

Female athlete triad

Popper, Rebecca Rachael

Master's thesis / Diplomski rad

2023

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet**

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:687663>

Rights / Prava: [In copyright](#) / [Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2024-05-16**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)



UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Rebecca Rachael Popper

Female Athlete Triad

GRADUATE THESIS



Zagreb, 2023

This graduate thesis was made at the Department of Obstetrics and Gynecology,
University Hospital Petrova, School of Medicine,
University of Zagreb

Mentor: Dr. Trpimir Goluža, MD

This paper was submitted for evaluation in the academic year
2022/2023.

Abbreviations

American College of Sports Medicine (ACSM)

American International Society for Clinical Densitometry (AISCD)

Anorexia nervosa (AN)

Body mass index (BMI)

Bone mineral density (BMD)

Cardiovascular disease (CVD)

Cognitive behavioral therapy (CBT)

Corticotrophin-releasing hormone (CRH)

Dehydroepiandrosterone (DHEA-S)

Estradiol (E2)

Follicle-stimulating hormone (FSH)

Functional hypothalamic amenorrhea (FHA)

Gonadotropin-releasing hormone (GnRH)

Growth hormone (GH)

Hypothalamic-pituitary-ovarian (HPO)

International Olympic Committee (IOC)

Lean body mass (LBM)

Low energy availability (LEA)

Luteinizing hormone (LH)

Oral contraceptives (OCP)

Peptide YY (PYY)

Relative Energy Deficiency in Sport (RED-S)

Release insulin-like growth factor-1 (IGF-1)

Thyroid-stimulating hormone (TSH)

Thyroxine (T4)

Triiodothyronine (T3)

5-HT_{2A} (5-hydroxytryptamine – 2A)

Table of Contents

Abbreviations	3
Table of Contents	4
Abstract.....	5
Sažetak	6
Introduction.....	7
Methodology.....	8
Epidemiology.....	8
Pathophysiology	9
1.1 Low Energy Availability	9
1.1.1 Hypothalamic-Pituitary-Growth Hormone Axis	9
1.1.2 Leptin & Adipokines.....	10
1.1.3 Hypothalamic-Pituitary- thyroid axis	11
1.1.4 Hypothalamic-Pituitary-Adrenal axis.....	11
1.2 Menstrual Irregularities (Hypothalamic Amenorrhea)	12
1.3 Altered Bone Mineral Density	14
Psychological Dysfunction	15
Fertility complications	16
Cardiovascular Consequences	17
Diagnosis.....	18
Diagnostic Tests.....	18
Treatment	19
Non-pharmacological	19
Pharmacological Treatment.....	20
Conclusion.....	21
Acknowledgments	22
References	23
Biography.....	31

Abstract

The female athlete triad is a complex and multifaceted condition affecting women engaged in athletic pursuits. This phenomenon occurs in a considerable percentage of high-performance athletes, arising due to a relative energy deficiency. Low energy availability is a result of insufficient caloric repletion to support exercise energy expenditure. This leads to compromised physiologic processes, ensuing a spectrum of dysregulation related to menstrual function, bone mineral density, and impaired sports performance. This graduate thesis aims to explore the interplay between energy availability, menstrual function, and bone health, which collectively constitute the triad. This study intends to enhance our understanding of the unique set of challenges faced by female athletes, through investigation of the etiology, pathogenesis, prevalence, and consequences of this condition. Furthermore, this thesis highlights the lack of efficacy of current screening in athletes and seeks to shed light on the significance of early identification, prevention, and intervention strategies. Treatment is centered on restoring energy availability to ensure the well-being and long-term health of women participating in sports. Drawing upon a comprehensive analysis of existing literature from a wide range of peer-reviewed work, this graduate thesis serves to promote the acquisition of more consolidated knowledge into an understudied theme of the hormonal imbalance and the altered metabolic milieu in female athletes.

Sažetak

Trijas sportašica složen je poremećaj fizioloških procesa u žena koje se bave sportom. Javlja se u mnogih vrhunskih sportašica kao posljedica relativnog manjka energije zbog nedovoljnog unosa kalorija nužnih za potporu potrošnje energije tijekom tjelovježbe. Nedostatak energije uzrokuje spektar poremećaja povezanih s menstrualnim ciklusom, nepovoljno utječe na metabolizam odnosno mineralnu gustoću kostiju te rezultira slabijim sportskim ostvarenjima. Ovaj diplomski rad istražuje povezanost dostupnosti energije, menstrualne funkcije i zdravlja kostiju, koji zajedno čine fenomen trijasa u sportašica. Ova studija ima za cilj, kroz istraživanje prevalencije, etiologije, patogeneze i posljedica ovog specifičnog stanja, unaprijediti razumijevanje ovog specifičnog patofiziološkog mehanizma s kojim se suočavaju sportašice. Radom se naglašava nedostatak učinkovitosti trenutnog probira trijasa kod sportaša i nastoji pojasniti važnost njegove rane identifikacije i prevencije kao i strategija intervencije nakon utvrđene dijagnoze. Liječenje je usmjereno na obnavljanje raspoloživosti energije kako bi se osigurala dobrobit i dugoročno zdravlje žena koje se bave sportom. Na temelju sveobuhvatne analize postojeće literature o predmetnoj tematici, ovim diplomskim radom daje se konsolidirani prikaz postojećih spoznaja i znanja o još uvijek nedovoljno i nepotpuno proučenoj temi hormonske neravnoteže i promijenjenog metaboličkog miljea kod sportašica.

Introduction

Over the past few decades, the participation of women in competitive sports has observed an astonishing surge. The demanding nature of sports exposes females to a unique set of challenges. The American College of Sports Medicine (ACSM) first devised the term Female Athlete Triad in 1997. The distinct clinical features of the condition were initially defined as the presence of eating disorders, amenorrhea, and osteoporosis in physically active women (1).

Since then, the components of the triad extended beyond these terms, redefining the condition as low energy availability (LEA), menstrual dysfunction, and altered bone mineral density (BMD) (2). An athlete's condition may fall anywhere along a spectrum of optimal energy availability, from an eating disorder, and menstrual regularity to amenorrhea, and low BMD to osteoporosis. As a result, the female athlete may present with some aspects of the condition without meeting the full triad criteria (3).

According to the International Olympic Committee (IOC), the condition requires a holistic approach and the term Relative Energy Deficiency in Sport (RED-S) may be more appropriate. RED-S highlights that an imbalance between caloric intake and metabolic demand of energy expenditure results in a disastrous effect on several physiologic functions. Some of these compromised functions include growth, development, gastrointestinal, endocrine, immunological, reproductive, and bone health. The deleterious effect of low energy availability ultimately negatively influences the performance and health of the female athlete (4,5).

Understanding the etiology, prevalence, and consequences of the female athlete triad is critical for optimizing the health and performance of female athletes. The multifactorial nature of the syndrome requires stakeholders involved in sports to recognize and collaborate toward implementing effective preventative measures and interventional strategies. Seeing as the female athlete triad poses significant potential long-term implications, it is imperative to address this issue proactively and promote overall well-being for female athletes (3,6).

The primary objective of this graduate thesis is to provide a comprehensive overview of the female athlete triad. Conduction of extensive research into relevant literature, this thesis aims to synthesize an overview of the prevalence, risk factors, pathophysiology, clinical manifestations, consequences, and treatment approaches related to the female athlete triad.

