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The Walking Well: Effects of Hypothalamic Amenorrhea on Athletic Performance

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TITLE

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ABSTRACT

Hormonal balance and normal menstrual cycles are key factors in athletic performance. Unfortunately, female athletes themselves are often under the impression that a lighter weight will improve their performance. Even many healthcare providers do not emphasize or are unaware of the health consequences of prolonged irregular menstruation. The main purpose of this article is to review the health consequences hypothalamic amenorrhea has on female athletes and to provide education for healthcare providers regarding the importance of recovery.

A literature search was conducted utilizing PubMed, Scopus, PLOS One and EBSCO. The following keywords were input into the search bar: hypothalamic amenorrhea, female athletes, irregular menstruation, health consequences, RED-S, female athlete triad, bone health, cardiovascular health, immunity, recovery time, and psychological health. Of the results, 26 pertinent articles were chosen to be included in this literature review.

Current evidence suggests that hypothalamic amenorrhea is indirectly associated with decreased athletic performance due to hormonal effects on various body systems. Performance may be affected by increasing the risk of stress fractures, impairing immunity, affecting cognition and mood, prolonging recovery time, altering gastrointestinal (GI) symptoms, and increasing reaction time. At present, there are many unknowns related to this topic. Minimal research has been conducted regarding the direct impact of hypothalamic amenorrhea on short-term and long-term health. Future studies should consider how performance indicators differ between female athletes with normal menstruation cycles versus those with developed amenorrhea.

KEYWORDS

Hypothalamic amenorrhea (HA), female athletes, female athlete triad (FAT), relative energy deficiency syndrome (RED-S), low energy availability (LEA), health consequences, bone health, cardiovascular, immunity, psychological.

BACKGROUND

Amenorrhea, defined as the absence of menstruation, occurs in 2 to 5% of reproductive age women in general, but a broad 3.4% to 70% of female athletes.[1] Primary amenorrhea takes place when a female has not menstruated by the age of 14 without secondary sexual characteristic development, or by the age of 16 with secondary sexual characteristic development.[2] Secondary amenorrhea occurs when a female has had menstrual cycles in the past, but has not menstruated for more than three consecutive months if previously normal cycles or more than six consecutive months if previously irregular cycles.[2] Hypothalamic amenorrhea (HA), a subtype of secondary amenorrhea, is menstrual cessation due to an underlying hypothalamic abnormality. The hypothalamus can become dysfunctional from stress, disordered eating, low body weight, and excessive exercise (figure 1).[3]

Figure 1.

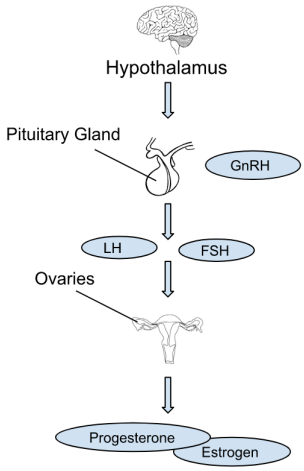

Figure 1. The hypothalamus secretes GnRH in a pulsatile fashion. GnRH tells the anterior pituitary gland to secrete LH and FSH. These hormones then tell the ovaries to secrete progesterone and estrogen. In hypothalamic amenorrhea, there is a dysfunction in the secretion of GnRH, and therefore a disruption in the secretion of progesterone and estrogen.

The female athlete triad was coined in 1993 with the three components of disordered eating, irregular menstruation, and decreased bone density (figure 2).[3] In 2014, the International Olympic Committee (IOC) renamed this as relative energy deficiency syndrome (RED-S) in order to create a more holistic view, as the former was often underdiagnosed.[3] The primary cause of RED-S is an imbalance between energy intake and output, also referred to as low energy availability (LEA).[4] This imbalance results in irregular or absent menstruation and diminished bone, immunological, psychological, and cardiovascular health. All of these components contribute to how well an athlete performs; if any one of them is abused, the performance of that athlete may be inhibited.

Figure 2.

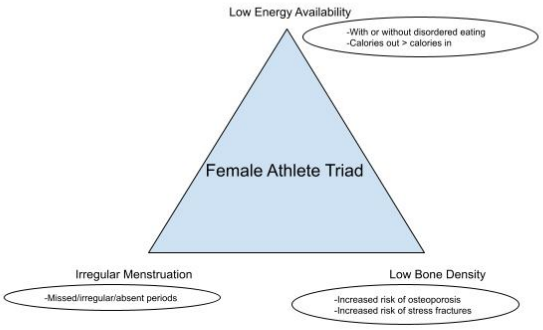

Figure 2. The female athlete triad is composed of low energy availability, irregular menstruation, and low bone density. These three components are associated with further health complications.

