Review Article

Female athlete triad: past, present, and future directions

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Abstract: Since the passage of Title IX in 1972, female participation in athletics has increased significantly. More girls and young women have been able to experience the psychosocial and physical health-related benefits of organized sports. Hand-in-hand with increased participation, however, has been a dramatic increase in a dangerous yet widely underdiagnosed sports-related condition—the female athlete triad. The triad was originally defined as the presence of disordered eating (DE), amenorrhea, and osteoporosis. Further research revealed these diagnostic criteria to be too narrow in scope however, and today's definition has evolved into that of a dynamic interrelationship between decreased energy availability (EA), menstrual dysfunction, and low bone mineral density (BMD). If left untreated, long-term consequences include irreversible decreases in BMD and a predisposition to potentially debilitating musculoskeletal injuries. First line therapy is generally non-pharmacological with treatments aimed at altering eating and exercise behavior. In behavior modification refractory cases, certain pharmacological treatments may be utilized but this practice remains controversial. While no pharmacological approach to treatment is yet recommended, a recent clinical trial provides compelling evidence and its implications warrant further investigation.

Keywords: Female athlete triad; triad; amenorrhea; bone health; energy availability (EA)

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Background

From the passage of Title IX federal legislation in 1972 to modern day, female participation in organized sports at all levels has increased dramatically. The stated intention of the law was to eliminate sex-based discrimination in all educational activities receiving federal financial support, including school sanctioned sports teams (1). In 1971, the year prior to enactment of Title IX, there were approximately 310,000 female athletes in the US, just 0.29% of the female population (2,3). By 2012, female participation in sports had climbed to 3,373,000, with 2.15% of the female population in the US participating in some level of organized athletics (4). Perhaps unsurprisingly, with increased female participation, a parallel increase in sports-related injury and disease has been observed.

Throughout the 1970's, increases in self-reporting and physician observation of altered menarche in female athletes caught the attention of researchers. In 1977, Malina and Spirduso reported delayed menarche in high school-, college-, and Olympic-level athletes in comparison to non-athletes (5). Throughout the 1980's, published literature investigated a connection between altered menarche, disordered eating (DE), and reduced bone mass in young female athletes (6-8). With increasing concern backed by a growing body of literature, the American College of Sports Medicine (ACSM) convened a panel in 1992 to lay the groundwork for a coordinated approach to prevention and treatment (9). During this meeting, the term the female athlete triad was first defined as a syndrome consisting of, but not limited to, DE, amenorrhea, and osteoporosis found in physically active girls and women.

Almost immediately following publication of the ACSM definition of the triad in 1992, the literature began to

reveal growing dissatisfaction with its limits. Of particular concern was that athletes with less severe manifestations of these symptoms were being overlooked, as the diagnostic definition at the time included only clinical endpoints of each component (10). De Souza and Williams addressed this in 2004 by proposing an expansion of the definition to include subclinical presentations of DE, amenorrhea, and osteoporosis (11). This proposal was successfully integrated into the 2007 ACSM Position Stand and the triad's diagnostic criteria underwent several important alterations. First, the Position Stand established a sliding model in which an athlete can fall anywhere on a continuum, from the disease state to optimal health, for each of the three interrelated components at any given point in time. Additionally, the definition was broadened, replacing DE with low energy availability (EA), amenorrhea with menstrual dysfunction, and osteoporosis with low bone mineral density (BMD) (12). In 2014, a comprehensive consensus statement was published by the Female Athlete Triad Coalition (FATC), and subsequently endorsed by the ACSM, that reaffirmed the diagnostic definition of the triad established in the 2007 ACSM Position Stand and emphasized the importance of early intervention in avoiding long-term damage (13).

Definition

According to the ACSM, the female athlete triad is a spectrum of abnormalities in EA, menstrual function, and BMD (12). The three abnormalities have been shown to be intimately connected and for each of the three a patient may present anywhere from good health to the disease state at any given time. Importantly, as one of the components may have a subclinical presentation yet still pose serious long-term danger if not addressed, an athlete need present with only one of the three components to be diagnosed under the umbrella of female athlete triad syndrome (13).