Methodology

To accomplish the objectives outlined above, this graduate thesis serves as a review of the female athlete triad and its components using a comprehensive search of electronic databases – such as PubMed and Google Scholar. This extensive search utilized relevant scientific literature – including peer-reviewed articles, reports, books, and authoritative guidelines. The following search terms were used: “female athlete triad”, “amenorrhea”, “menstrual function”, “energy availability”, “low energy availability”, “anorexia”, “osteoporosis”, “bone health”, “athletic performance” and “intervention strategies”. The inclusion criteria for the review encompassed articles addressing the empirical evidence, theoretical framework, prevalence, screening, and management of the female athlete triad.

Epidemiology

The concept of the female athlete triad has evolved, and the syndrome is now recognized as part of a broader condition, RED-S. Understanding RED-S increases awareness that although the overall estimated prevalence of the triad is low, individual components of the triad are common among athletes at multiple tiers of competing levels and ages (7).

A meta-analysis on the prevalence of the triad in athletes across all levels of activity reported a relatively small percentage (0% to 15.9%) exhibiting all three triad conditions. However, the prevalence of individual disorders of the triad is much higher, whereby athletes demonstrating any 2 conditions of the triad ranged from 2.7% to 27%. Furthermore, the prevalence of athletes with one condition of the triad ranged from 16% to 60% (8).

Prevalence of low energy availability (LEA) in various sports ranges from 22 to 58% (3,9,10). Moreover, 23.5% of female athletes experience menstrual dysfunction, with 18.2% exhibiting disordered eating, whereby 4.1% have low BMD (11). In addition to this, according to current data, the prevalence of the female athlete triad ranges widely depending on the population and sport examined. The triad in sports that emphasize weight leanness – such as ballet, endurance running, and endurance cycling – is three times more prevalent than other sports (3).

Pathophysiology

1.1 Low Energy Availability

Exercise has a well-documented positive outcome on health in most individuals. However, excessive energy expenditure and food scarcity in the setting of exercise appear to initiate several physiological adaptations. These adjustments are crucial to ensure the maintenance of essential processes at the detriment of secondary functions such as growth, development, and reproduction (12).

1.1.1 Hypothalamic-Pituitary-Growth Hormone Axis

Body fat serves as an energy storer, which is vital for the regulation of many endocrine axes. One of which includes the hypothalamic-pituitary-growth hormone axis. It regulates a group of hormones that are involved in both catabolic and anabolic responses, which are also known to be disrupted due to LEA. Under energy equilibrium states, the pituitary gland releases growth hormone (GH). GH acts on the liver to release insulin-like growth factor-1 (IGF-1), and IGF-1 receptors are found in most tissues. In addition to exerting its physiologic effects, it provides a source for a negative feedback loop on the pituitary to decrease GH secretion (13). Low body fat in amenorrheic athletes is inversely related to circulating GH levels. The gluconeogenic properties of GH serve as an adaption to maintain euglycemia in LEA athletes (14).

During LEA, the liver becomes insensitive GH, which increases the pituitary release of GH. This, however, is not associated with higher insulin-like growth factor 1 (IGF-

1). In fact, athletes with caloric deficit translate to lower IGF-1 secretion. This is consistent with the development of a state of resistance to GH (15). Murphy and Koehler (2020) et al. Investigated the post-exercise GH/IGF-1 response in athletes with LEA after a resistance training effort. They demonstrated that LEA in athletes performing resistance training resulted in reduced IGF-1 secretion by 20-30%. Furthermore, these athletes exhibited a 2.5 times greater GH surge compared to controls. This data presents an impairment in the GH-IGF-1 axis in LEA athletes. Overall, this skewed axis decreases the anabolic response to exercise and contrastingly promotes catabolism in these athletes (16).

Supplementally, the orexigenic hormone ghrelin - secreted by gastric oxyntic cells - is also inversely related to fat mass. Ghrelin is a peptide and GH secretagogue, levels of which are elevated in LEA and its release reflects energy status. Ghrelin secretion is elevated in amenorrheic athletes compared to eumenorrheic athletes and non-athletes (17)(18).

1.1.2 Leptin & Adipokines

The anorexigenic hormone, leptin, is secreted by adipocytes and under the regulation of energy status. It is a key hormone in energy homeostasis, acting as a sensor of energy availability. A balance between intake and expenditure is regulated by the neuroendocrine axis involving hypothalamic control and peripheral tissue metabolism (19).

In contrast to many hormones, leptin exerts its effect predominantly when its circulating levels decrease. LEA - due to dietary restriction alone or related to exercise - is related to decreased circulating leptin, independent of menstrual status (20,21). Interestingly, leptin levels appear to follow a dose-dependent response to decreasing energy availability. This finding has not been reported in men, suggesting that females have a higher predisposition to the negative consequences of LEA (22).

A cross-sectional study conducted by Ackerman (2012) et al. investigated the effect of low leptin levels and increased ghrelin on gonadotropin pulsatility. It was concluded that young amenorrheic athletes with higher ghrelin and lower leptin than

eumenorrheic athletes and nonathletes have lower luteinizing hormone (LH) secretion (17). Both low leptin levels and high circulating ghrelin in athletes has been reported to disrupt gonadotropin-releasing hormone (GnRH) pulsatility, thereby altering LH secretion (23)(24).

Peptide YY (PYY) is secreted by endocrine L cells found in the distal gut. PYY is a signal for satiety and is released after a meal. Paradoxically, PYY concentrations are inversely related to body mass index (BMI) and fat mass, whereby high PYY concentrations were associated with LEA (13). The lack of adaptation of PYY to low nutritional status is believed to contribute to restrictive eating patterns observed in anorexia nervosa (AN) (25). Consequently, PYY has demonstrated osteoblastic inhibitory effects, leading to decreased bone mineral density in amenorrheic athletes and AN (26). Furthermore, increased PYY in physically active women plays a role in decreased GnRH and gonadotropins (27).

1.1.3 Hypothalamic-Pituitary- thyroid axis

The hypothalamic-pituitary-thyroid axis plays a critical role in the control of energy balance and metabolic regulation. Thyroid hormones are responsible for processes related to growth, development, differentiation, and metabolism (28,29). Adaptation to decreased available energy leads to decreased total triiodothyronine (T3) concentrations. Low T3 levels are positively correlated with BMI and leptin levels, and inversely related to ghrelin and cortisol concentrations (13). Given the impact of T3 on resting energy expenditure, lower total T3 is consistent with the required adaptations to conserve energy in LEA (22,30)

1.1.4 Hypothalamic-Pituitary-Adrenal axis

Similar to GH, LEA is associated with higher cortisol concentration in female athletes. (28)(31). Both individuals with anorexia nervosa and female athletes with low body fat have disrupted hypothalamic-pituitary-cortisol axes. Cortisol is gluconeogenic and acts to maintain euglycemia. Consequently, hypercortisolism has inhibitory effects on LH pulsatility. Amenorrheic athletes have lower overnight LH concentrations than

eumenorrheic athletes as well as an increase in basal cortisol (28) (32). Furthermore, hypercortisolism has a deleterious effect on bone metabolism, increasing resorption and decreasing formation (33). Data collected from various studies point toward an understanding that lower leptin and higher ghrelin drive cortisol secretion in the undernourished athlete. Together these hormones decrease GnRH pulsatility and disrupt the hypothalamic-pituitary-gonadal axis (24)(33).

1.2 Menstrual Irregularities (Hypothalamic Amenorrhea)

Menstrual dysfunction in active females is complex. Menstrual irregularities present with a spectrum of disorders, from delaying the onset of menarche to causing subclinical menstrual disorders, oligomenorrhea, and amenorrhea (34).

