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FUNCTIONAL HYPOTHALAMIC AMENORRHOEA IN FEMALE ATHLETES - PATHOPHYSIOLOGY, RISK FACTORS, CONSEQUENCES AND POSSIBLE TREATMENTS

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ABSTRACT

Introduction: Functional hypothalamic amenorrhoea is a prevalent endocrine disorder among female athletes, primarily caused by low energy availability (LEA). LEA induces a cascade of endocrine and neurohormonal changes, leading to disrupted GnRH pulsatility, anovulation, and hypoestrogenism. The health consequences of FHA are extensive, affecting bone density, cardiovascular function, fertility, and neuropsychiatric health.
Purpose: The aim of this paper was to review FHA in female athletes, focusing on its pathophysiology, clinical consequences, diagnosis, and treatment, while emphasising the need for early detection and multidisciplinary care.
Methodology: A narrative literature review was conducted using Google Scholar and PubMed. Relevant original research articles, systematic reviews, clinical guidelines, and authoritative textbooks were included to ensure comprehensive coverage of the topic.
Conclusions: Untreated FHA leads to serious health consequences. Early diagnosis and timely intervention are critical. Multidisciplinary approach should be implemented. Further studies are needed particularly in the areas of early identification, pathophysiological mechanisms, and effective, evidence-based treatment strategies.

KEYWORDS

Functional Hypothalamic Amenorrhoea, Female Athlete Triad, Hypoestrogenism, Low Energy Availability

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Introduction

Menstruation is recognised as an integral component of women's overall physical health from menarche to menopause. According to the International Federation of Gynaecology and Obstetrics, a healthy menstrual cycle is defined as subjectively normal-flow bleeding lasting up to 8 days, occurring every 24 to 38 days, with cycle length variability of 7 to 9 days and no intramenstrual bleedings (Rosen Vollmar, Mahalingaiah, & Jukic, 2025). Amenorrhoea is defined as an absence of menstrual cycles during reproductive years and is categorised as either primary or secondary. Primary amenorrhoea is general absence of menarche, while secondary amenorrhoea is defined as a cessation of previously regular menstrual cycles for ≥3 months or ≥6 months in women who have had at least one spontaneous menstruation and have been menstruating irregularly. The aetiology of amenorrhoea is diverse and it can include ovarian failure or insufficiency, hypothalamic or pituitary disorders, or may be induced medically or physiologically (Nawaz, Rogol, & Jenkins, 2024)).

This review focuses on amenorrhea of hypothalamic origin, specifically Functional Hypothalamic Amenorrhea (FHA), which arises from disruption of hypothalamus-pituitary gland-ovaries axis (HPO). There are 3 main causes associated with this phenomenon - psychological stress, significant weight loss or low body mass, and excessive physical exercise (Sowińska-Przepiera et al., 2015). These disruptions impair gonadotropin-releasing hormone (GnRH) secretion, altering luteinising hormone (LH) pulsatility and reducing oestrogen production, thereby interfering with the menstrual cycle (Gimunová et al., 2022; Meczekalski et al., 2014). FHA affects 17.4 million women worldwide, making it responsible for 1/3 cases of secondary amenorrhoea (Saadedine, Kapoor, & Shufelt, 2023).

Female athletes are particularly susceptible to FHA, especially those involved in sports that emphasise leanness, require weight categorisation, or demand high endurance, such as gymnastics, long-distance running, or swimming (Nazem & Ackerman, 2012; Raj et al., 2023). Moreover, FHA is one of the components of Female Athlete Triad, firstly described in 1992 by American College of Sports Medicine. The triad consists of amenorrhoea, low energy availability (LEA) and lowered bone mineral density (BMD) (Nazem & Ackerman, 2012). Menstrual irregularities and associated hormonal imbalances in athletes with FHA may lead to broader health consequences, including infertility, osteoporosis, cardiovascular disease, and mental and sexual dysfunction (Gimunová et al., 2022). This review explores the pathophysiology of FHA in female athletes, its clinical implications, and current treatment strategies.

Pathophysiological Mechanisms Underlying Functional Hypothalamic Amenorrhoea

The primary mechanism underlying Functional Hypothalamic Amenorrhea (FHA) is the dysregulation of the HPO, commonly triggered by psychological stress, undernutrition, and excessive physical exercise (Kyriakidis et al., 2016; Meczekalski et al., 2014; Męczekalski et al., 2023). Previously conducted studies introduced such term as "critical weight", referring to a threshold below which FHA typically develops. However further research has shown that it is not the weight itself that causes the alterations, but rather low energy availability (LEA) defined as the gap between dietary energy intake and energy expenditure. In terms of physical activity, the development of FHA usually takes place when the energy expenditure from training is larger than the combined total of energy consumed and stored in the body (Kyriakidis et al., 2016). Energy deficit initiates a cascade of neuroendocrine adaptations that disrupt normal GnRH secretion, impairing the function of the HPO axis and ultimately leading to menstrual disturbances (Męczekalski et al., 2023). Suppression of reproductive function in this setting is considered an adaptive survival mechanism, allowing the body to conserve energy under conditions of perceived metabolic stress (Kyriakidis et al., 2016).

A central alteration in the pathophysiology FHA is the disruption of GnRH pulsatility. Hypothalamic secretion of GnRH is reduced (Gimunová et al., 2022), leading to impaired release of follicle stimulating hormone (FSH) (Gimunová et al., 2022; Męczekalski et al., 2023) and luteinising hormone (LH) from the anterior pituitary (Gimunová et al., 2022; Kamel-ElSayed et al., 2023; Kyriakidis et al., 2016; Męczekalski et al., 2023) . Adequate levels of FSH are essential for maintaining folliculogenesis and oestrogen production (Orlowski & Sarao, 2023), whereas LH plays a critical role in ovarian steroidogenesis, ovulation, and progesterone production by the corpus luteum following ovulation (Kamel-ElSayed et al., 2023). The resulting hormonal imbalance disrupts the menstrual cycle, often leading to anovulation and amenorrhea (Saadedine, Kapoor, & Shufelt, 2023).