(I) Decreased EA

Originally termed "disordered eating", this component of the triad was refined in 2007 to refer to a spectrum of "energy availability", defined as dietary energy intake minus exercise energy expenditure. Low EA may result from insufficient dietary intake, excessive energy expenditure, or a combination of the two. Importantly, patients may still be defined as experiencing low EA even if they have not been diagnosed with a specific eating disorder (ED) or DE (12). Overt signs of low EA include BMI ≤17.5 kg/m^2 or <85% of expected weight for adolescents (12). Quantitatively, low EA is defined as energy intake (kcals) less energy expenditure due to exercise (kcals) divided by kilograms of fat free body mass (FFM), with low EA for female athletes considered to be less than 45 kcal kg^{-1} fat-free body mass per day (12,14). Additionally, reduced resting metabolic rate (RMR) and low triiodothyronine (T_3) are physiologic adaptations to chronic energy deficits and should be considered diagnostic indicators of low EA (15,16).

(II) Menstrual dysfunction

Menstrual dysfunction is a spectrum of symptoms ranging from luteal phase defects to amenorrhea (both primary and secondary) (17). Primary amenorrhea is defined as the failure to reach menarche. The American College of Obstetricians and Gynecologists (ACOG) states that an absence of menarche by 15 years of age or lack of menarche greater than three years after thelarche (Tanner stage II breast development) warrants further investigation (18). Secondary amenorrhea is defined by the achievement of menarche and establishment of a normal menstrual cycle for some period of time before an absence of menses in three consecutive months (19). Oligomenorrhea is similar to secondary amenorrhea in that it occurs following menarche, but rather than a complete halt of the menstrual cycle, menstruation occurs less frequently than every 35 days (20). Anovulation and luteal phase deficiency are additional findings that qualify an individual as having menstrual dysfunction. However, unlike amenorrhea and oligomenorrhea, they are asymptomatic and thus difficult to diagnose on clinical history alone (17).

(III) Low BMD

Low BMD, the third defining characteristic of the triad, is thought to be a downstream effect of amenorrhea and associated disturbances in physiologic hormone cycling. The gold standard for BMD assessment is dual energy X-ray absorptiometry (DEXA) measurements of skeletal elements. From these scans, a Z-score is calculated to compare the patient's BMD to that of a sample of the general population matched for both sex and age. The International Society for Clinical Densitometry (ISCD) definition of low BMD is utilized in establishing the diagnosis in children, adolescents and pre-menopausal women (21). For both children and adults, a Z-score <–1.0 is considered abnormal and a Z-score

<–2.0 is diagnostic of low BMD (22). Low BMD can manifest clinically as stress fractures of the vertebra or long bones in female athletes.

Epidemiology

Over the past several decades, a plethora of research has been conducted on the prevalence of the three triad characteristics in populations ranging from sedentary high school students to elite female endurance athletes (23-41). Prevalence rates in these studies, however, vary substantially for nearly all symptoms and combinations due to differing study methodology and changing diagnostic criteria. The 2007 change in ACSM position stand, replacing DE with low EA, for example, has made determination of prevalence more difficult. To date no studies have been conducted to determine the prevalence of low EA in female athletes (24).

With the current consensus that the underlying etiology of the triad is low EA, it is not surprising that "lean sport athletes", i.e., participants in sports that place an emphasis on endurance training, low body weight, lean physique, and aestheticism, tend to be affected in greater proportions than their non-lean sport counterparts (23,25). The three studies to date investigating rates of all three triad conditions simultaneously in young female athletes found a prevalence of 1.5–6.7% in lean sport athletes while non-lean sport athletes had a prevalence of 0.0–2.0% (25-27). Additionally, in a study of 186 elite female athletes under the age of 40, 35.6% lean sport athletes displayed DE and menstrual dysfunction while only 13.5% of non-lean sport athletes displayed such symptoms (25). Similar trends in DE and menstrual dysfunction between lean and non-lean sport athletes have been echoed by multiple other investigators (26,28,29).

The reported prevalence of any single triad characteristic varies greatly between studies. The prevalence of DE, for example, ranges from 7.1% in a study of 84 collegiate athletes to 89.2% in a study of 67 elite female Malaysian athletes. Despite this, most studies place the prevalence of DE among female athletes between 15% and 30% (30-36). Similarly, reported prevalence of menstrual dysfunction among studies utilizing self-reported menstrual history or menstrual history surveys ranges from 6% to 79% (25,27,28,32,42). In an attempt to improve both accuracy and precision, several studies have utilized hormone level measurements to diagnose menstrual dysfunction. The studies utilizing this approach found the prevalence of menstrual dysfunction to be between 41% and 50% for female athletes (37-39).