Oligomenorrhea is defined as menstrual cycles occurring at intervals longer than 35 days. Secondary amenorrhea is defined as the absence of menstrual cycles for greater than 3 months in a previously menstruating individual (35). Functional hypothalamic amenorrhea (FHA) is defined as amenorrhea for at least 3 consecutive months, with the exclusion of other etiologies of secondary amenorrhea. Some other causes that are essential to rule out include hyperprolactinemia, thyroid dysfunction, premature ovarian failure, and polycystic ovarian syndrome. FHA results in severe hypoestrogenism and cessation of the menstrual cycle (36).

Seeing as oligomenorrhea is present in most girls during the first year after menarche, diagnosing menstrual dysfunction in this age group can be challenging (35). Nonetheless, an investigation of over 400 college athletes demonstrated that up to 22.2% of female athletes had not menstruated by age 16 years (37). Contrastingly, in the general population, 1% of females have not reached menarche by 16 years (38).

As previously explained, the stress response to LEA leads to increased corticotrophin-releasing hormone (CRH), cortisol, ghrelin, PYY, and adiponectin. LEA also has a role in decreased leptin, insulin, and IGF-1. Overall, studies have shown that these altered concentrations suppress the hypothalamic-pituitary-ovarian (HPO) axis.

Increased CRH, cortisol and decreased leptin negatively influence the release of GnRH. A decrease in the GnRH drive disrupts follicle-stimulating hormone (FSH) and LH pulsation frequency from the anterior pituitary (39). The altered secretion of FSH and LH alters ovulatory function and folliculogenesis, leading to a state of lower progesterone and estradiol levels (40)(41–43). Without FSH, follicles are not stimulated and granulosa cells are not probed to produce estradiol. As a result, endometrial thickening does not occur during the follicular phase. With the lack of pulsatile LH and the resulting spike in estrogen, the athlete remains in an anovulatory state. The consequences of this include infertility during the peak of a woman's reproductive years (39).

The suppression of the HPO axis during periods of LEA proves to be an adaptive effect to preserve vital functions and prevent pregnancy. Pregnancy would divert energy toward the growing fetus, further decreasing available energy for essential body functions (44). Importantly, LEA can present with a spectrum of menstrual irregularities in addition to frank amenorrhea, namely, luteal phase defects, and subclinical menstrual dysfunctions (45).

Studies have shown that despite a relationship existing between LEA and menstrual dysfunction, there appears to be no specific threshold. Each female athlete, thus, has her own energy availability threshold to which LH pulsation is disrupted (46,47). Contrastingly, other studies argue that there is a cutoff for energy availability that can identify women at risk. Energy availability is determined by the difference between energy intake and energy expenditure, divided by lean body mass (LBM) (6). Loucks (2003) et al. presented a study that revealed stable LH pulsatility when energy availability remained 45 kcals/kg of LBM/day or higher and disrupted when it dropped below 30 kcals/kg of LBM/day (48). This was supported by another study conducted by Koltun (2020) et al. demonstrating that the pulse frequency of LH over 3 months was disturbed by a decreased energy availability of 28 kcals/kg of LBM/day (49).

Numerous investigations have determined that menstrual dysfunction prevalence is highly dependent on the nature of the sport, the intensity of training, and the athlete's nutritional status. Endurance athletes are associated with lower body weight than other athletes and are at a higher risk for FHA (34).

1.3 Altered Bone Mineral Density

Prolonged energy deficiency and hormonal imbalances seen in the female athlete contribute to compromised bone health, reduced BMD, osteoporosis, and increased fracture risk. BMD in children and premenopausal women is expressed as Z scores. The Z score of the athlete is compared to the average healthy BMD for their age. Athletes have up to 15% higher BMD than nonathletes (50). As a result, the American International Society for Clinical Densitometry (AISCD) has defined a Z score between -1.0 and -1.9 as low BMD. This range applies to female athletes with a history of hypoestrogenism, nutritional deficiencies, and stress fractures. Moreover, osteoporosis in this group is defined as Z scores < -2.0 (3).

Bone tissue constantly undergoes remodeling, regulated by osteoblasts (form new bone) and osteoclasts (resorb formed bone). Bone metabolism is coordinated by an intricate interplay between several growth factors, polypeptides, and thyroidal and gonadal hormones. The dynamics of bone in hypoestrogenic and LEA states lead to a loss of bone repair mechanisms, which have cumulative consequences on bone health (51,52).

A decrease in bone formation and bone turnover serves as the main culprit of altered BMD in female athletes (53). Amenorrheic athletes have abnormal bone architecture due to changes in the metabolic milieu such as decreased IGF-1, leptin, and PYY as well as nutrient deficiencies in vitamin D and calcium (54).

Numerous investigations among amenorrheic athletes exhibited a significantly higher prevalence of low BMD at the lumbar spine, femoral neck, and whole body, compared to both eumenorrheic and oligomenorrheic athletes (55,56). It is important to mention that low BMD has been reported in athletes with eating disorders (LEA) but maintain regular menstruation (57). Therefore, the combination of amenorrhea and LEA together increase the likelihood of stress fractures (55).

Lastly, the triad may pose detrimental effects on adolescent female athletes, who may not reach optimal peak bone mass during the narrow pubertal window. Adolescence serves as an important time for bone acquisition, a time characterized by a maximal increase in bone accrual. Young amenorrheic adolescents can suffer from long-lasting

effects on their bone health, whereby the biological potential for peak bone mass may not be reached (58,59).

Unfortunately, the beneficial nature of weight-bearing exercises in improving bone microarchitecture and strength does not hold true for adolescent athletes without a normal hormonal status (60). A 3-year longitudinal study followed adolescent endurance runners with low BMD at baseline, to investigate the possibility of an increase in bone mass. Despite weight gain and return of normal menses at the 3-year follow-up, these athletes continued to exhibit low bone mass compared to their healthy peers (60).

As a result, further research into the triad is required to promote a potential restoration during adulthood. Effective behavioral treatment options must be explored, geared toward promoting healthy behaviors to optimize healthy bone mass.

Psychological Dysfunction

Current data suggest a deleterious psychological impact of FHA on female athletes. The hypoestrogenic state influences many areas of the brain, including the brainstem, amygdala, mesolimbic and nigrostriatal system, hypothalamus, cerebellum, and cerebral cortex (61). Various fluctuations occur regarding verbal memory, executive function, mood, attitudes, drive for thinness, and cognitive flexibility, in amenorrheic athletes compared to eumenorrheic athletes (62).

States of low estrogen alter neuromodulatory systems ensuing fluctuations in serotonin and dopamine, neurotransmitters that regulate mood. Estrogen influences cognitive function and emotion regulation by increasing cortical 5-HT_{2A} binding. Thus, low levels of these neurotransmitters in the brain are linked to the onset of depression (63,64). In addition to this, women with FHA have a higher incidence of psychological fixation on their physical appearance compared to women with normal menstrual cycles (65).

Women with FHA also present with dysfunctional feelings of inadequacy, lack of control, and internal feelings of insecurity (66). In comparison to their eumenorrheic counterparts, female athletes with FHA divert a higher degree of attention to the judgments of others. This is correlated with the higher prevalence of perfectionistic behavior seen among amenorrheic women (64). A study conducted by Baskaran (2017) et al. demonstrated that combined hormonal replacement over a 6-month period improved verbal memory, and cognitive flexibility as well as increased body satisfaction scores (62). The negative psychological impact of hypoestrogenism in female athletes worsens the state of hypercortisolism, exacerbating the disruption to the GnRH neural network (66).