RED-S is especially prevalent in athletes as they often expend more energy than they take in, whether intentionally or unintentionally.[2,4] Sports associated with this condition include, but are not limited to: long distance running, gymnastics, swimming, and ballet. Athletes in these sports often stereotypically desire lean and aesthetic appearances, or assume a smaller physique

will yield higher performances.[5] Clinical eating disorders are also common among female athletes, ranging from 16% to 47%.[3] When a female athlete initially goes into a caloric deficit, weight loss will ensue and may ultimately lead to hypothalamic amenorrhea.[6]

A key contributor to normal menstruation is adequate fat mass which many females in lean sports lack. Leptin is a hormone released by fat cells. When there is an insufficient amount of fat tissue in a female, less leptin is released which has a negative effect on the secretion of GnRH, leading to amenorrhea.[3] Less fat availability also causes increased ghrelin (which decreases GnRH, FSH, and LH secretion), decreased oxytocin (which suppresses the hypothalamic-pituitary axis), and decreased insulin (which negatively impacts GnRH signaling).[3] Castanier et al. also noted that adipose tissue is associated with the conversion of androgens to estrogen.[1] All of these factors may contribute to loss of regular cycles.

Amenorrheic individuals have lower estrogen, progesterone, triiodothyronine (T3), and insulin-like growth factor one (IGF1). Vanheest et al. studied this in junior elite female swimmers. They found that a decrease in estrogen, progesterone, T3, and IGF-1 levels were associated with a decrease in performance, and thus amenorrheic athletes did not perform as well as eumenorrheic athletes.[1,7] Many of the causes for decreased performance have been attributed to a decrease in estrogen.

Unfortunately, HA is a condition that can seem harmless on the surface. If fertility is not desired at the present time, an absence of period is not alarming to many athletes. Cheng et al. found that only one quarter of the athletes in their study reported having a goal of regaining a regular menstrual cycle after losing it from exercise.[5] This indicates that nearly 75% did not desire this and were likely unaware of the long term health consequences. Verhoef et al. did a focused interview study regarding why many female athletes do not seek help when struggling

with irregular menstruation.[4] In the interview, the athletes indicated that they themselves were unaware of how serious HA is.[4]

In a study done by Brook et al. that looked at potential factors associated with RED-S, 59% of their female subjects aimed to improve their performance by changing their body physique and losing fat. Additionally, under 10% of all subjects, which included both male and female athletes, were even aware that RED-S existed.[8] In another questionnaire by Witkoś et al., researchers asked female runners if they were familiar with the concept of the female athlete triad. Nearly 78% of the participants declared they were unaware of this term. Of the remaining subjects, almost 16% stated it was synonymous with amenorrhea, and about 3% said it was only energy imbalance. About 5.5% of the female runners were able to accurately report all three components of the female athlete triad.[9]

Indeed, coaches in the study conducted by Verhoef et al. also highly desired top athletic performance and thus the women were fearful of approaching them with their concerns. Still other women knew that they were receiving warning signs from their bodies, yet did not want to bring it up to coaches due to their own refusal to change their habits.[4] It is vital for coaches to understand the health consequences of amenorrhea. While some coaches become concerned for the health of their athletes struggling with this condition, others view absence of period as an indication that their training intensity is sufficient.

Even numerous healthcare providers do not understand the severity of HA in female athletes, and do not attempt to discuss the importance of regaining ones' menstrual cycle until the female desires to have children.[10] They may prescribe hormonal contraceptives to induce shedding of the endometrium and mimic restoration of menstruation. However, this does not restore ovulation or the homeostasis necessary to have a normal cycle that is regulated by a

functioning hypothalamus.[4] Given the current research demonstrated above, it seems there is a clear need to increase awareness and further educational access on the subject of RED-S so long term health consequences may be avoided.

HA is not merely reproductive imbalance, but there is disruption to multiple body systems. Various studies have shown that athletes with LEA and amenorrhea are at higher risk for cognitive and concentration impairment, increased recovery time, low bone density, decreased endurance performance, and gastrointestinal impairment (figure 3).[1,11] Therefore, when an athlete struggles with LEA long term in an attempt to achieve a certain physique and body composition, their sports performance may suffer.[6] The following components of this paper will go into further detail on this relationship.

Figure 3.