Despite extensive historical use of the World Health Organization T-score, recent practice has shifted towards the utilization of the ISCD Z-score for the diagnosis of low BMD. Unlike the T-score, which controls only for gender (43), the Z-score controls for both age and gender and is thought to be a better measure of low BMD in younger populations (44). Studies utilizing the Z-score have shown the prevalence of low BMD, defined as a Z-score <–1.0, in young female athletes to be between 10% and 25% (24,27,28,35) while that of endurance athletes tends to be greater, between 30% and 40% (40,41).

Diagnosis

Low EA

Screening for low EA always begins with a thorough history of diet, exercise, and eating habits. Determination of an individual's EA can be accomplished through 3- or 7-day dietary logs, a 24-hour food recall log, or food-frequency questionnaire (13). While relatively simple to administer and complete, this method relies on self-reporting and can be inaccurate (45). When self-reporting is suspicious or unreliable, physical indicators become more important. These include recent weight loss or signs of DE or ED such as bradycardia, lanugo, poor dentition, orthostatic hypotension, parotitis, and Russell's sign, calluses on the knuckles or back of the hand due to repeated self-induced vomiting of long periods of time (12,13,46,47). Importantly, absence of recent weight loss does not rule out the presence of low EA, as studies have demonstrated the body's preferential disruption of physiological function in favor of stabilizing mass under certain conditions (8,12,48-50).

Studies have shown certain metabolic abnormalities to be associated with triad symptoms. Elevated concentrations of serum growth hormone (GH) (51), ghrelin (52,53), peptide YY (PYY) (53), and urinary 24 hour cortisol (39) as well as decreased levels of insulin (54), plasma glucose (54), serum triiodothyronine (TT_3) (15,52) and insulin-like growth factor-1 (IGF-1) (55) have been linked with this population. While these findings are not pathognomonic, blood testing for these species may be used to aid in diagnosis when history and physical examination alone prove insufficient (13).

Menstrual dysregulation

The diagnosis of menstrual dysfunction secondary to low

EA is one of exclusion (13). When a patient presents with complaints that arouse clinical suspicion of menstrual dysfunction, the 2014 FATC Consensus Statement suggests using an algorithm modified from the Jameson *et al.* textbook of endocrinology (56). First, history and physical examination should be performed to rule out uterine pathology, outflow tract obstruction, and disorders of sexual differentiation as causes of primary amenorrhea. Pregnancy must be ruled out with a urine test. Primary ovarian insufficiency, one of the most common causes of amenorrhea, can be ruled out by testing follicle stimulating hormone (FSH) levels. Hyperprolactinemia and thyroid dysfunction can be ruled out via prolactin and thyroid stimulating hormone (TSH) tests, respectively. The presence of hypothalamic and pituitary disorders can be assessed with a serum estradiol or progesterone challenge test to quantify the degree of hypoestrogenism. Finally, hyperandrogenic conditions including polycystic ovary syndrome, virilizing ovarian tumors, adrenal tumors, nonclassic congenital adrenal hyperplasia, and Cushing's syndrome (13,57,58) may be ruled out by measuring testosterone (total and free) and dehydroepiandrosterone and its sulfate (DHEA/S) (13) paired with an early morning 17-hydroxyprogesterone test (to assess for non-classic 21-hydroxylase deficiency), and a pelvic ultrasound.

Low BMD

The third component of the triad, low BMD, is analyzed using DXA measurements. For children and adolescents <20 years of age, a posterior-anterior (PA) radiographic view of the spine and a total body less head (TBLH) image should be utilized (59). In adults aged ≥20 years, a PA view of the lumbar spine and an image of the hip should be used (60). From these scans, a Z-score can be calculated. For both children and adults, a Z-score <–1.0 is considered abnormal and a Z-score <–2.0 is diagnostic of low BMD (22). In both cases, prior history of fracture and associated trauma should be investigated in depth.