Fertility complications

As previously described, LEA results in decreased or inhibited GnRH secretion, preventing the pulsatile secretion of LH and FSH from the pituitary, ultimately leading to estrogen deficiency and anovulation (41). Furthermore, the lack of cyclical estrogen and progesterone prevents endometrial thickening. FHA occurs in women of peak reproductive years, causing an infertile state. Despite its reversibility, prolonged and untreated FHA negatively impacts reproductive health. The estrogen deficiency seen in these athletes parallels that of postmenopausal women - atrophic changes of the urogenital mucosa, decreased vaginal reggaeton and lubrication, increased laxity of uterine muscles as well as a higher vaginal pH which predisposes the genitourinary tract to infection (67). Moreover, women with low BMI who become spontaneously pregnant have a higher risk of miscarriage in the first trimester (68). In addition to this, low BMI is related to preterm delivery (69)

Cardiovascular Consequences

Estrogen plays a critical role in the maintenance of cardiovascular health in women. This hormone has potent vasodilatory effects. The beneficial effects of estrogen are well-studied in post-menopausal women, who suffer the consequences of the lack thereof (70).

Contrastingly, investigations into the cardiovascular consequences of hypoestrogenism in premenopausal women are lacking. Nonetheless, animal studies in young female monkeys have demonstrated that poor psychological health led to FHA. These hypoestrogenic monkeys subsequently developed accelerated atherosclerosis as well as abnormal regulation of vessel diameter. Furthermore, the administration of oral contraceptives to these premenopausal hypoestrogenic monkeys resulted in a protective effect regarding the development of atherosclerosis (71).

In addition to animal studies, early menopause (≤ 45 years old) and primary ovarian insufficiency is associated with a 2.5-fold increased risk of developing cardiovascular disease (CVD) compared to premenopausal women of the same age (72,73). Interestingly, research in young women with irregular menstrual cycles reported up to a 50% increased risk for future CVD (34). Turner's syndrome is a genetic condition with an X-chromosome defect (45X), which results in severe estrogen deficiency due to ovarian dysgenesis. Individuals with this syndrome have a reduced life expectancy with the main cause of death being that of cardiovascular complications. Women with Turner syndrome have a higher rate of hyperlipidemia, hypertension, diabetes, and obesity, with a 7-fold higher rate of CVD (74,75).

This data sheds light on a potential link between hypoestrogenism in premenopausal women and premature CVD development.

Diagnosis

The diagnosis of a female athlete with LEA either due to low input, excessive expenditure, or both, requires a low threshold of suspicion. A detailed medical history is required, and questions including diet, exercise intensity and duration, stress, mood, sleep, stress, menstruation, and weight fluctuations should be explored.

The IOC created a standardized clinical screening tool, with an aim to be used as part of an athlete's annual health assessment. The tool should also be used when an athlete presents with evidence of amenorrhea (both primary and secondary), significant weight loss, and mood changes. Adolescents with LEA often display a stunt in height regarding growth velocity curves (76).

The first manifestation of hypoestrogenism is typically dysregulation of the menstrual cycle, ranging from irregularity, oligomenorrhea, or amenorrhea for more than 3 months. The diagnosis of FHA is one of exclusion and can be made in the absence of anatomical or organic pathology (77).

Therefore, it is critical to consider other main causes of amenorrhea. Some of these include genetic conditions (Kallman syndrome, Turner's, Mullarian dysgenesis, androgen insensitivity syndrome), thyroid dysfunctions, drugs, and prolactinomas. A complete physical examination and gynecological imaging studies often complement the diagnosis. Identifying accompanying signs in the female athlete is useful in the diagnosis of hypoestrogenism, such as androgen excess, bradycardia, BMI < 18.5 kg/m², parotid hypertrophy, and breast and vaginal atrophy (77).

Diagnostic Tests

The initial investigation into amenorrhea includes the study of hCG, prolactin, FSH, and thyroid-stimulating hormone (TSH). The presence or suspicion of an eating disorder should include blood count, electrolyte panel, erythrocyte sedimentation rate, C-reactive protein, liver and kidney function, and glycemia studies (77). When signs of androgen excess are present, total testosterone, dehydroepiandrosterone (DHEA-S), and 17-OH-progesterone should be considered (78).

Results in female athletes with FHA are expected to display normal FSH, low normal to decreased LH, and Estradiol (E2) < 50pg/ml. TSH, free thyroxine (T4), and testosterone remain at the lower limit of normal. There is preservation in the response to GnRH stimulation (77) (79).

BMD should be assessed in athletes with BMI < 17.5 kg/m², significant weight loss (>5% of body mass in 1 month), stress fractures, eating disorders, and menstrual dysfunction. The Z-score scale is used since it is adapted to the age and gender of these young athletes. BMD is considered lower than normal if Z-score is > -1. Stress fractures, nutritional deficiency and hypoestrogenism are risk factors for low BMD with Z-score between -1 and -1.9. Z-score < -2 presenting with osteoporosis (80,81).

Treatment

Non-pharmacological

Treating the female athlete triad is multifaceted. The success of treatment largely depends upon the ability to identify the multifactorial nature of its etiologies – excessive exercise, psychological stress, disordered eating, and weight loss.

Nonpharmacological treatment is a first-line modality in the approach to the female athlete triad. Seeing as the central cause is based on LEA, restoring homeostasis regarding an individual approach is crucial. Achieving an individualized plan that aims to balance nutrition, psychology, and sports with the goal of reestablishing the HPO axis (82).

Cognitive behavioral therapy (CBT) is a successful treatment option to address the psychological component of the athlete. CBT lowers cortisol levels and provides profound insight to the athlete about their condition. Through education and focus on the psychological domain, athletes make constructive decisions regarding their metabolic health (83).

Calcium and vitamin D supplementation have shown benefits in decreasing the risk of stress fractures. A recommended daily dose of up to 1,500 mg/day of calcium and 1000 IU of vitamin D (84,85).

Pharmacological Treatment

Pharmacological treatment is generally only customary if the reestablishment of the menstrual cycle failed after 12 months of nonpharmacological therapy. The use of oral contraceptives (OCP) is often prescribed as an adjunct to normalize menstrual cycles. Despite it serving as an estrogen replacement and providing a withdrawal bleed, it does not support the resumption of normal endogenous hormonal activity. Often, OCPs falsely provide psychological confidence to the athlete on their condition. In addition to this, studies have not shown the efficacy of prescription OCPs in the recovery of BMD (86).

Moreover, OCPs potentially suppress liver production of IGF-1 and further impair the bone trophic effect (87). Therefore, when estrogen replacement is considered, it is generally in the form of an E2 transdermal patch, which eliminates the issue of first-pass metabolism as seen in OCP use (88).

A promising investigational therapy targets low leptin levels in women with FHA. Leptin replacement therapy was administered subcutaneously twice daily for 3 months in women with FHA. Results showed an increased concentration and pulse of LH, increased follicular growth, and circulating estradiol. These findings all support a promising treatment for the re-establishment of ovulation in these athletes. Furthermore, leptin replacement therapy in women with FHA showed an increase in markers of bone formation, such as IGF-1, bone alkaline phosphatase, and osteocalcin (89).

Unfortunately, female athletes with restored menstrual cycles may maintain altered follicular dynamics and decreased gonadotropins for years. As a result of decreased progesterone secretion, luteal phase defects present as both longer and shorter cycles, ultimately adversely affecting fertility. In addition to this, menstrual reestablishment does not fully recover ideal BMD (90).

Therefore, it is essential to promote education and awareness among athletes, coaches, and healthcare professionals about the risk and warning signs associated with the triad. Timely intervention and a multidisciplinary approach, including nutritional counseling, psychological support, and a modified training regimen are imperative to prevent and manage the consequences associated with the female athlete triad.