In addition, stressors such as low energy availability, psychological stress of excessive exercise primarily activate the hypothalamus-pituitary-adrenal (HPA) axis and the autonomic nervous system. This activation leads to increased secretion of corticotropin-releasing hormone (CRH), which stimulates the production of glucocorticoids, particularly cortisol (Męczekalski et al., 2023; Saadedine, Kapoor, & Shufelt, 2023). Patients who suffer from FHA typically exhibit elevated cortisol levels, both in morning measurements and 24-hour assessments, compared to healthy controls. Cortisol suppresses reproductive function by directly inhibiting the synthesis and secretion of GnRH from hypothalamic neurons. Moreover, both CRH itself and cortisol contribute to the suppression of the HPO axis by down-regulating kisspeptin receptor signalling on GnRH neurons (Saadedine, Kapoor, & Shufelt, 2023). Research shows that under favourable conditions kisspeptin stimulates the pulsatility of GnRH and thereby promotes pulsatile LH secretion. Consequently, CRH and cortisol inhibit the HPO axis by acting antagonistically to kisspeptin (Patel et al., 2024). Additionally, athletes with FHA show an exaggerated cortisol response to exercise, suggesting an enhanced endocrine sensitivity compared to eumenorrheic women (Sanders et al., 2018). This heightened responsiveness implies that additional regulatory mechanisms may be involved in FHA. Studies also suggest that these patients may exhibit resistance to cortisol feedback inhibition, potentially involving altered corticosteroid receptor activity and dysfunction in serotonergic and GABAergic neural pathways (Brundu et al., 2006).

Low energy availability causes also other hormonal changes that affect kisspeptin neuron activity (Saadedine, Kapoor, & Shufelt, 2023). In energy-deficient states, levels of leptin and insulin decrease, while concentrations of ghrelin, a hormone that stimulates appetite (Young & Jialal, 2023), increase. In optimal conditions insulin and leptin stimulate kisspeptin neurons and therefore they promote GnRH pulsatility. However, in women with FHA, kisspeptin signaling is suppressed due to elevated ghrelin levels and insufficient concentrations of leptin and insulin (Saadedine, Kapoor, & Shufelt, 2023). One study reported significantly lower leptin levels in women with FHA, even among those with normal body weight and BMI, further underscoring leptin's critical role in the condition's pathophysiology (Andrico et al., 2002).

Another neuroendocrine factor influenced by LEA is neuropeptide Y (NPY), which regulates energy balance, sexual behaviour, circadian rhythms, and appetite through the hypothalamic pathways. NPY promotes GnRH release when oestrogen levels are adequate but exerts an inhibitory effect in hypoestrogenic states. Studies have shown, that patients with FHA have lower basal serum NPY concentrations than menstruating controls (Meczekalski et al., 2014), suggesting another pathway by which LEA disrupts reproductive function.

The genetic basis of Functional Hypothalamic Amenorrhea (FHA) remains an area of ongoing research. Several genes associated with congenital GnRH deficiency have also been identified in women diagnosed with FHA, suggesting a potential genetic predisposition to the condition. Additionally, many patients with FHA exhibit reduced expression of brain-derived neurotrophic factor (BDNF), a key molecule involved in neuroplasticity and the adaptation to stress. This diminished BDNF expression may contribute to increased vulnerability to psychological stressors, thereby facilitating the development of FHA in predisposed individuals (Saadedine, Kapoor, & Shufelt, 2023).

Clinical Evaluation and Diagnostic Criteria for Functional Hypothalamic Amenorrhoea

Functional hypothalamic amenorrhea is a frequent but often underrecognized cause of secondary amenorrhea in reproductive-age women, which can be diagnosed only by exclusion. The condition is characterised by low oestrogen levels (typically <50 pg/mL), low gonadotropins (FSH and LH often <10 mIU/mL), a normal to low LH to FSH ratio, and normal testosterone levels, which helps differentiate it from other conditions such as polycystic ovary syndrome (PCOS), premature ovarian insufficiency (POI), thyroid dysfunction, and hyperprolactinemia. A multidirectional clinical evaluation is essential, including a detailed medical and psychosocial history focusing on dietary habits, physical activity, stress, and weight changes. Although not all patients with FHA meet the criteria for eating disorders, many report disordered eating behaviors, and validated screening tools such as the Eating Disorder Examination Questionnaire (EDE-Q) and the Eating Attitude Test can help identify at-risk individuals. Laboratory testing should be performed to exclude other causes, including measurement of LH, FSH, TSH, and estradiol, along with a pelvic ultrasound to assess ovarian morphology. Importantly, PCOS and FHA can overlap, particularly in lean women or those with polycystic ovarian morphology without hyperandrogenism. A progesterone withdrawal test or direct estrogen measurement can help confirm hypoestrogenism. Accurate diagnosis of FHA is critical, as it allows clinicians to implement appropriate treatment and distinguishes it from other aetiologies with different pathophysiologic mechanisms and management approaches (Saadedine, Kapoor, & Shufelt, 2023).

From Female Athlete Triad to RED-S: Evolving Understanding of Energy Deficiency in Sport

In 1992, the American College of Sports Medicine (ACSM) first described the Female Athlete Triad as a syndrome encompassing disordered eating, amenorrhea, and osteoporosis. In 2007, the definition was expanded to include a spectrum of interrelated conditions affecting energy availability, menstrual function, and bone mineral density. It was also recognised that female athletes may present with only one or two components of the triad, rather than all three simultaneously (Javed et al., 2013). Further research prompted the International Olympic Committee (IOC) to introduce a broader concept known as Relative Energy Deficiency in Sport (RED-S). RED-S refers to impaired physiological functioning caused by relative energy deficiency, which impacts not only reproductive and skeletal health, but also metabolic rate, protein synthesis, immune function, and cardiovascular health, among other systems (Mountjoy et al., 2014).