Etiologies and consequences

A deficit in EA is the cornerstone of the triad and precipitates a trickle-down effect, altering menstrual function, BMD, and cardiovascular health (11). When EA drops below a certain threshold, approximately 30 kcal/kg FFM/day, a physiologic shift occurs in which metabolic fuels are redirected from costly reproductive functions toward processes essential for sustaining life (61). As a result, release of gonadotropin releasing hormone (GnRH) from the hypothalamus is reduced, producing a stark decline in circulating estrogen levels. Lending to the importance of early recognition and treatment, studies have shown that decreases in EA below 30 kcal/kg FFM/day can lead to menstrual disturbances within 5 days (50,62-67).

Musculoskeletal health is of particular concern in female athletes with menstrual dysregulation as high levels of estrogen are needed to reverse bone resorption (68,69). In amenorrheic athletes, BMD declines consistently for as long as estrogen levels are depressed (70,71) resulting in constantly increasing risk of musculoskeletal injury (72-75). Even more troubling is that by 18 years of age, females have typically accumulated 90–95% of their peak BMD and will work to maintain this bone mass throughout adulthood (76-78). Failure to achieve peak bone mass during this period predisposes these individuals to clinically low BMD throughout adulthood, leading to increased incidence of painful and potentially debilitating stress fractures throughout their adult life (79,80). Emphasizing the importance of early detection and intervention, it has been shown that accumulated loss of BMD due to low EA and menstrual dysfunction may not be reversible in all cases (70,81,82).

Although it is not one of the three defining symptoms, recent literature has proposed that deleterious changes in cardiovascular health may also be associated with the triad (11). It is hypothesized that disruption of the HPG (hypothalamic-pituitary-gonadal) axis may decrease endothelial function and predispose female athletes to early heart disease. Estrogen is necessary to promote nitric oxide (NO) production and vascular endothelial release (83). Endothelial-derived NO and its vasodilatory properties promote anti-atherosclerotic effects while suppressed NO release in amenorrheic athletes has been associated with decreased flow mediated dilation (FMD) of vessels, increased total cholesterol and LDL, and decreased overall cardiovascular health (84-86). Additional long-term, prospective studies are necessary.

Interventions

Non-pharmacological treatment

Nutritional intervention is the first line therapy for female athletes with symptoms as it most directly targets the underlying etiology (87). Through either modification of

diet, exercise frequency and intensity, or both, the energy status of the athlete must first be normalized. In the return to play (RTP) guidelines published by the FATC in 2014, a gradual increase in body mass is advised with patients ideally increasing their energy intake to 20–30% above baseline needs for a weight gain goal of approximately 0.5 kg every 7 to 10 days (13). Additional studies have suggested that gain of between 1–4 kg of body mass is associated with the resumption of menses, however this number varies between individuals. A target EA of 45 kcal kg^{-1} FFM d^{-1} is a better goal than absolute weight gain (47,87-89).

While increasing EA is a mainstay of treatment in every athlete, specific recommendations vary to match the manner in which the individual came to develop low EA. For cases in which the cause of low EA is undereating in the absence of DE, referral to a sports dietitian for nutritional education is sufficient. If the cause of low EA is DE, the athlete should be directed to a physician for assessment and management, a mental health professional for psychological treatment, and a dietitian (12,90).

The goal for treatment of low EA via non-pharmacological methods is to reverse the patient's energy deficit, allowing normalization of the HPG axis and bone metabolism. In the first few days following the initiation of treatment, likely before weight gain is even noticeable, metabolic hormone profiles will improve and bone formation will be upregulated (13,64). Weight gain to a target EA of 45 kcal kg^{-1} FFM d^{-1} will take months, but may be shorter depending on the severity of symptoms at presentation (13). Weight gain has been associated with the resumption of menses in exercising women (89,91-93). However, in several cases menstruation didn't occur for more than a year following treatment initiation and weight gain (47,92,94). Improvements in BMD, secondary to the effects of improved metabolic hormone profiles, increased weight bearing upon weight gain, and restored LH pulsatility, are thought to be the final physiological change to occur. However, existing literature is in disagreement as to whether BMD levels appropriate for age and build can be fully restored (81,95,96).