Conclusion

The female athlete triad arises due to a relative energy deficiency in sport. The low energy availability status in female athletes has demonstrated deleterious effects on menstrual function, bone health, cognitive outcomes, cardiovascular compromise and eating disorders. Evidence suggests that altered endocrine functionality occurs secondary to low energy availability. The condition presents a wide variation in the energy deficit that female athletes of all ages may sustain before they present with menstrual dysfunction or altered bone metabolism. Females may experience one disorder of the triad and need not exhibit the other components for diagnosis. However, an athlete displaying one aspect of the triad should be evaluated for all three components.

Due to deficient knowledge of signs and symptoms, the prevalence of the triad is underestimated resulting in a lack of and/or late diagnosis. The cornerstone of current treatment focuses on energy repletion, whereby pharmacological intervention has shown limited success. This necessitates a multidisciplinary approach including nutritional counseling, psychological support, and a modified training regimen to prevent and manage the consequences associated with the female athlete triad.

Future research should be aimed at identifying athletes at risk, allowing its prevention, early diagnosis, and adequate treatment. This involves a widespread educational effort involving coaches, athletes, and their families to increase alertness to this condition.

Acknowledgments

I would like to thank my family, friends, and partner for all their love and support throughout my studies. A special thank you to my mentor for his assistance and contribution to the development of this thesis.

References

1. Yaeger K, Agostini R, Nattiv A, Drinkwater B. The female Athlete Triad. *Official Journal of the American College of Sports Medicine*. 1993 Apr;755–77.
2. De Souza MJ, Nattiv A, Joy E, Misra M, Williams NI, Mallinson RJ, et al. 2014 Female Athlete Triad Coalition Consensus Statement on Treatment and Return to Play of the Female Athlete Triad: 1st International Conference held in San Francisco, California, May 2012 and 2nd International Conference held in Indianapolis, Indiana, May 2013. *Br J Sports Med [Internet]*. 2014 Feb 1 [cited 2023 Mar 24];48(4):289–289. Available from: <https://bjsm.bmj.com/content/48/4/289>
3. Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sundgot-Borgen J, Warren MP. American College of Sports Medicine position stand. The female athlete triad. *Med Sci Sports Exerc [Internet]*. 2007 Oct [cited 2023 May 23];39(10):1867–82. Available from: <https://pubmed.ncbi.nlm.nih.gov/17909417/>
4. Mountjoy M, Sundgot-Borgen J, Burke L, Carter S, Constantini N, Lebrun C, et al. The IOC consensus statement: beyond the Female Athlete Triad—Relative Energy Deficiency in Sport (RED-S). *Br J Sports Med [Internet]*. 2014 Apr 1 [cited 2023 Mar 24];48(7):491–7. Available from: <https://bjsm.bmj.com/content/48/7/491>
5. Mountjoy M, Sundgot-Borgen JK, Burke LM, Ackerman KE, Blauwet C, Constantini N, et al. IOC consensus statement on relative energy deficiency in sport (RED-S): 2018 update. *Br J Sports Med [Internet]*. 2018 [cited 2023 Mar 24];52(11):687–97. Available from: <https://pubmed.ncbi.nlm.nih.gov/29773536/>
6. Mountjoy M, Sundgot-Borgen JK, Burke LM, Ackerman KE, Blauwet C, Constantini N, et al. IOC consensus statement on relative energy deficiency in sport (RED-S): 2018 update. *Br J Sports Med [Internet]*. 2018 [cited 2023 Apr 1];52(11):687–97. Available from: <https://pubmed.ncbi.nlm.nih.gov/29773536/>
7. Nichols DL, Sanborn CF, Essery E V. Bone density and young athletic women. An update. *Sports Med [Internet]*. 2007 [cited 2023 May 23];37(11):1001–14. Available from: <https://pubmed.ncbi.nlm.nih.gov/17953469/>
8. Gibbs JC, Williams NI, De Souza MJ. Prevalence of individual and combined components of the female athlete triad. *Med Sci Sports Exerc [Internet]*. 2013 May [cited 2023 May 23];45(5):985–96. Available from: <https://pubmed.ncbi.nlm.nih.gov/23247706/>
9. Logue DM, Madigan SM, Melin A, Delahunt E, Heinen M, Mc Donnell SJ, et al. Low Energy Availability in Athletes 2020: An Updated Narrative Review of Prevalence, Risk, Within-Day Energy Balance, Knowledge, and Impact on Sports Performance. *Nutrients [Internet]*. 2020 Mar 1 [cited 2023 May 23];12(3). Available from: <https://pubmed.ncbi.nlm.nih.gov/32245088/>
10. Condo D, Lohman R, Kelly M, Carr A. Nutritional Intake, Sports Nutrition Knowledge and Energy Availability in Female Australian Rules Football Players. *Nutrients [Internet]*. 2019 May 1 [cited 2023 May 23];11(5). Available from: <https://pubmed.ncbi.nlm.nih.gov/31035346/>

11. Nichols JF, Rauh MJ, Lawson MJ, Ji M, Barkai HS. Prevalence of the female athlete triad syndrome among high school athletes. *Arch Pediatr Adolesc Med* [Internet]. 2006 Feb [cited 2023 May 23];160(2):137–42. Available from: <https://pubmed.ncbi.nlm.nih.gov/16461868/>
12. Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sundgot-Borgen J, Warren MP. American College of Sports Medicine position stand. The female athlete triad. *Med Sci Sports Exerc* [Internet]. 2007 Oct [cited 2023 Mar 24];39(10):1867–82. Available from: <https://pubmed.ncbi.nlm.nih.gov/17909417/>
13. Misra M, Klibanski A. Endocrine consequences of anorexia nervosa. *Lancet Diabetes Endocrinol* [Internet]. 2014 [cited 2023 Apr 15];2(7):581–92. Available from: <https://pubmed.ncbi.nlm.nih.gov/24731664/>
14. Christo K, Prabhakaran R, Lamparello B, Cord J, Miller KK, Goldstein MA, et al. Bone metabolism in adolescent athletes with amenorrhea, athletes with eumenorrhea, and control subjects. *Pediatrics* [Internet]. 2008 Jun [cited 2023 Apr 15];121(6):1127–36. Available from: <https://pubmed.ncbi.nlm.nih.gov/18519482/>
15. Christo K, Prabhakaran R, Lamparello B, Cord J, Miller KK, Goldstein MA, et al. Bone metabolism in adolescent athletes with amenorrhea, athletes with eumenorrhea, and control subjects. *Pediatrics* [Internet]. 2008 Jun [cited 2023 Apr 4];121(6):1127–36. Available from: <https://pubmed.ncbi.nlm.nih.gov/18519482/>
16. Murphy C, Koehler K. Caloric restriction induces anabolic resistance to resistance exercise. *Eur J Appl Physiol* [Internet]. 2020 May 1 [cited 2023 Apr 15];120(5):1155–64. Available from: <https://pubmed.ncbi.nlm.nih.gov/32236752/>
17. Ackerman KE, Slusarz K, Guereca G, Pierce L, Slattery M, Mendes N, et al. Higher ghrelin and lower leptin secretion are associated with lower LH secretion in young amenorrheic athletes compared with eumenorrheic athletes and controls. *Am J Physiol Endocrinol Metab* [Internet]. 2012 Apr 1 [cited 2023 Apr 4];302(7). Available from: <https://pubmed.ncbi.nlm.nih.gov/22252944/>
18. Christo K, Cord J, Mendes N, Miller KK, Goldstein MA, Klibanski A, et al. Acylated ghrelin and leptin in adolescent athletes with amenorrhea, eumenorrheic athletes and controls: a cross-sectional study. *Clin Endocrinol (Oxf)* [Internet]. 2008 Oct [cited 2023 Apr 15];69(4):628–33. Available from: <https://pubmed.ncbi.nlm.nih.gov/18331605/>
19. Blüher S, Mantzoros CS. Leptin in humans: lessons from translational research. *Am J Clin Nutr* [Internet]. 2009 Mar 1 [cited 2023 Apr 15];89(3). Available from: <https://pubmed.ncbi.nlm.nih.gov/19176740/>
20. Misra M, Miller KK, Kuo K, Griffin K, Stewart V, Hunter E, et al. Secretory dynamics of leptin in adolescent girls with anorexia nervosa and healthy adolescents. *Am J Physiol Endocrinol Metab* [Internet]. 2005 Sep [cited 2023 Apr 4];289(3). Available from: <https://pubmed.ncbi.nlm.nih.gov/15811876/>
21. Christo K, Cord J, Mendes N, Miller KK, Goldstein MA, Klibanski A, et al. Acylated ghrelin and leptin in adolescent athletes with amenorrhea, eumenorrheic athletes and