Sport-Specific Patterns and Risks

Gimunová and colleagues analysed 48 studies examining menstrual disorders among female athletes. The paper included studies that described both primary and secondary amenorrhoea and also oligomenorrhoea, defined as irregular and prolonged bloodflow, >35 days apart, 5-7 cycles a year, also caused by HPO axis disturbances. The highest prevalence of menstrual disturbances was reported in studies involving rhythmic gymnasts, with similarly elevated rates among artistic gymnasts and other gymnastics disciplines when compared to the general population. Among team sports, soccer and volleyball players were identified as being particularly at risk. Athletes competing in middle- and long-distance running (>400 meters), cycling, and endurance sports also showed a higher susceptibility to menstrual dysfunction. Specifically, primary amenorrhoea was most common in rhythmic gymnasts (up to 25% of studied populations), soccer players (20%) and swimmers (19%). Secondary amenorrhoea affected mostly cyclists (56%), triathlon athletes (40%) and rhythmic gymnasts. Oligomenorrhoea, on the other hand, had highest percentage in boxers (55%), rhythmic gymnasts (44%) and artistic gymnasts (32%). Current evidence suggests that disturbances of the HPO axis are most prevalent in sports that demand low body weight or leanness. However, the generalisability of these findings is limited, as there remains insufficient data on the prevalence of menstrual disorders across many other athletic disciplines (Nazem & Ackerman, 2012).

Systemic Health Consequences of Functional Hypothalamic Amenorrhoea

FHA can lead to a range of adverse health outcomes in premenopausal women, primarily due to prolonged oestrogen deficiency (Shufelt et al., 2017) and broader endocrine dysregulation. Oestrogen plays a critical role in maintaining the integrity of multiple physiological systems, including the metabolic, skeletal, neuropsychiatric, and reproductive systems. In addition to hypoestrogenism, imbalances in hormones such as cortisol, leptin, and peptide YY are also implicated in FHA and may contribute to neurocognitive impairments and mood disturbances (Pedreira et al., 2022).

Reproductive and Sexual Health Consequences of Functional Hypothalamic Amenorrhea in Female Athletes

The absence of menstruation during peak reproductive years, as seen in Functional Hypothalamic Amenorrhea (FHA), can lead to infertility. Disruptions in the HPO axis, along with subsequent oestrogen deficiency, impair follicular development and prevent ovulation. Additionally, the lack of cyclical fluctuations in oestrogen and progesterone inhibits the normal proliferation and transformation of the endometrium, leaving it in a persistent early proliferative phase (Meczekalski et al., 2014; Shufelt et al., 2017). Interestingly, many women with FHA exhibit normal or even elevated levels of anti-Müllerian hormone (AMH), a marker of ovarian reserve produced by developing follicles, suggesting that the infertility may reversible (Saadedine, Kapoor, & Shufelt, 2023). On the other hand prolonged hypoestrogenism can have more enduring effects on reproductive health. Oestrogen deficiency in FHA can result in atrophic changes to the urogenital mucosa and myometrium, similar to those observed during menopause, potentially causing reduced vaginal lubrication and increased susceptibility to urogenital infections (Shufelt et al., 2017). Moreover, as indicated in the review by Gimunová et al. (2022), female athletes at risk of FHA are predominantly those in sports that emphasise leanness. Low body mass index (BMI) has been associated with increased risks of miscarriage, preterm birth, and high-risk pregnancies. Women with FHA may also experience difficulty with gestational weight gain and are more likely to have restricted foetal growth (Meczekalski et al., 2014).

If FHA occurs during adolescence, before the uterus and ovaries have reached full maturity, hormonal imbalances, particularly oestrogen deficiency, can impair reproductive organ development. A study by Bumbulienė et al. (2015) found that adolescent girls aged 13.28 to 18.64 years with FHA had significantly smaller uterine and ovarian volumes and shorter cervical lengths compared to eumenorrheic peers of the same chronological and gynaecological age. Moreover, a positive correlation was observed between body weight and BMI and several reproductive parameters, including uterine volume, cervical length, endometrial thickness, ovarian volume, and luteinising hormone (LH) levels. Evidence from this study also suggests that uterine underdevelopment may have long-term consequences, including impaired uterine function, an increased risk of miscarriage, restricted foetal growth, a higher likelihood of cesarean delivery, preterm labor, and preeclampsia. Encouragingly, appropriate weight gain during adolescence, while growth potential remains, may reverse or mitigate these complications.

Sexual dysfunction is relatively common in women with FHA. Clinicians often attribute this to hypoestrogenism, which can lead to reduced genital sensitivity, vaginal dryness, and lowered sexual desire. However, emerging evidence suggests that the aetiology of sexual dysfunction in FHA is multifactorial and not solely explained by hormonal deficiencies. Studies have shown that hormone replacement therapy (HRT) provides only limited benefit in addressing sexual dysfunction, indicating that psychological and neuroendocrine factors may also play significant roles. Patients with FHA are documented to often present with mood disorders, including depression and anxiety, both of which are independently associated with sexual impairment. Depression in women has been linked to reduced sexual satisfaction, decreased libido, diminished arousal, and impaired orgasmic function. Similarly, anxiety disorders are associated with lower sexual desire and reduced sexual activity compared to healthy controls. These findings support a potential link between the high prevalence of mood disorders and sexual dysfunction in women with FHA, underscoring the importance of a comprehensive, multidirectional approach to diagnosis and treatment (Dundon et al., 2010).

Neuropsychiatric and Cognitive Implications of Functional Hypothalamic Amenorrhea

As previously noted, mental health disorders are frequently diagnosed in women with FHA (Dundon et al., 2010). Female mental well-being is closely linked to oestrogen levels, as hypoestrogenism may lead to alterations in the activity of neuropeptides, neurotransmitters, and neurosteroids within the central nervous system (CNS). However, due to the limited amount of research in this area and the bidirectional nature of the relationship between FHA and psychological disorders, in many cases it remains challenging to determine whether hypoestrogenism is a cause or a consequence of mental health disturbances in this population (Bumbuliene et al., 2015; Gimunová et al., 2022; Saadedine, Kapoor, & Shufelt, 2023).

