secretion>. This search yielded a total of eight articles included in this review (15,19,25-26,30,54,56,59).

Two reviewers conducted the initial screening of article titles and abstracts. Articles were included that examined factors associated with exercise-associated hyponatremia and inappropriate AVP secretion syndrome. We excluded articles where subjects had inappropriate AVP secretion or cases of EAH development that were not associated with exercise or physical activity since those types of cases were not the focus of this review article. In addition to the electronic database search, reference lists from previously published reviews were also examined. This research was carried out fully in accordance with the ethical standards of the International Journal of Exercise Science (32).

## INAPPROPRIATE AVP SECRETION AND EAH

Water excretion and its regulation is a crucial factor impacting the onset of EAH in athletes and in non-athletes. Arginine vasopressin (AVP) is an antidiuretic hormone responsible for the regulation of water excretion and fluid homeostasis (24). AVP is a peptide hormone produced in the hypothalamus and secreted from the posterior pituitary gland and supraoptic nucleus (22). Secretion of this hormone is primarily under kidney osmoregulatory control and an increase in plasma levels. Water retention is induced by AVP through the activation of the vasopressin $V_2$ receptors in the kidney (22). Changes in plasma osmotic pressure are detected by osmoreceptors located in the brain and activate the release of AVP from the posterior

pituitary gland, and others indicate that this threshold for AVP secretion is between 280 and 285 mOsmol/kg $H_2O$ in most individuals (22).

Plasma osmolality is maintained within a normal physiological range by one's thirst mechanism and AVP levels and is closely maintained to protect the intracellular volume (22). An increase in plasma AVP concentration normally results in urine production while a decrease in the hormone results in diuresis (13). AVP can also be secreted by the posterior pituitary gland in response to non-osmoregulatory factors such as reduced blood volume and reduced blood pressure (13). Normally, this hormone is suppressed in the presence of hypoosmolality, however in some cases, AVP is not appropriately suppressed during exercise.

The secretion of AVP is only considered inappropriate when secreted during a state of hypoosmolality which could lead to fluid retention and dilutional hyponatremia (22). If serum sodium falls below 135 mmol/L, AVP secretion should be maximally suppressed to prevent fluid retention. In this state of maximal AVP suppression, the kidney free water excretion rates would be increased between 800 and 1000 mL/h to return serum sodium back to normal levels (28). Research suggests any concentration of inappropriately secreted AVP would inhibit the maximal rate of urinary free water excretion, increase urine osmolality, and decrease serum sodium during exercise (22). Both high urine osmolarities and inappropriate AVP levels have been reported in hospitalized athletes with EAH (4, 10, 17, 32, 48, 59). There are several biomarkers that are currently being investigated that are indicative of inappropriate AVP secretion.

Inappropriate AVP secretion is a possible pathology in the development of EAH and one of the consequences is an impaired water excretion by causing water retention in the distal tubule of the kidney. This water retention can also occur with excessive water intake, which together, greatly increase the risk for the development of EAH (13). During endurance exercise, it is possible that the osmotic regulation of AVP is inhibited and overridden by non-osmotic stimuli such as pain, physical exercise, emotion, exposure to heat, nausea/vomiting, hypoglycemia, and medication use such as NSAIDs (22). Specific biomarkers associated with these stimuli include Interleukin-6 (IL-6), angiotensin II, brain natriuretic peptide, corticosterone, and oxytocin (7). IL-6 has been identified to increase during exercise as it contributes to both mobilization of energy and muscle breakdown and stimulate AVP release (7). Increases in angiotensin II, brain natriuretic peptide, corticosterone, and oxytocin have also been identified during prolonged exercise. These increases in these biomarkers may contribute to an increase of postrace plasma AVP which is observed during non-osmotic stimulation and decreased plasma volume (21).

## AVP SECRETION AND EXERCISE

The impact of exercise on AVP secretion has been investigated during high-intensity exercise (>90% of maximal oxygen consumption), steady-state exercise (submaximal exercise), and prolonged endurance (exercise lasting longer than 1-hour). During high-intensity and steady-state exercise, AVP levels increased linearly (22). During long-distance endurance exercise

significant increases in AVP secretion has been found with or without changes in serum sodium or osmolality (21, 42). This exercise-induced elevation in AVP has been shown to exist for 2-hours and for 31-hours post endurance event, displaying a large variation for persistent plasma secretion that be related to other factors, such as exercise intensity, sex, or genetics (3, 16). Research suggests there is an intensity-dependent effect on AVP secretion during long-distance endurance exercise. No change in AVP or plasma osmolality was noted in a 5-day hill walking (57). A moderate increase in AVP was detected after a 24-hour track run at a low-moderate intensity between (16). A significant increase in AVP was seen in well trained marathon runners completing a 42.2km run, with the highest post-race AVP detected in the fastest runners (12).