- controls: a cross-sectional study. *Clin Endocrinol (Oxf)* [Internet]. 2008 Oct [cited 2023 Apr 4];69(4):628–33. Available from: <https://pubmed.ncbi.nlm.nih.gov/18331605/>
22. Papageorgiou M, Elliott-Sale KJ, Parsons A, Tang JCY, Greeves JP, Fraser WD, et al. Effects of reduced energy availability on bone metabolism in women and men. *Bone* [Internet]. 2017 Dec 1 [cited 2023 Apr 15];105:191–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/28847532/>
 23. Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, et al. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med* [Internet]. 2004 Sep 2 [cited 2023 Apr 4];351(10):987–97. Available from: <https://pubmed.ncbi.nlm.nih.gov/15342807/>
 24. Kluge M, Schüssler P, Uhr M, Yassouridis A, Steiger A. Ghrelin suppresses secretion of luteinizing hormone in humans. *J Clin Endocrinol Metab* [Internet]. 2007 [cited 2023 Apr 15];92(8):3202–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/17550958/>
 25. Scheid JL, Williams NI, West SL, VanHeest JL, Souza MJ De. Elevated PYY is associated with energy deficiency and indices of subclinical disordered eating in exercising women with hypothalamic amenorrhea. *Appetite* [Internet]. 2009 Feb [cited 2023 Apr 15];52(1):184–92. Available from: <https://pubmed.ncbi.nlm.nih.gov/18929607/>
 26. Russell M, Stark J, Nayak S, Miller KK, Herzog DB, Klibanski A, et al. Peptide YY in adolescent athletes with amenorrhea, eumenorrheic athletes and non-athletic controls. *Bone* [Internet]. 2009 Jul [cited 2023 Apr 15];45(1):104–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/19344792/>
 27. Scheid JL, De Souza MJ. Menstrual irregularities and energy deficiency in physically active women: the role of ghrelin, PYY and adipocytokines. *Med Sport Sci* [Internet]. 2010 [cited 2023 Apr 15];55:82–102. Available from: <https://pubmed.ncbi.nlm.nih.gov/20956862/>
 28. Ackerman KE, Patel KT, Guereca G, Pierce L, Herzog DB, Misra M. Cortisol secretory parameters in young exercisers in relation to LH secretion and bone parameters. *Clin Endocrinol (Oxf)* [Internet]. 2013 Jan [cited 2023 Apr 4];78(1):114–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/22671919/>
 29. Mcaninch EA, Bianco AC. Thyroid hormone signaling in energy homeostasis and energy metabolism. *Ann N Y Acad Sci* [Internet]. 2014 [cited 2023 Apr 15];1311(1):77–87. Available from: <https://pubmed.ncbi.nlm.nih.gov/24697152/>
 30. Kim B. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. *Thyroid* [Internet]. 2008 Feb 1 [cited 2023 Apr 15];18(2):141–4. Available from: <https://pubmed.ncbi.nlm.nih.gov/18279014/>
 31. Misra M, Miller KK, Almazan C, Ramaswamy K, Lapcharoensap W, Worley M, et al. Alterations in cortisol secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. *J Clin Endocrinol Metab* [Internet]. 2004 Oct [cited 2023 Apr 4];89(10):4972–80. Available from: <https://pubmed.ncbi.nlm.nih.gov/15472193/>

32. Breen KM, Karsch FJ. Does cortisol inhibit pulsatile luteinizing hormone secretion at the hypothalamic or pituitary level? *Endocrinology* [Internet]. 2004 Feb [cited 2023 Apr 4];145(2):692–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/14576178/>
33. Ackerman KE, Patel KT, Guereca G, Pierce L, Herzog DB, Misra M. Cortisol secretory parameters in young exercisers in relation to LH secretion and bone parameters. *Clin Endocrinol (Oxf)* [Internet]. 2013 Jan [cited 2023 Apr 15];78(1):114–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/22671919/>
34. Solomon CG, Hu FB, Dunaif A, Rich-Edwards JE, Stampfer MJ, Willett WC, et al. Menstrual cycle irregularity and risk for future cardiovascular disease. *J Clin Endocrinol Metab* [Internet]. 2002 [cited 2023 Apr 26];87(5):2013–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/11994334/>
35. Legro RS, Lin HM, Demers LM, Lloyd T. Rapid maturation of the reproductive axis during perimenarche independent of body composition. *J Clin Endocrinol Metab* [Internet]. 2000 Mar [cited 2023 May 25];85(3):1021–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/10720033/>
36. Merz CNB, Johnson BD, Delia Sharaf BL, Bittner V, Berga SL, Braunstein GD, et al. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: A report from the NHLBI-sponsored WISE study. *J Am Coll Cardiol* [Internet]. 2003 Feb 5 [cited 2023 Apr 1];41(3):413–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/12575968/>
37. Beals KA, Manore MM. Disorders of the female athlete triad among collegiate athletes. *Int J Sport Nutr Exerc Metab* [Internet]. 2002 [cited 2023 May 25];12(3):281–93. Available from: <https://pubmed.ncbi.nlm.nih.gov/12432173/>
38. Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA, Himes JH, et al. Age at menarche and racial comparisons in US girls. *Pediatrics* [Internet]. 2003 Jan 1 [cited 2023 May 25];111(1):110–3. Available from: <https://pubmed.ncbi.nlm.nih.gov/12509562/>
39. Meethal SV, Atwood CS. The role of hypothalamic-pituitary-gonadal hormones in the normal structure and functioning of the brain. *Cell Mol Life Sci* [Internet]. 2005 Feb [cited 2023 Apr 1];62(3):257–70. Available from: <https://pubmed.ncbi.nlm.nih.gov/15723162/>
40. Rickenlund A, Thorén M, Carlström K, Von Schoultz B, Lindén Hirschberg A. Diurnal profiles of testosterone and pituitary hormones suggest different mechanisms for menstrual disturbances in endurance athletes. *J Clin Endocrinol Metab* [Internet]. 2004 [cited 2023 Apr 1];89(2):702–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/14764784/>
41. Rickenlund A, Thorén M, Carlström K, Von Schoultz B, Lindén Hirschberg A. Diurnal profiles of testosterone and pituitary hormones suggest different mechanisms for menstrual disturbances in endurance athletes. *J Clin Endocrinol Metab* [Internet]. 2004 [cited 2023 Apr 1];89(2):702–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/14764784/>

42. Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M, et al. Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* [Internet]. 2017 May 1 [cited 2023 Apr 1];102(5):1413–39. Available from: <https://pubmed.ncbi.nlm.nih.gov/28368518/>
43. Elliott-Sale KJ, Tenforde AS, Parziale AL, Holtzman B, Ackerman KE. Endocrine Effects of Relative Energy Deficiency in Sport. *Int J Sport Nutr Exerc Metab* [Internet]. 2018 Jul 1 [cited 2023 Apr 1];28(4):335–49. Available from: <https://pubmed.ncbi.nlm.nih.gov/30008240/>
44. Shufelt CL, Torbati T, Dutra E. Hypothalamic Amenorrhea and the Long-Term Health Consequences. *Semin Reprod Med* [Internet]. 2017 May 1 [cited 2023 Apr 1];35(3):256–62. Available from: <https://pubmed.ncbi.nlm.nih.gov/28658709/>
45. Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M, et al. Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* [Internet]. 2017 May 1 [cited 2023 Apr 1];102(5):1413–39. Available from: <https://pubmed.ncbi.nlm.nih.gov/28368518/>
46. Lieberman JL, De Souza MJ, Wagstaff DA, Williams NI. Menstrual Disruption with Exercise Is Not Linked to an Energy Availability Threshold. *Med Sci Sports Exerc* [Internet]. 2018 Mar 1 [cited 2023 Apr 1];50(3):551–61. Available from: <https://pubmed.ncbi.nlm.nih.gov/29023359/>
47. Williams NI, Leidy HJ, Hill BR, Lieberman JL, Legro RS, De Souza MJ. Magnitude of daily energy deficit predicts frequency but not severity of menstrual disturbances associated with exercise and caloric restriction. *Am J Physiol Endocrinol Metab* [Internet]. 2015 Jan 1 [cited 2023 Apr 1];308(1):E29–39. Available from: <https://pubmed.ncbi.nlm.nih.gov/25352438/>
48. Loucks AB, Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly menstruating women. *J Clin Endocrinol Metab* [Internet]. 2003 Jan 1 [cited 2023 Apr 1];88(1):297–311. Available from: <https://pubmed.ncbi.nlm.nih.gov/12519869/>
49. Koltun KJ, de Souza MJ, Scheid JL, Williams NI. Energy Availability Is Associated With Luteinizing Hormone Pulse Frequency and Induction of Luteal Phase Defects. *J Clin Endocrinol Metab* [Internet]. 2020 Jan 1 [cited 2023 Apr 1];105(1):185–93. Available from: <https://pubmed.ncbi.nlm.nih.gov/31539053/>
50. Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi ML, et al. International Society for Clinical Densitometry 2007 Adult and Pediatric Official Positions. *Bone* [Internet]. 2008 Dec [cited 2023 May 25];43(6):1115–21. Available from: <https://pubmed.ncbi.nlm.nih.gov/18793764/>
51. Misra M. Effects of hypogonadism on bone metabolism in female adolescents and young adults. *Nat Rev Endocrinol* [Internet]. 2012 Jul [cited 2023 May 25];8(7):395–404. Available from: <https://pubmed.ncbi.nlm.nih.gov/22271187/>

52. Meczekalski B, Podfigurna-Stopa A, Genazzani AR. Hypoestrogenism in young women and its influence on bone mass density. *Gynecol Endocrinol* [Internet]. 2010 Sep [cited 2023 May 25];26(9):652–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/20504098/>
53. Viapiana O, Gatti D, Dalle Grave R, Todesco T, Rossini M, Braga V, et al. Marked increases in bone mineral density and biochemical markers of bone turnover in patients with anorexia nervosa gaining weight. *Bone* [Internet]. 2007 Apr [cited 2023 May 25];40(4):1073–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/17240212/>
54. MJ DS, NI W. Beyond hypoestrogenism in amenorrheic athletes: energy deficiency as a contributing factor for bone loss. *Curr Sports Med Rep* [Internet]. 2005 Jun 3 [cited 2023 May 25];4(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/15659278/>
55. Ackerman KE, Sokoloff NC, De Nardo Maffazioli G, Clarke HM, Lee H, Misra M. Fractures in Relation to Menstrual Status and Bone Parameters in Young Athletes. *Med Sci Sports Exerc* [Internet]. 2015 [cited 2023 May 25];47(8):1577–86. Available from: <https://pubmed.ncbi.nlm.nih.gov/25397605/>
56. Barrack MT, Rauh MJ, Nichols JF. Cross-sectional evidence of suppressed bone mineral accrual among female adolescent runners. *J Bone Miner Res* [Internet]. 2010 Aug [cited 2023 May 25];25(8):1850–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/20200979/>
57. Kadel NJ, Teitz CC, Kronmal RA. Stress fractures in ballet dancers. *Am J Sports Med* [Internet]. 1992 [cited 2023 May 25];20(4):445–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/1357994/>
58. Singhal V, Reyes KC, Pfister B, Ackerman K, Slattery M, Cooper K, et al. Bone accrual in oligo-amenorrheic athletes, eumenorrheic athletes and non-athletes. *Bone* [Internet]. 2019 Mar 1 [cited 2023 May 25];120:305–13. Available from: <https://pubmed.ncbi.nlm.nih.gov/29758361/>
59. Ackerman KE, Misra M. Bone Health in Adolescent Athletes with a Focus on Female Athlete Triad.
60. Burghardt AJ, Buie HR, Laib A, Majumdar S, Boyd SK. Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. *Bone* [Internet]. 2010 Sep [cited 2023 May 25];47(3):519–28. Available from: <https://pubmed.ncbi.nlm.nih.gov/20561906/>
61. McEwen BS, Akama KT, Spencer-Segal JL, Milner TA, Waters EM. Estrogen effects on the brain: actions beyond the hypothalamus via novel mechanisms. *Behavioral neuroscience* [Internet]. 2012 Feb [cited 2023 Apr 23];126(1):4–16. Available from: <https://pubmed.ncbi.nlm.nih.gov/22289042/>
62. Baskaran C, Cunningham B, Plessow F, Singhal V, Woolley R, Ackerman KE, et al. Estrogen Replacement Improves Verbal Memory and Executive Control in Oligomenorrheic/Amenorrheic Athletes in a Randomized Controlled Trial. *J Clin Psychiatry* [Internet]. 2017 May 1 [cited 2023 Apr 23];78(5):e490–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/28297591/>