Pharmacological treatment

Pharmacological treatment of the triad remains controversial, with the most recent FATC Consensus Statement stating that, due to a lack of evidence-based research, pharmacological therapy cannot be recommended unequivocally (13). Despite this guideline, concerned physicians often prescribe pharmacological treatment regimens when more conservative non-pharmacological management has proven ineffective. In such scenarios, worsening BMD with recurrent long bone fractures, prolonged amenorrhea, or development of ED despite 12 months of conservative treatment is generally considered sufficient to warrant pharmacological intervention (13,87).

Young females presenting with ED require an interdisciplinary approach to treatment, particularly the inclusion of a mental health professional. While treatment in these cases may initially utilize non-pharmacological approaches such as positive psychology and behavioral therapy (97), prescription of certain medications may be highly beneficial. In particular, utilization of selective serotonin reuptake inhibitors (SSRI) has been shown to be helpful in the treatment of bulimia nervosa (98) while a growing body of evidence has found olanzapine useful in weight-related outcomes of anorexia nervosa (AN) treatment (99-101).

The majority of pharmacological therapies utilized both currently and in recent years to treat low BMD in young females have revolved around the replacement of gonadal steroids (13). Following recognition of low estrogen levels and their effects in the amenorrheic athlete, treatment with combined oral contraceptives (COC) became a primary interest. In theory, COC therapy would artificially elevate estrogen levels, decrease osteoclastic bone resorption activity and ultimately increase BMD (87). Further studies showed, however, that while COC does indeed increase estrogen levels, this treatment has not yielded consistent improvements in BMD in amenorrheic athletes (102-106). It is thought that the first pass metabolism of COC drugs in the liver decreases the hepatic production of IGF-1 (107-109). Overall, COC therapy does slow osteoclastic bone resorption, but its negative effect on bone trophic hormone levels predominates (103,105).

In a recent RCT assessing adolescent girls with AN by Misra *et al.*, a transdermal estradiol (100 mg 17-B-estradiol) patch coupled with cyclic oral progestin (2.5 mg d^{-1} medroxyprogesterone, 10 d mo^{-1}) (110) was administered. In the 18-month trial, increases in lumbar spine BMD were reported at each of the three measurement time points included in the study. Additionally, the change in IGF-1 across the 18 month intervention showed no significant difference between the group receiving transdermal estradiol and placebo (110). It is thought that non-oral administration of estradiol bypasses first-pass metabolism, avoiding a decrease of hepatic IGF-1 secretion and

ultimately producing the desirable effect of increased BMD (109-112).

In addition, some medications typically used in the treatment of low BMD in older and postmenopausal women have been utilized in young female athletes (113,114). Bisphosphonates, compounds that impair osteoclast function and slow bone resorption, have been considered (115). However, they have a very long half-life and substantial teratogenicity (116,117). Due to this side effect, it is generally recommended that bisphosphonates only be used with extreme caution as a last line of treatment (13,118). Recombinant parathyroid hormone (rPTH) is being investigated for use in young amenorrheic athletes, but no public studies regarding its safety and efficacy exist yet (114,118,119).

RTP

Despite continued research into risk factors, diagnosis, and treatment, there were no standardized guidelines for athlete clearance and RTP until recently. In hopes of solving this issue, the 2014 FATC consensus statement outlined a score-based cumulative risk assessment calculation and corresponding RTP risk stratification rubric for ease of physician use and standardization of patient management (13). The cumulative risk assessment worksheet grades the clinical presentation of six risk factors on a scale of increasing severity. Upon summation of the score, the patient falls into one of three categories: full clearance, provisional/limited clearance, or restricted from training and competition. To date, no studies have been conducted to assess the efficacy of the proposed RTP protocols.

When making the RTP decision, input from the multidisciplinary team of healthcare professionals treating the patient is advisable and input from other concerned parties such as parents and coaches can be valuable. Ultimately, however, it is of the utmost importance that the athlete's physician make the ultimate decision on RTP (120-122). Because of a current lack of evidence to validate the proposed RTP assessment and guidelines as well as the unique circumstances of each individual athlete, the RTP decision is seen as more of an art than a science. The physician must consider input from involved parties in conjunction with the patient's past medical history, lab tests, sport played, and any conflicts of interest that may be present (123). In making such a difficult decision the patient's current and future health must, in all cases, supersede external pressures and circumstances.

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