An underlying effect of exercise and AVP secretion is the under-replacement of sodium and water losses. Which would result in a negative fluid balance; however, a positive fluid balance may occur from the overconsumption of hypotonic fluids or abnormal renal water clearance during exercise to prevent the onset of dehydration (22). The overconsumption of hypotonic fluids, in some cases, may be the only causation factor for the development of EAH in some individuals. During exercise, AVP may not be maximally suppressed, and even small amounts of circulating AVP can decrease the maximal kidney excretory capacity. This potentially may lead to water retention of all ingested fluids during exercise and continued dilution of serum sodium (22). Non-osmotic AVP secretion has been identified as the main pathogenic element in the development of EAH. However, the exact stimulus remains unknown (36). Due to these varied responses and effects, it is then pertinent to investigate if there are any individual differences between AVP secretion and if these differences are associated with EAH development.

## THE INTERACTION BETWEEN SEX AND EAH ONSET DUE TO INAPPROPRIATE AVP SECRETION

The development of EAH seems to be more common in women than men (24). Until recently, it was standard practice to assume that the female sex was a risk factor for the development of EAH since the incidence of EAH is higher in females than males (2, 9, 11, 46). Current research suggests sex alone is not a risk factor, however, females tend to be associated with multiple risk factors due to other environmental or genetic factors. A recent study by Almond et al., investigated the presence of EAH in Boston marathon runners and found that EAH occurred at greater rates in female participants (2). However, once BMI, race times, and weight changes were included in the modeling, there was no statistical significance between the sexes (2). This is indicative of other possible influencing variables associated with BMI, endurance capacity, and fluctuations and body weight may impact EAH onset more so than sex differences (27).

Total body water is the percentage of the body composed of water located within various compartments such as the tissues, blood, and bones (5). Males have a greater total body water percentage than females, even at the same given body weight (5). Specifically, female total body water percentage ranges from 45% to 50% and in contrast, male body water range between 55% and 65% (14). Many individuals participating in endurance exercise follow a hydration strategy

to ensure proper hydration throughout a sporting event or recreational physical activity. Some publishable hydration guidelines, such as the 2000 National Athletic Training Association position statement on fluid replacement guidelines for athletes, are not sex specific (8). Since males and females have different total body water percentages and other physiological differences, this begs the question if males and females should have separate hydration guidelines for participation in sport. If a female follows the same hydration strategy and consumes the same amount of fluid as a male, they may be at risk for developing EAH due to the overconsumption of fluids in comparison to male counterparts.

Quantitative and qualitative research suggests females tend to consume more water and are more compliant than males with regard to following hydration guidelines. A survey by Volpe et al., investigated which sex consumed more water before and during an athletic event in NCAA division 1 athletes, and their results showed that females consumed an average of 53 fl oz and males consumed about 51 fl oz. Furthermore, 47% of the males were hypohydrated prior to the event, while only 28% of females were hypohydrated prior (54). Studies have also identified that females are more likely to be compliant when following hydration guidelines than males. One study surveyed French adult's total daily water intake and found 72% of men were non-adherent to the daily recommended fluid intake while only 46% of women were non-compliant (18). This is further supported by others that showed female participants were more likely to intentionally increase fluid consumption during their runs when the weather is hot outside (39).

Slower pace times and less experienced runners are each risk factors for the development of EAH (39). During the 1998 and 1999 San Diego Marathon, the average race time for participants who developed EAH was 5-hours and 38-minutes (11). In addition, a more recent study suggested that participants in the Boston Marathon who developed EAH on average had a lower number of marathons completed when compared to those who did not develop EAH (2). These slower pace times and less experience runners may consume more fluids over a longer time period, increasing the risk for diluting serum sodium and developing EAH during the sporting event.

The specific influence of sex on AVP secretion has not been heavily investigated, with majority of the studies involving only male participants. A series of laboratory studies sought to outline sex differences and influence of sex hormones in response to plasma AVP. These studies found neither sex nor menstrual cycle impacted plasma AVP and men appeared more sensitive to plasma AVP in response to plasma osmolality (49-50). There may also be different osmotic threshold for AVP release during different phases of the female menstrual cycle, making this difficult to understand plasma AVP secretion in women at various points in their menstrual cycle (22). Furthermore, women without a history of hyponatremia, had no correlation between sex hormone levels and depletion of blood sodium during 3-hours of cycling (51). However, those with a previous history of hyponatremia or females who are considered more susceptible, retained more fluid and had greater serum sodium depletion when both estrogen and progesterone levels were elevated (51). Thus, it is difficult to draw forth distinct conclusions

regarding the effect of sex on AVP secretion and development of EAH. Further research should investigate AVP secretion and sex differences with greater scientific rigor during prolonged endurance exercise since hyponatremia is more prevalent in females while assessing hormone levels, the menstrual cycle, and sex specific hormones.