Oestrogens are known to modulate several key neurotransmitter systems involved in mood and cognition, including serotonin, dopamine, and glutamate. They exert these effects by regulating the region-specific expression of neurotransmitter receptor subtypes. Evidence indicates that oestrogens selectively act on serotonin receptors that are related to cognitive functions, which appear to be commonly impaired in psychiatric disorders, for example learning, memorising and cognitive flexibility. Some studies have even proposed that oestrogens may possess antipsychotic properties comparable to those of atypical neuroleptics.

Oestrogens enhance dopamine synthesis and release, and reduce its reuptake, thereby amplifying dopaminergic signalling in key brain regions. They may also affect the density of D1 and D2 dopamine receptors, thereby prolonging dopaminergic signalling. In the serotonergic system, oestrogens upregulate the expression and activity of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis. Furthermore, they modulate serotonin receptor subtypes such as 5HT2A and 5HT2C, both of which are implicated in the pathophysiology of depression. Oestrogens also act on the 5HT1A autoreceptor, influencing serotonin's auto-inhibitory feedback loop. Additionally, oestrogens inhibit monoamine oxidase (MAO), the enzyme responsible for serotonin degradation after reuptake to the pre-synaptic neurone, thereby enhancing overall serotonin availability. Studies suggest that oestrogens influence N-Methyl-D-aspartic acid (NMDA) glutamate receptors, which are essential for cognitive functions and synaptic transmission. Oestrogens upregulate the expression and increase the distribution of these receptors, enhancing neural signalling. Conversely, oestrogens also appear to reduce glutamate-induced neurotoxicity, particularly in cortical and hippocampal neurones, offering a neuroprotective effect. Oestrogens exert their effects on cognition through various receptors, including oestrogen receptor alpha (ERα), oestrogen receptor beta (ERβ), selective oestrogen receptor modulators (SERMs), and the G protein-coupled oestrogen receptor (GPER). These receptors activate both genomic and non-genomic signalling pathways, which are central to neuroprotection, synaptic plasticity, and cognitive function. In addition to their role in neurotransmission, oestrogens support antioxidative defences, regulate apoptosis, and offer protection against excitotoxicity. They also promote the expression and activity of brain-derived neurotrophic factor (BDNF), which is a key neurotrophin involved in neuronal survival, differentiation, and synaptic plasticity (Hwang et al., 2020). Available evidence shows that women with FHA exhibit reduced cognitive function compared to healthy controls, likely due to insufficient oestrogen levels and diminished BDNF activity (Raj, Creech, & Rogol, 2023).

Numerous studies and reviews (Bonazza et al., 2023; Nazem & Ackerman, 2012; Saadedine, Kapoor, & Shufelt, 2023) provide evidence that women with FHA experience significantly higher rates of depression compared to eumenorrheic controls. This phenomenon is believed to result primarily from disruptions in serotonin and dopamine neurotransmitter systems, as previously discussed. Additionally, elevated cortisol levels, commonly observed in FHA patients, are thought to further contribute to the development of mood disorders (Saadedine, Kapoor, & Shufelt, 2023). Anxiety disorders are also diagnosed more frequently in women with FHA than in the regularly menstruating controls. Furthermore, emerging evidence suggests that sleep disturbances are more prevalent among FHA patients, indicating broader neuropsychiatric vulnerability associated with the condition (Podfigurna & Meczekalski, 2021).

FHA woman repeatedly present with more dysfunctional cognitive and behavioural traits. These may include difficulties with self-control, perfectionism, a pathological need for approval, heightened concern over mistakes, and elevated levels of interpersonal dependence (Podfigurna & Meczekalski, 2021; (Roberts, Farahani, Webber, & Jayasena, 2020). A study by Bomba et al. (2007) reported that 80% of adolescent patients with FHA perceived their mothers as demanding, controlling, and intrusive, suggesting a potential association between parenting style and the development of FHA-related psychological characteristics. Amenorrhoeic women tend to have greater difficulty coping with everyday stress (Podfigurna & Meczekalski, 2021). This may be attributed to reduced levels of brain-derived neurotrophic factor (BDNF) resulting from chronic oestrogen deficiency. Although the exact role of BDNF in FHA remains unclear, existing evidence strongly suggests that mood disorders and poor stress adaptability are associated with impaired structural plasticity and reduced cellular resilience. Given the central role of neuroplasticity in stress regulation, these findings support a potential role for BDNF dysregulation in the pathophysiology of FHA (Fontana et al., 2022).

Functional Hypothalamic Amenorrhoea and Bone Loss: Mechanisms, Risks, and Clinical Implications

The influence of FHA on bone health is multifactorial. Woman with FHA are at risk of developing osteopenia and osteoporosis at a young age, primarily due to hypoestrogenism (Meczekalski et al., 2014), but also as a result of other hormonal and neuroendocrine disturbances. Low bone mineral density (BMD) is a hallmark of the Female Athlete Triad and significantly compromises skeletal homeostasis. In FHA, chronic energy deficiency triggers physiological adaptations that prioritise survival over bone mass accrual, leading to impaired bone development and maintenance (Fontana et al., 2022)

Adequate oestrogen levels are essential for maintaining healthy bone metabolism. Oestrogen exerts a threefold effect: it stimulates bone remodelling, promotes bone formation, and inhibits bone resorption. These effects are mediated through the regulation of several key growth factors, including transforming growth factor

beta (TGF-β), which supports bone preservation by enhancing osteocyte survival (Meczekalski et al., 2014; Streicher et al., 2017); bone morphogenetic protein 6 (BMP6), which promotes osteogenesis and can differentiate into bone, cartilage, adipose, muscle, hematopoietic, synovial, and other tissues (Vukicevic & Grgurevic, 2009); and insulin-like growth factor 1 (IGF-1), which regulates longitudinal bone growth, skeletal maturation, and bone mass acquisition during preadolescence, while also playing a crucial role in the maintenance of bone mass in adulthood (Fang et al., 2023). Oestrogen also enhances the expression of $1,25(OH)_2D_3$ (active vitamin D) receptors, supporting calcium metabolism and bone health (Meczekalski et al., 2014; Li et al., 2023; Streicher et al., 2017). Its role is also fundamental in mediating osteoprotegerin (OPG)/receptor activator of NF-κB ligand (RANKL) system. RANKL is responsible for osteoclasts activation, differentiation and survival, whereas OPG is a soluble receptor, that acts as RANKL inhibitor. OPG deficiency leads to loss of bone mass. Evidence suggests that increased RANKL expression and suppression of osteoclasts apoptosis may underlie oestrogen deficiency-related osteoporosis (Streicher et al., 2017). Oestrogens stimulate the secretion of semaphorin 3A, a protein that reduces resorption and increases bone formation (Behary & Comninos, 2022). Finally they inhibit secretion of pro-resorptive cytokines such as macrophage-colony stimulating factor (M-CSF), interleukin-6 and tumour necrosis factor α (TNF-α) (Meczekalski et al., 2014).