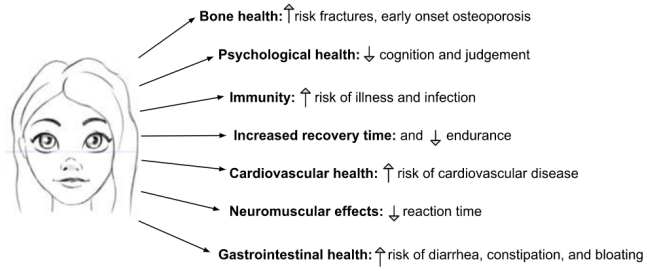

Figure 3. A summary of the various indirect effects HA has on athletic performance that will be discussed in this dissertation.

CLINICAL SIGNIFICANCE: HA EFFECTS ON ATHLETIC PERFORMANCE

Bone Health

Estrogen is essential for bone remodeling. In order to keep a proper balance of skeletal formation, there are two key types of cells involved: osteoblasts which help build bone, and osteoclasts which aid in destroying bone. Estrogen assists by increasing the proliferation of osteoblasts to build bone, and allowing for the destruction of osteoclasts to inhibit bone breakdown.[1] Athletes with HA have decreased estrogen, and thus more osteoclasts and less

osteoblasts. In response, bone more easily breaks down and gets destroyed (figure 4).[1] IGF-1, which normally stimulates osteoblastogenesis and promotes bone formation, is also decreased when HA is present. Other elements of bone health that are negatively impacted by HA include leptin and T3.[3] It is important for athletes to have between 5% and 15% more bone density than individuals who are not athletes due to the strenuous demands that they put on their bodies.[2] To improve bone density, athletes ought to incorporate an increased amount of weight bearing exercises into their training regimen.[1] While HA can affect athletes regardless of body size, there is evidence supporting a significantly lower amount of fat mass in amenorrheic individuals versus eumenorrheic individuals.[1]

Figure 4.

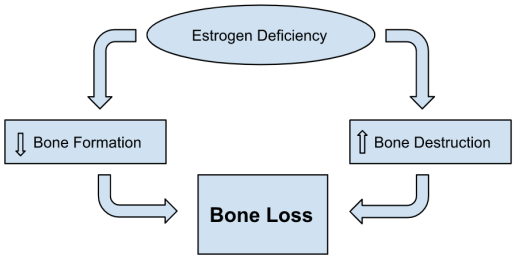

Figure 4. Estrogen deficiency leads to increased bone destruction and decreased bone formation, ultimately resulting in bone loss.

Because of the decrease in estrogen and impaired bone health associated with HA, athletes in an HA state are more prone to injuries.[6] Cheng et al. observed the correlation between menstrual irregularities and bone stress fractures. They reported an association between sports with lean profiles and stress fractures, with one-quarter of the participants admitting to a history of stress fractures. However, it must be considered that many of these women were also on hormonal contraceptives. Even then, more athletes with current HA had higher amounts of stress

fractures compared to eumenorrheic athletes.[5] This is because female athletes with HA tend to have lower bone densities, making them more susceptible to fractures.[5]

Bone density and recovery time are inversely related such that lower bone density leads to longer recovery times from a stress fracture.[12] Any athlete is susceptible to stress injuries due to the intense training; however, frequent and severe stress injuries occur when bone mineral density is decreased. Examples include fractures of the pelvis, femoral neck, or sacrum.[12] When the athlete becomes injured continuously, they are unable to train and thus performance takes a toll.[4]

Psychological Health

In addition to bone health, estrogen has been shown to correlate with other essential aspects of athletic performance including psychological health. In a study done by Ackerman et al., female athletes with irregular menstruation were shown to have decreased concentration, judgment, and coordination, and increased depression and irritability. They attributed this to the decrease in estrogen and neurotransmitters, such as serotonin and dopamine, associated with HA.[11] Serotonin and dopamine serve to regulate mood and, when disrupted, can lead to depression.[10]

Baskaran et al. postulated that estrogen plays a role in psychological health related to athletic performance; therefore, they researched the relationship of estrogen replacement and cognition. After six months of estrogen replacement therapy with either the patch or oral modalities, athletes with HA showed improvement in executive control and verbal memory.[13] Although the purpose of this paper is not to discuss the use of hormonal contraceptives in relation to menstrual health, the findings support the vitality estrogen has on cognitive health. Estrogen acts on regions in the brain including the prefrontal cortex (responsible for cognitive

control functions) and the hippocampus (responsible for learning, spatial navigation, and memory). Thus, a decrease in estrogen due to HA may lead to cognitive impairment, such as a decline in judgment and coordination, which as a result affects athletic performance.[14]