## GENETIC POLYMORPHISMS ASSOCIATED WITH FLUID BALANCE AND ONSET OF EAH

There are trends in the literature to suggest that the tissues and physiological mechanisms underlying AVP secretion have key regulating genetic factors that may play a role in AVP secretion and thus, possibly EAH onset (15). As stated previously, there are many factors that impact EAH onset beyond sex difference; inappropriate AVP secretion, markers of the renin-angiotensin aldosterone system (RAAS) such as AngII and Corticosterone, and oxytocin. Others have reported that there are significant polymorphisms within the AVP gene (also known as the ADH Gene) and the Oxytocin Receptor (OXTR) gene that can influence AVP secretion, and thus, EAH (19, 25, 26, 29, 53, 55, 58).

The AVP gene is responsible for the coding of a member of the vasopressin/oxytocin family that generates a variety of proteins (15). One of these such proteins, is arginine vasopressin (AVP), and is a dominant pathophysiological factor in the onset of EAH during sporting events. It has been reported that the Kidneys and adrenal glands have high levels of transcription of the AVP gene, as measured through RNA-sequencing of tissue samples (15). This high level of transcription and expression in these organs is indicative of control of fluid homeostasis and could influence AVP secretion (15, 53, 58).

Via directly impacting AVP secretion, polymorphisms in the AVP gene have been associated with the development of Diabetes Insipidus, or an imbalance in fluid levels (53, 58). A previous study by Turkkahraman and colleagues confirmed the presence of genetic mutations impacting this clinical syndrome and fluid balance (53). Specifically, they confirmed the reporting of a heterozygous mutation (pC98X) and a identified a new nutation (p G45C) within the AVP gene leading to the onset of fluid imbalance. This new novel mutation causes a genetic substitution by TGC (Cys) replacing the GGC (Gly) found normally (53, 58). Both of these mutations are associated with increased onset of the development of Diabetes Insipidus (53, 58). Although this mutation is associated with a clinical abnormality, this sheds light on possible genetic markers that could impact AVP secretion and fluid homeostasis. Both of which are associated with the onset of EAH.

Others have reported alterations in the AVP gene may interact with environmental factors discussed earlier in this review. For example, others have reported that animals can regulate AVP gene expression in response to certain environmental stressors, such as fluid deprivation (26). Indicating the possibility that alterations in the gene may interact with other environmental stressors, such as exercise (26, 55). For example, a recent study indicated that a polymorphism within the AVP gene was associated with an augmented response to exercise in improving

cholesterol (55). Specifically, the results from Wang and colleagues indicated that the TT genotype in the rs1042615 polymorphism resulted an improved LDL level in response to the exercise training (55). Although not related to fluid homeostasis and EAH specifically, these results indicate that the gene may impact responses to exercise.

In support of our hypothesis that alterations in the AVP gene could impact fluid homeostasis, a study in rats indicated that AVP gene transcription was associated with regulating plasma volume, an important regulator of blood viscosity and the sweat response to endurance exercise (19). Interestingly, this effect was not observed in rats that were dehydrated, supporting that this mechanistic interaction occurs in a setting of euhydrated and hyperhydrated conditions (19). Both of which could lead to the onset of EAH as a result of participation in exercise. Other studies indicated that alteration in the AVP and the oxytocin (OXT) gene may be associated with chronic stress, both of which could be affected by exercise (19, 25). In mice, repeated bouts of exercise increased levels of G9a and the H3K9me2 at the promotor regions of the OXT and AVP gene (19, 25). Taken together, these support our hypothesis that the AVP gene may be an underlying variable influencing individual differences in EAH onset by; impacting fluid homeostasis, activation in euhydrated and hyperhydrated states, and possibly interacting with exercise.

The other possible genetic influence on AVP secretion could be associated with the Oxytocin Receptor (OXTR) gene and its interaction with exercise endocrinology (29). Interestingly, studies indicate only moderate levels of expression of the OXTR gene in the kidney, yet there have been reports of high levels of transcription in the endometrium and the ovary in females (15). It is hypothesized that these transcription levels support the OXTR gene in regulation blood pressure and the gene's role in regulating response to exercise (29).