Furthermore, there are also several other mechanisms that contribute to bone loss in FHA. Reduced leptin concentrations negatively affect bone metabolism. Low leptin levels are associated with decreased levels of IGF-1, oestrogen, and thyroid hormones. Leptin receptors are expressed on osteoblasts, where leptin promotes their survival. Meanwhile, IGF-1, as previously noted, stimulates bone formation by enhancing osteoblast activity and collagen synthesis (Behary & Comninos, 2022; Pedreira et al., 2022). Energy deficiency present in FHA leads to growth hormone (GH) resistance, likely due to loss of GH receptors on target tissues, and results in decreased levels of IGF-1. High-intensity training is negatively correlated with IGF-1 concentrations, and low IGF-1 levels are associated with reduced bone mass in individuals with FHA (Pedreira et al., 2022).

Additionally, disruptions in the hypothalamic–pituitary–adrenal (HPA) axis and elevated cortisol levels, commonly observed in patients with FHA, further contribute to bone loss. Cortisol promotes osteoclast activity, inhibits osteoblast function, impairs intestinal calcium absorption, disrupts renal calcium handling, and suppresses the secretion of GH and IGF-1. Research indicates that elevated cortisol levels in FHA patients are correlated with decreased bone mass. Some researchers suggest that cortisol may also exert its effects on bone metabolism through the OPG/RANKL axis (Behary & Comninos, 2022). In contrast, ghrelin, typically elevated in women with FHA, has a beneficial effect on bone health by stimulating osteoblastic activity. However, its positive action appears to be largely counterbalanced by other dominant catabolic factors present in FHA (Pedreira et al., 2022).

Bone health is one of the major concerns associated with amenorrhoea and hormonal imbalance in female athletes with FHA. When hypothalamic amenorrhoea occurs during adolescence, it may interfere with the attainment of peak bone mass (PBM), which is defined as the maximum amount of bone tissue an individual accumulates during their lifetime. The majority of PBM is acquired during puberty, therefore, disruptions to bone formation during this critical period can have long-term consequences. Although multiple factors influence bone metabolism, oestrogen plays a central role in females. To maintain proper bone turnover, serum oestrogen concentrations should be at least 40–50 pg/mL. However, studies have shown that in women with FHA, oestrogen levels often fall below 20 pg/mL. A reduced PBM significantly increases the risk of pathological fractures and premature bone loss. Early identification of individuals at risk is essential. According to the International Society for Clinical Densitometry, amenorrhoea lasting six months warrants a dual-energy X-ray absorptiometry (DEXA) scan of the spine to assess bone mineral density (Meczekalski et al., 2014).

As the diagnostic approach differs between premenopausal and postmenopausal women, this section also addresses skeletal evaluation. BMD is typically assessed by DEXA scan. In premenopausal women, there are no specific densitometric criteria for diagnosing osteopenia or osteoporosis. Instead, low BMD is defined by a Z-score below –2.0, which reflects values significantly lower than expected for the individual's chronological age. This contrasts with postmenopausal women, for whom the T-score is the primary diagnostic measure. In adult premenopausal women, a diagnosis of osteoporosis requires the presence of secondary causes of low BMD or evidence of fragility fractures. In adolescents, the diagnosis is generally considered in the presence of at least one clinically significant fracture alongside low BMD (Indirli et al., 2022). The prevalence of low bone mineral density (BMD) among female athletes appears to vary across different sport disciplines. Mudd et al. (2007) conducted a study involving 99 female collegiate varsity athletes across sports including gymnastics, softball, distance running (≥800 m), sprinting and field events (<800 m), field hockey, soccer, rowing, and swimming/diving. Overall, 25.2% of participants reported a history of oligomenorrhoea or

amenorrhoea, with the highest prevalence observed among distance runners (44%) and gymnasts (37.5%). BMI was significantly lower among runners and rowers, and BMD measurements were notably reduced in athletes engaged in running, sprinting/field events, rowing, and swimming/diving. Among the variables assessed, only body mass and sport type consistently predicted lower BMD. However, due to the study's limited sample size, the generalisability of these findings remains constrained. Larger-scale studies are warranted to validate and expand upon these associations. A systematic review by Barrack et al. (2013) highlighted that adolescent girls participating in endurance sports, particularly long-distance running, are at increased risk for low bone mineral density and other conditions encompassed within the Female Athlete Triad. Notably, nearly 40% of runners were found to have low BMD, a significantly higher proportion compared to athletes in other disciplines. Key risk factors identified include oligomenorrhoea or amenorrhoea, dietary restriction, and prolonged engagement in high-volume endurance training. These athletes frequently exhibit decreased levels of critical metabolic hormones such as leptin and IGF-1, both of which are essential for bone formation and maintenance. Importantly, most adolescents with low BMD did not achieve "catch-up" bone mass accrual even after improvements in nutritional status and the resumption of menstruation. This highlights the importance of early diagnosis and intervention to prevent permanent skeletal deficits. A systematic review by Khan et al. (2002) reported that the prevalence of osteopenia among female athletes ranges from 22% to 50%, and osteoporosis from 0% to 13%, compared to 12% and 2.3%, respectively, in non-athletic controls. However, these estimates are based on T-scores, which are not considered appropriate for premenopausal populations, as they compare DXA values to those of postmenopausal women rather than age-matched controls (Nazem & Ackerman, 2012).