Immunity

Both estrogen and leptin are involved in the maintenance and proper functioning of the immune system. As a reminder, leptin is released by fat cells; therefore, an individual with less fat mass has less leptin in their body which affects immunity.[15] Low estrogen in an amenorrheic state can also lead to decreased immune system functionality.[6] A study done by Drew et al. correlated the relationship between HA and suppressed immune systems amongst athletes involved in the Rio 2016 Olympic Games. Out of the 317 athletes they interviewed, every single one of them reported a viral illness lasting anywhere from two to seven days during the previous month. HA was a leading variable in this study.[16]

Shimizu et al. recognized that amenorrheic athletes are more susceptible to upper respiratory tract infections due to decreased immunity.[17] They compared long distance runners with HA to eumenorrheic long distance runners and focused on their salivary secretory immunoglobulin A (SIgA). SIgA is involved in preventing pathogens from entering the body, and decreased salivary SIgA has been associated with an increased prevalence of upper respiratory infections. Shimizu et al. found that amenorrheic distance runners had lower salivary SIgA than eumenorrheic runners. They concluded that amenorrhea makes one more susceptible to upper respiratory infections.[17] When an athlete is struggling with sickness, they cannot train to their full potential and therefore performance is affected.

Increased recovery time

A few studies have correlated long term HA with increased recovery time and decreased optimal muscle mass for performance.[6] Recovery time in sport is difficult to assess because it is individualized and self-reported. However, Ackerman et al. used online questionnaires in an attempt to make a correlation between HA and recovery time. In their research, the women with HA were 2.1 times more likely to experience longer recovery times and decreased endurance.[11] While many athletes associate low body mass with improved achievements, Tornberg et al. compared amenorrheic individuals with eumenorrheic individuals and found no improvements in aerobic capacity in the women with low body weights.[18] Additionally, poor immunity and illnesses contribute to increased recovery time.[19]

Cardiovascular Health

The pre-menopausal years are considered to be cardioprotective which may be linked to estrogen status. Females with low estrogen due to intense exercise and underfueling are at increased risk of cardiovascular disease.[20] O'Donnell et al. reviewed a connection between low estrogen and accelerated atherosclerosis development.[21] Atherosclerosis is most commonly associated with obesity and inactivity, but there has been evidence showing endothelial dysfunction in athletes with HA despite their activity level. Chronic inflammation as seen in amenorrheic athletes due to low estrogen may also be associated with increased atherosclerosis progression. An important note is that women with HA due to intense exercise may reverse this effect once menstrual cycles are restored.[20]

Additionally, hypoestrogenemia may decrease the release of nitric oxide (NO) and contribute to accelerated cardiovascular disease in other ways by damaging the endothelial layer. Nitric oxide is produced by the endothelial cells and is responsible for vasodilation, which aids in adequate blood flow, blood pressure, and overall heart health. If there is decreased nitric oxide,

there will be constriction of the coronary vessels going to the heart during exercise, as well as constriction of other vessels leading to overall poor circulation.[20] Decreased NO and hypoestrogenemia also have been associated with increased LDL cholesterol (LDLc) and total cholesterol (TC), which may be the reason some athletes with HA are seen to have increased LDLc and TC.[20]

Despite these pieces of evidence, the full cardiovascular effects from HA continue to remain unclear and are controversial in some regards. In a cardiology study done by Wenner et al., there was no autonomic dysfunction or impaired orthostatic response in amenorrheic individuals compared to eumenorrheic individuals.[21] Female athletes, including those with amenorrhea, are shown to have lower blood pressures, lower resting heart rates, and higher HDL cholesterol (HDLc), all of which are cardioprotective.[20] Overall, research on short-term and even long-term cardiovascular health consequences in relation to HA is lacking. It is vital to continue research in this area so it may be understood more fully.

Neuromuscular Effects

Neuromuscular performance involves executing movements and plays in sports by proper coordination, sensory feedback, energy availability, and reflexes. This concept allows athletes to perform well in a stable and dynamic manner.[22] Interestingly, HA may negatively affect a female athlete's neuromuscular performance. Tornberg et al. found that in elite endurance athletes, amenorrheic individuals had decreased reaction times and decreased knee muscle strength compared to eumenorrheic individuals.[18] The athletes with decreased neuromuscular performance had decreased estrogen, T3, and fat mass, and increased cortisol. This suggests the performance decline was associated with absence of menstruation.[18] Estrogen may also have a

profound negative effect on muscle growth.[23] For example, Kitajima et al. revealed that a deficiency in estrogen for 24 weeks led to a 10% decrease in muscle strength.[24]

Gastrointestinal Health

Gastrointestinal (GI) upset is another consequence of LEA.[6] The gut-brain axis is a connection linking the central and enteric nervous systems (figure 5). This creates a relationship between both cognitive and emotional areas in the brain. Exercise is a form of stress. Because of the gut-brain connection, over-exercising may manifest as bloating, diarrhea, or constipation.[25] GI difficulty can be discouraging for many athletes and can cause athletes to struggle with malabsorption, dehydration, and electrolyte imbalances.