63. Ruhé HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Mol Psychiatry* [Internet]. 2007 Apr 30 [cited 2023 Apr 23];12(4):331–59. Available from: <https://pubmed.ncbi.nlm.nih.gov/17389902/>
64. Amin Z, Canli T, Epperson CN. Effect of estrogen-serotonin interactions on mood and cognition. *Behav Cogn Neurosci Rev* [Internet]. 2005 Mar [cited 2023 Apr 23];4(1):43–58. Available from: <https://pubmed.ncbi.nlm.nih.gov/15886402/>
65. Laughlin GA, Dominguez CE, Yen SSC. Nutritional and endocrine-metabolic aberrations in women with functional hypothalamic amenorrhea. *J Clin Endocrinol Metab* [Internet]. 1998 Jan [cited 2023 Apr 23];83(1):25–32. Available from: <https://pubmed.ncbi.nlm.nih.gov/9435412/>
66. Marcus MD, Loucks TL, Berga SL. Psychological correlates of functional hypothalamic amenorrhea. *Fertil Steril* [Internet]. 2001 [cited 2023 Apr 23];76(2):310–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/11476778/>
67. Samsioe G. Urogenital aging--a hidden problem. *Am J Obstet Gynecol* [Internet]. 1998 [cited 2023 Apr 26];178(5). Available from: <https://pubmed.ncbi.nlm.nih.gov/9609599/>
68. Maconochie N, Doyle P, Prior S, Simmons R. Risk factors for first trimester miscarriage--results from a UK-population-based case-control study. *BJOG* [Internet]. 2007 Feb [cited 2023 Apr 26];114(2):170–86. Available from: <https://pubmed.ncbi.nlm.nih.gov/17305901/>
69. Schleußner E. The prevention, diagnosis and treatment of premature labor. *Dtsch Arztebl Int* [Internet]. 2013 Mar 29 [cited 2023 Apr 26];110(13). Available from: <https://pubmed.ncbi.nlm.nih.gov/23596503/>
70. Stevenson JC, Crook D, Godsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis* [Internet]. 1993 Jan 4 [cited 2023 May 1];98(1):83–90. Available from: <https://pubmed.ncbi.nlm.nih.gov/8457253/>
71. Kaplan JR, Manuck SB, Anthony MS, Clarkson TB. Premenopausal social status and hormone exposure predict postmenopausal atherosclerosis in female monkeys. *Obstetrics and Gynecology* [Internet]. 2002 [cited 2023 Apr 26];99(3):381–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/11864663/>
72. Dwyer KM, Nordstrom CK, Merz CNB, Dwyer JH. Carotid wall thickness and years since bilateral oophorectomy: the Los Angeles Atherosclerosis Study. *Am J Epidemiol* [Internet]. 2002 Sep 1 [cited 2023 Apr 26];156(5):438–44. Available from: <https://pubmed.ncbi.nlm.nih.gov/12196313/>
73. Mack WJ, Slater CC, Xiang M, Shoupe D, Lobo RA, Hodis HN. Elevated subclinical atherosclerosis associated with oophorectomy is related to time since menopause rather than type of menopause. *Fertil Steril* [Internet]. 2004 Aug [cited 2023 Apr 26];82(2):391–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/15302289/>
74. Swerdlow AJ, Hermon C, Jacobs PA, Alberman E, Beral V, Daker M, et al. Mortality and cancer incidence in persons with numerical sex chromosome abnormalities: a

- cohort study. *Ann Hum Genet* [Internet]. 2001 Mar [cited 2023 May 1];65(Pt 2):177–88. Available from: <https://pubmed.ncbi.nlm.nih.gov/11427177/>
75. Ostberg JE, Donald AE, Halcox JPJ, Storry C, McCarthy C, Conway GS. Vasculopathy in Turner syndrome: arterial dilatation and intimal thickening without endothelial dysfunction. *J Clin Endocrinol Metab* [Internet]. 2005 Sep [cited 2023 May 1];90(9):5161–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/15985480/>
 76. Melin A, Tornberg ÅB, Skouby S, Faber J, Ritz C, Sjödin A, et al. The LEAF questionnaire: a screening tool for the identification of female athletes at risk for the female athlete triad. *Br J Sports Med* [Internet]. 2014 [cited 2023 May 1];48(7):540–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/24563388/>
 77. Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M, et al. Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* [Internet]. 2017 May 1 [cited 2023 May 1];102(5):1413–39. Available from: <https://pubmed.ncbi.nlm.nih.gov/28368518/>
 78. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab* [Internet]. 2007 [cited 2023 May 1];92(2):405–13. Available from: <https://pubmed.ncbi.nlm.nih.gov/17090633/>
 79. Berga SL, Mortola JF, Girton L, Suh B, Laughlin G, Pham P, et al. Neuroendocrine aberrations in women with functional hypothalamic amenorrhea. *J Clin Endocrinol Metab* [Internet]. 1989 [cited 2023 May 1];68(2):301–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/2493024/>
 80. De Souza MJ, Nattiv A, Joy E, Misra M, Williams NI, Mallinson RJ, et al. 2014 Female Athlete Triad Coalition Consensus Statement on Treatment and Return to Play of the Female Athlete Triad: 1st International Conference held in San Francisco, California, May 2012 and 2nd International Conference held in Indianapolis, Indiana, May 2013. *Br J Sports Med* [Internet]. 2014 Feb [cited 2023 May 1];48(4):289. Available from: <https://pubmed.ncbi.nlm.nih.gov/24463911/>
 81. Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sundgot-Borgen J, Warren MP. American College of Sports Medicine position stand. The female athlete triad. *Med Sci Sports Exerc* [Internet]. 2007 Oct [cited 2023 May 1];39(10):1867–82. Available from: <https://pubmed.ncbi.nlm.nih.gov/17909417/>
 82. Mountjoy M, Sundgot-Borgen JK, Burke LM, Ackerman KE, Blauwet C, Constantini N, et al. IOC consensus statement on relative energy deficiency in sport (RED-S): 2018 update. *Br J Sports Med* [Internet]. 2018 [cited 2023 May 17];52(11):687–97. Available from: <https://pubmed.ncbi.nlm.nih.gov/29773536/>
 83. Michopoulos V, Mancini F, Loucks TL, Berga SL. Neuroendocrine recovery initiated by cognitive behavioral therapy in women with functional hypothalamic amenorrhea: a randomized, controlled trial. *Fertil Steril* [Internet]. 2013 [cited 2023 May 17];99(7). Available from: <https://pubmed.ncbi.nlm.nih.gov/23507474/>

84. Moreira CA, Bilezikian JP. Stress Fractures: Concepts and Therapeutics. *J Clin Endocrinol Metab* [Internet]. 2017 Feb 1 [cited 2023 May 17];102(2):525–34. Available from: <https://pubmed.ncbi.nlm.nih.gov/27732325/>
85. Klibanski A, Adams-Campbell L, Bassford T, Blair SN, Boden SD, Dickersin K, et al. Osteoporosis prevention, diagnosis, and therapy. *JAMA* [Internet]. 2001 Feb 14 [cited 2023 May 17];285(6):785–95. Available from: <https://pubmed.ncbi.nlm.nih.gov/11176917/>
86. Cobb KL, Bachrach LK, Sowers M, Nieves J, Greendale GA, Kent KK, et al. The effect of oral contraceptives on bone mass and stress fractures in female runners. *Med Sci Sports Exerc* [Internet]. 2007 Sep [cited 2023 May 17];39(9):1464–73. Available from: <https://pubmed.ncbi.nlm.nih.gov/17805075/>
87. Southmayd EA, De Souza MJ. A summary of the influence of exogenous estrogen administration across the lifespan on the GH/IGF-1 axis and implications for bone health. *Growth Horm IGF Res* [Internet]. 2017 Feb 1 [cited 2023 May 17];32:2–13. Available from: <https://pubmed.ncbi.nlm.nih.gov/27693042/>
88. Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M, et al. Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* [Internet]. 2017 May 1 [cited 2023 May 17];102(5):1413–39. Available from: <https://pubmed.ncbi.nlm.nih.gov/28368518/>
89. Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, et al. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med* [Internet]. 2004 Sep 2 [cited 2023 May 17];351(10):987–97. Available from: <https://pubmed.ncbi.nlm.nih.gov/15342807/>
90. Santoro N. Update in hyper- and hypogonadotropic amenorrhea. *J Clin Endocrinol Metab* [Internet]. 2011 Nov [cited 2023 May 17];96(11):3281–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/22058375/>

Biography

Rebecca Rachael Popper was born in 1994. She graduated from Reddam House Constantia high school in 2012. Thereafter, she studied at the University of Cape Town, attaining her undergraduate Bachelor of Science (BSc) degree in Anatomy and Physiology. Thereafter, she completed her Honours degree in Biomedical Science (Cancer cell biology) in 2016. She was enrolled at the University of Zagreb, School of Medicine, Croatia between 2017-2023.