Despite growing awareness, the true prevalence of bone metabolism disturbances in female athletes remains difficult to assess due to inconsistent methodologies and limited longitudinal data.

Cardiovascular Implications of Functional Hypothalamic Amenorrhoea

Physical exercise provides numerous benefits on cardiovascular health. During physical activity, both blood flow and vascular pressure increase, stimulating the production of nitric oxide (NO) via the phosphoinositide 3-kinase/protein kinase B pathway. NO plays a critical role in vasodilation by inhibiting vascular smooth muscle cell adhesion and proliferation. Regular aerobic training is associated with a reduced age-related decline in endothelial function, whereas endothelial dysfunction is a key contributor to the development of atherosclerosis. In premenopausal women, oestrogen also functions as a cardioprotective agent. It enhances vascular function by modulating calcium and potassium channel activity in vascular smooth muscle cells and promoting NO production through the same phosphoinositide 3-kinase/protein kinase B signaling pathway. Additionally, oestrogen also positively influences lipid profile. It increases high density lipoprotein (HDL) levels, reduces low-density lipoprotein (LDL) concentrations, and inhibits LDL oxidation. Hypoestrogenism, as seen in conditions such as FHA, results in the loss of these cardioprotective effects (Tegg et al., 2024). Furthermore, oestrogen deficiency has been associated with adverse cardiovascular consequences, including autonomic nervous system dysregulation, reduced NO bioavailability, and activation of the renin-angiotensin system (Simoncini et al., 2017). Recent evidence suggests that athletes with secondary amenorrhoea are at increased risk of developing cardiovascular disease (CVD). A systematic review of 18 observational studies by Tegg et al. (2024) identified a statistically significant association between oestrogen deficiency and adverse cardiovascular alterations. However, the authors also noted the involvement of additional, yet unidentified, contributing factors. The review reported that amenorrhoeic athletes exhibited significantly lower flow-mediated dilation (FMD) of blood vessels, supporting the conclusion that the hormonal disturbances characteristic of FHA may negate the typically beneficial cardiovascular effects of physical exercise. A proposed mechanism underlying this pathology is reduced bioavailability of nitric oxide (NO), resulting in endothelial dysfunction. Additionally, individuals with FHA consistently demonstrate elevated levels of total cholesterol, triglycerides, LDL, HDL cholesterol. Contrary to common belief, it remains unclear whether increased HDL levels can offset the adverse cardiovascular effects of elevated LDL and triglycerides. These athletes also present with heightened vascular resistance and increased variability in autonomic nervous system activity, further indicating cardiovascular dysregulation. Moreover, the Women's Ischemia Syndrome Evaluation (WISE) study provided evidence that hypothalamic hypoestrogenism is an independent risk factor for coronary artery disease in premenopausal women (Bairey Merz et al., 1999). FHA has also been positively correlated with a higher prevalence of diabetes mellitus (DM). This association is particularly significant in the context of cardiovascular disease, as the prevalence of coronary artery disease was found to be greater among individuals with both DM and FHA compared to those with DM alone. These findings highlight the critical role of the menstrual cycle, and by extension, oestrogen, in maintaining cardiovascular health (Simoncini et al., 2017).

Restoring Health in Functional Hypothalamic Amenorrhoea: Evidence-Based Strategies for Menses, Bone, Fertility, and Cardiovascular Function

A study conducted by Falsetti et al. (2002) demonstrated that around 71% of FHA patients recovered during follow-up period of 7-9 years. Positive predictors of recovery included higher baseline BMI and lower basal cortisol levels. Importantly, BMI trajectories were found to be predictive of outcomes. All patients who recovered exhibited either stable or increasing BMI over time, whereas those who remained amenorrhoeic showed either stable or declining BMI patterns.

Current approach in treating FHA is to resolve its underlying cause. Due to complicated and multifactorial pathophysiology of this condition, it is a real challenge for healthcare workers. Emerging evidence indicates that, for some patients, restoring menses and fertility can be achieved through lifestyle modifications aimed at re-establishing energy balance. The precise threshold of weight gain required to resume menstruation in women with FHA remains undefined. However, it is generally recommended to regain the weight at which menstruation ceased, or to exceed it by 1–2 kg (Roberts et al., 2020), or alternatively, to achieve a 5% increase in body weight. Data received from studies on this issue shows that about 75% of women with FHA who followed recommendations on weight gain resumed menses after 20 weeks of improving energy balance, what was accompanied by increases in BMD (Falsetti et al., 2002).

However, in amenorrhoeic female athletes multidisciplinary approach was found to be the most effective in promoting recovery. This typically includes nutritional rehabilitation, psychological therapy, and modification of the exercise regimen (Falsetti et al., 2002). Among psychological interventions, cognitive behavioural therapy (CBT) has shown particular promise in facilitating the return of menstruation. As stated before, women who develop hypothalamic amenorrhoea due to excessive exercise often exhibit more dysfunctional attitudes, heightened stress sensitivity, and greater interpersonal dependence compared to their eumenorrheic counterparts (Fontana et al., 2022; Podfigurna & Meczekalski, 2021; Roberts et al., 2020). They also tend to have higher incidence of primary mood and psychiatric disorders. Evidence indicates that CBT can lead to the resumption of menses, along with reductions in nocturnal cortisol levels and increases in thyroid-stimulating hormone (TSH) and leptin concentrations. These effects were observed independently of weight gain. CBT has also shown beneficial effects in women experiencing infertility related to stress, with improvements noted in clinical pregnancy rates (Roberts et al., 2020). There is also some evidence suggesting that hypnotherapy could also be beneficial in restoring menses and conceiving (Falsetti et al., 2002). While these findings highlight the potential of psychological interventions in the treatment of FHA, the current body of evidence remains limited. More high-quality clinical trials are needed to better understand the efficacy and long-term outcomes of psychotherapy in managing FHA.