Few studies have investigated this gene in association with exercise, two of which directly relate to possible mechanisms of EAH discussed earlier; inflammatory markers and psychology of fluid consumption (1, 30). Basic animal studies indicate that exercise increases activation of the OXTR gene and oxytocin secretion (1). This activation was found to be associated with activation of pathways associated with inflammation and tumor development in cancers (1). Interestingly, another study indicated that the OXTR gene may be associated the effects of exercise training on improve performance, and the improved cardiovascular system associated with exercise, occurred to a greater extent resulting in greater training-induced cardiovascular performance (30).

In summary, the narrow scope of current literature on the genetic influences on EAH onset and AVP secretion are suggestive at best. Taken together however, the AVP and OXTR gene may impact EAH onset and could be viable factors in determining recommendations for performance-based events. These initial hypothesis generating studies indicate the possibility of a genetic influence on EAH onset, which requires further studies with greater rigor and control in determining if the genetic polymorphisms in the AVP and OXTR gene could directly impact development of EAH.

## PRACTICAL APPLICATIONS

Although very informative, the 2000 National Athletic Training Association fluid replacement guidelines were not sex specific. These guidelines were utilized as the gold standard of hydration strategies for athletic trainers for almost two decades. In 2017, the National Athletic Training Association released new hydration guidelines which mentioned the importance of individualization for hydration strategies but did not stress the importance of sex-specific hydration guidelines or the difference in total body water percentages amongst males and females. Hydration guidelines should be sex-specific since females have a lower total body water percentage than males. EAH also seems to be more prevalent amongst females, thus supporting the need for sex specific guidelines. For example, if a female were to consume the same amount of fluid as a male, according to the findings of this review, it could predispose the female to developing EAH due to the overconsumption of fluids. Among these individual differences, anecdotal evidence suggests that certain polymorphisms in the AVP and OXTR gene may play a role in fluid homeostasis and possibly, onset of EAH. More evidence is required to make sensible recommendations; however, these hypothesis generating data suggest the possible adoption of genetic testing to determine altered balance of fluid homeostasis that may predict EAH onset.

EAH still remains a condition with multiple complex pathologies. The overconsumption of hypotonic fluids remains the most common underlying cause for the development of EAH. The inappropriate secretion of AVP may be another factor leading for the developing of EAH, especially when combined with the overconsumption of fluids and an altered fluid balance. AVP may also be stimulated by increases of other biomarkers during exercise, such as IL-6, angiotensin II, brain natriuretic peptide, corticosterone, and oxytocin. All of which when combined with the genetic polymorphisms seen in the AVP and OXTR gene, may be useful in creating a suite of an initial and continuous testing procedures that could identify risk of developing EAH on an individual basis. These biomarkers might be stimulated due to heat exposure and NSAID usage which are both common stimuli exposures in endurance exercise, that should be taken into account when evaluating these testing procedures. Athletes participating in exercise in a hot environment or currently taking NSAIDs may be more at risk for inappropriate release of AVP and the development of EAH due to the altered fluid balance that occurs when exercises in a hot environment. These include altered plasma volume due to sweating and an increased strain placed on the cardiovascular system (22).

## CONCLUSION

The purpose of this review was to summarize multiple factors associated with EAH in relation to the inappropriate release of AVP during exercise, differences in sex, and genetic effects. The inappropriate secretion of AVP during exercise may lead to the development of EAH especially when combined with the overconsumption of hypotonic fluids. Not every individual that develops EAH has increased plasma AVP secretions and not all cases of inappropriate AVP secretion leads to EAH. AVP secretion may be stimulated by exercise, heat exposure, altered

genome, or NSAID usage. These stimuli may also induce the secretion of other biomarkers associated with the increased AVP plasma concentrations. The role of sex may also play a role in both the development of EAH and the inappropriate release of AVP secretion since both seem to be more common in females than males during exercise. Although hypothesis generating in nature, polymorphisms in the AVP and OXTR gene are indicative of altered fluid homeostasis. This altered fluid balance may lead to further development of EAH in specific populations.

It is still unknown exactly why EAH seems to be more common in female athletes, however future research should continue to focus on the prevention of EAH through sex-specific hydration protocols. More research investigating the role of plasma AVP concentration during or after endurance running and its relationship to the development of EAH. Future research should also look at the relationship of AVP secretion in EAH cases between the sexes. The identification of other biomarkers which may stimulate the release of AVP should also be looked at to identify a relationship associated with EAH development and exercise. Other future research should expand upon these initial conclusions associated with the AVP and OXTR gene and look to directly confirm that these polymorphisms may lead to greater prevalence and onset of EAH. Taken together with possible differences in sex, this review further highlights the importance of personalized exercise prescription in order to maximize exercise benefits and enhance performance.

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