Figure 5.

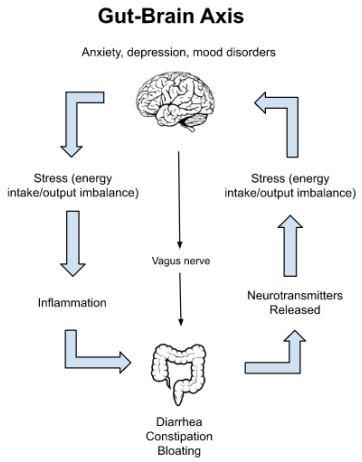

Figure 5. This image shows the correlation between the gut and the brain. Stress can lead to the brain sending the gut signals, and vice versa. Symptoms that may manifest include diarrhea, constipation, and bloating.

CONCLUSION

Overall, HA indirectly affects the performance of female athletes by acting on various systems in the body. The hormones involved in menstruation are vital for bone health, recovery, immunity, the cardiovascular system, and others. Physician Assistants (PAs) and other healthcare providers must be further educated on the impacts HA has on a female's overall health and athletic performance. There is misinformation that athletes abide by in order to achieve the

performance results they desire. Unfortunately, this often leads athletes to choose dangerous paths in the pursuit of their goals. Once this concept is understood more clearly, the vicious cycle of FAT or RED-S can be identified, addressed, and corrected earlier to avoid any lasting long-term damage to female athletes susceptible to it.

Lifestyle changes to decrease stress should be the first line of treatment for HA, which includes increasing caloric intake, decreasing intense exercise, and prioritizing sleep and recovery. Decreasing the intensity level of exercise can be a difficult conversation to have with competitive athletes. Thus, education on the health consequences of HA and the benefits of recovery is vital.[26] Additionally, lack of exercise may cause more stress to some individuals which must be taken into account. Therapy may be beneficial as well. Cognitive behavioral therapy (CBT) can help athletes learn stress management and relaxation techniques to promote ovulation and restoration of the reproductive system.[26] Because HA decreases bone density, weight bearing exercise and supplementation (vitamin D and calcium) are important for optimal health.[26]

There is a lack of specific research on the effects that HA has directly on performance. Future studies should include larger panels of female athletes and compare their times when they had regular menstrual cycles versus when they developed HA. Additionally, the length of time one struggles with HA should be evaluated to indicate what effects the duration of HA has on optimal performance and when irreversibility is reached.

The shedding of the endometrial lining to reveal the period is a vital marker of health, but what is seen physically may not be as important as regaining proper functions of the internal systems. While many providers prefer to prescribe OCP’s to cause the shedding, this merely masks the lack of the entire cycle and there is no ovulation. There is a lack of understanding

from female athletes and coaches that early onset osteoporosis is associated with amenorrhea, and thus they will be prone to more fractures in their older age if not healed. While there are many unknowns and evidence yet to be discovered, what is known is that HA is dangerous but often not addressed immediately. More conversations between athletes, coaches, and their healthcare providers is key so that they can avoid a continuous decline in their athletic performance.

LIST OF ABBREVIATIONS

Cognitive behavioral therapy (CBT), Female athlete triad (FAT), Gastrointestinal (GI), HDL cholesterol (HDLc), Hypothalamic amenorrhea (HA), Insulin like growth factor one (IGF1), International olympic committee (IOC), LDL cholesterol (LDLc), Low energy availability (LEA), Nitric oxide (NO), Oral contraceptive pills (OCPs), Relative energy deficiency syndrome (RED-S), Secretory immunoglobulin A (SIgA), Total cholesterol (TC), Triiodothyronine (T3)

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The data used are available at the corresponding citations.

Competing interests

AL ran track and cross country for George Fox University. AL declares no other conflicts of interest.

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Authors' contributions

AL researched, gathered, and analyzed the information. AL was the main contributor in writing the manuscript.

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EB proofread the manuscript for organizational, informational, and grammatical errors.

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