Hormonal therapy represents another treatment option for patients with FHA, particularly for those who do not resume menstruation after 6–12 months of non-pharmacological interventions or for individuals unwilling to pursue lifestyle-based strategies. The primary goal of pharmacological treatment in this context is the preservation and improvement of bone mineral density. While some studies have reported beneficial effects of combined oral contraceptives (COCs) on BMD, concerns have been raised about their potential to further suppress IGF-1, which is crucial for bone formation. Due to conflicting findings in the literature, COCs are generally not recommended as a therapy for FHA-related bone loss. In contrast, transdermal oestrogen replacement therapy has shown more consistent and promising effects on BMD. A randomised controlled trial conducted by Liu and Lebrun compared three groups: one receiving a 100 mcg 17β-estradiol transdermal patch twice a week combined with cyclic micronised progesterone (200 mg for 12 days per month), a second group taking a daily COC containing 30 µg ethinyl estradiol and 0.15 mg desogestrel, and a third receiving no hormonal treatment. At the 12-month follow-up, participants in the transdermal group had significantly higher spine and femoral neck BMD Z-scores compared to both the COC and control groups, as well as higher hip BMD Z-scores compared to the COC group (27). Transdermal oestrogen therapy was associated with an increase in circulating estradiol levels, which is positively correlated with improvements in bone density. Additionally, this form of therapy resulted in a reduction of factors known to inhibit osteoblastic activity, including sclerosin, preadipocyte factor-1 (Pref-1), and brain-derived neurotrophic factor (BDNF). Unlike COCs, transdermal oestrogen did not lead to an increase in sex hormone-binding globulin (SHBG) levels. As a result, it preserved the levels of bioavailable gonadal steroids, which are critical for maintaining bone health (Pedreira et al., 2022). During the preparation of this paper, no studies were identified investigating the use of bisphosphonates, denosumab, recombinant human IGF-1, leptin therapy, or androgen treatment specifically for low BMD in athletes with FHA. However, limited research exists on the application of these therapies in amenorrhoeic women with Anorexia Nervosa. Findings from those studies suggest some positive effects on

BMD, which may serve as an incentive to extend such research to the athletic population affected by FHA (Behary & Comninos, 2022; Brundu et al., 2006). It is important to note, that while hormonal treatments may offer skeletal benefits, they do not restore gonadotropin secretion or stimulate ovulation. Furthermore, they may give a false impression of recovery if withdrawal bleeding occurs in the absence of adequate nutritional status, persistent energy deficits, or unresolved psychological stressors (Roberts et al., 2020).

Infertility treatment is a key consideration for women with FHA who wish to conceive. First line of treatment should focus on restoring energy imbalance and increasing BMI to at least 18.5kg/m^2. As previously discussed, low BMI is associated with a heightened risk of spontaneous abortion, preterm delivery, impaired intrauterine growth, and an increased likelihood of caesarean section (Bumbuliene et al., 2015; Meczekalski et al., 2014; Roberts et al., 2020). Moreover, it is essential to consider the broader hormonal and neuroendocrine disruptions associated with chronic energy deficiency. Particular attention should be given to leptin, which plays a critical role as a metabolic signal to the hypothalamus, reflecting both energy availability and the magnitude of energy stores in the body (Zanker, 2006). Available evidence suggests that leptin levels serve as a signal to the hypothalamus, indicating that energy reserves are sufficient to support pregnancy, thereby enabling normal reproductive function. Leptin exerts its effects on the HPO axis indirectly, by modulating the secretion of neuropeptide Y, kisspeptins, and other neuroregulators involved in the control of GnRH production (Kyriakidis et al., 2016). Studies involving the administration of recombinant leptin to women with FHA have demonstrated that this treatment can restore ovulatory function. Additionally, leptin therapy has been shown to reverse other metabolic abnormalities commonly associated with FHA, further highlighting its therapeutic potential (Zanker, 2006). Currently, the gold standard for inducing ovulation in women with FHA is pulsatile administration of GnRH. Most women with FHA have a preserved ovarian reserve, as reflected by normal anti-Müllerian hormone (AMH) concentrations, which is a favourable prognostic indicator (Gibson et al., 2020; Saadedine et al., 2023). A 25-year cohort study involving 66 FHA patients who underwent 88 treatment cycles of subcutaneous pulsatile GnRH reported a live birth rate of 65.9%. The ovulation rate per cycle was 96%, with 75% of ovulations being monofollicular. The overall clinical pregnancy rate per treatment was 74.4%, and the miscarriage rate was 11.5% (Quaas et al., 2023). These findings confirm the efficacy of pulsatile GnRH therapy in inducing ovulation and achieving pregnancy in FHA patients. Moreover, pulsatile GnRH treatment was associated with higher conception rates and a lower incidence of multiple pregnancies, compared to gonadotropin injections (Gibson et al., 2020; Quaas et al., 2023). Naltrexone, an opioid receptor antagonist, has also been explored as a potential treatment option due to the inhibitory effect of endogenous opioids on GnRH secretion. It is hypothesised that opioid blockade may help restore normal GnRH pulsatility. Although preliminary studies have shown that naltrexone can enhance GnRH secretion and improve ovulation rates, it has not been widely adopted as a standard therapeutic approach in clinical practice (Gibson et al., 2020).

Research on the management of cardiovascular health in amenorrhoeic athletes remains limited. One study reported that administration of combined oral contraceptives (COCs) led to improvements in endothelial function after nine months of therapy, however, no significant changes were observed in lipid profiles. It is important to note that this study had a small sample size and lacked long-term follow-up, limiting the generalisability of its findings. Currently clinical recommendations for improving cardiovascular health in athletes with amenorrhoea primarily emphasise lifestyle modifications, including nutritional rehabilitation, weight restoration, and reduction in training intensity (Gibson et al., 2020).

Discussion

This review consolidates current evidence of the pathophysiology, epidemiology, clinical consequences and treatment of functional hypothalamic amenorrhoea. Affecting over 17 million women worldwide, FHA accounts for approximately one-third of secondary amenorrhoea cases (Saadedine et al., 2023) and up to 5% of primary amenorrhoea cases. Notably, up to 50% of regularly exercising women report some form of menstrual disturbance (Meczekalski et al., 2014). While physical activity has numerous health benefits, incorporating enhanced vascular function, reduced all-cause mortality, improved mental well-being (World Health Organization, 2020), excessive exercise alongside with restrictive eating creates conditions of low energy availability. Energy deficiency triggers adaptive physiological mechanisms that prioritise essential survival functions (Nazem & Ackerman, 2012; Kyriakidis et al., 2016). The pathophysiology of FHA is complex, involving suppression of pulsatile gonadotropin-releasing hormone (GnRH) secretion, resulting in reduced gonadotropin levels, and other hormonal and neurohormonal alterations such as low leptin and insulin, and elevated cortisol and ghrelin—all of which contribute to hypoestrogenism and a broad spectrum of systemic effects (Brundu et al., 2006; Kamel-ElSayed et al., 2023; Kyriakidis et al., 2016; Meczekalski et al.,

2014; Męczekalski et al., 2023; Orlowski & Sarao, 2023; Patel et al., 2024; Saadedine et al., 2023; Sanders et al., 2018; Young & Jialal, 2023).

Early identification of at-risk individuals is crucial to prevent reversible and irreversible health consequences of FHA. Risk factors include type of trained sport, body weight and appearance requirements, dysfunctional psychological traits, controlling family dynamics, and possible genetic predispositions, such as reduced BDNF expression (Nazem & Ackerman, 2012; Raj, Creech, & Rogol, 2023; Saadedine, Kapoor, & Shufelt, 2023). Physicians, coaches, parents, and athletes should be encouraged to monitor menstrual regularity, which serves as a key indicator of overall female physiological and mental health (Meczekalski et al., 2014; Rosen Vollmar, Mahalingaiah, & Jukic, 2025; Saadedine, Kapoor, & Shufelt, 2023; Shufelt, Torbati, & Dutra, 2017). Early recognition of FHA during adolescence is particularly important, as it may impair the development of peak bone mass, uterine maturation, and neuropsychiatric function, as normoestrogenemia is essential in those contexts (Bumbuliene et al., 2015; Meczekalski et al., 2014; Shufelt, Torbati, & Dutra, 2017). Since FHA may lead to primary amenorrhoea, it is crucial to pay special attention to pre-menarche individuals that engage in gymnastics or endurance disciplines, in order to prevent insidious development of health consequences (Meczekalski et al., 2014; Nazem & Ackerman, 2012). Screening adult female athletes for menstrual disturbances has equal importance. Prolonged hypoestrogenemia in this population may lead to involution of reproductive organs, causing women to have difficulties in maintaining a healthy pregnancy, increased risks of spontaneous abortion, preterm delivery, and cesarean section, all of which may reduce live birth rates (Meczekalski et al., 2014; Roberts et al., 2020; Shufelt, Torbati, & Dutra, 2017). Mental health monitoring is also essential, given the bidirectional relationship between FHA and psychiatric disorders. Screening for depression, anxiety, and sexual dysfunction is warranted, as these conditions may be both causes and consequences of hypoestrogenism, with implications for psychosexual well-being (Dundon et al., 2010; Shufelt, Torbati, & Dutra, 2017). Appropriate diagnosis of FHA is crucial in maintaining proper bone metabolism, as between 22 to 50% amenorrhoeic athletes develop osteopenia and between 0-13% develop osteoporosis. Studies show that just six months of hypoestrogenism may be sufficient to reduce BMD (Nazem & Ackerman, 2012; Shufelt, Torbati, & Dutra, 2017). Finally, hypoestrogenism present in FHA counteracts the otherwise cardioprotective effects of exercise, increasing the risk of endothelial dysfunction and cardiovascular disease (Tegg et al., 2024; Simoncini, Giannini, & Genazzani, 2017; Bairey Merz et al., 1999).

Treatment of FHA usually requires clinicians to adopt multidisciplinary approach. Restoring energy imbalance by weight gain to the pre-amenorrhoeic body weight or to increase it by ≥5% can be sufficient to resume menstrual cycle and implement positive effects on BMD (Roberts et al., 2020). Many patients benefit from nutritional counselling, CBT and modifications to the exercise regimen (Gibson et al., 2020; Roberts et al., 2020). For those who do not respond to lifestyle interventions, transdermal oestrogen therapy has been shown to improve BMD more effectively than combined oral contraceptives, without reducing IGF-1 or increasing sex hormone-binding globulin (SHBG) levels, which can lower bioavailable oestrogen (Gibson et al., 2020; Liu & Lebrun, 2006; Roberts et al., 2020). However, hormonal replacement does not restore ovulation, making it insufficient for women seeking pregnancy. In such cases, pulsatile GnRH therapy remains the gold standard, yielding high rates of monofollicular ovulation and live births with minimal risk of multiple gestation (Gibson et al., 2020; Roberts et al., 2020).

This review is limited by the narrow selection of clinical trials available across specific domains (e.g., cardiovascular health), the small sample sizes of many studies, the lack of long-term follow-up data, and the use of non-standardised methodologies across trials (Barrack et al., 2013; Gibson et al., 2020; Mudd et al., 2007; Nazem & Ackerman, 2012). These constraints highlight the need for larger, standardised, and longitudinal studies to better understand FHA and optimise its diagnosis and management.

Conclusions

Functional Hypothalamic Amenorrhoea (FHA) is a significant endocrine disorder with wide-ranging physiological and psychological consequences. While health benefits of physical activity remain indisputable, excessive exercise in the context of insufficient energy intake poses a serious threat to female health. Early diagnosis and timely intervention are critical in preventing essential to prevent hormonal, skeletal, and neuropsychiatric complications. Raising awareness among athletes, coaches, and healthcare providers about the risks of low energy availability (LEA) and the importance of menstrual regularity as a marker of health is critical. Ultimately, a multidisciplinary, individualised approach—encompassing nutritional, psychological, and medical support—offers the most effective path to recovery and long-term well-being.

This review underscores the alarming need for further research, particularly in the areas of early identification, pathophysiological mechanisms, and effective, evidence-based treatment strategies.

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