Update on the female athlete triad

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Abstract Updated prevalence estimates of all 3 components of the Female Athlete Triad, a syndrome characterized by low energy availability, functional hypothalamic amenorrhea, and osteoporosis, is low (0 %–16 %), however, estimates of 1 or 2 concurrent components approach 50 %–60 % among certain athlete groups. Recent research identifies components of the Triad among female adolescent athletes, particularly those participating in leanness sports, such as endurance running. This is alarming, as adolescents require adequate nutrition and normal hormone function to optimize bone mineral gains during this critical developmental period. Current literature highlights new assessments, such as measurements of bone microarchitecture and hormone levels to better evaluate bone strength and the hormonal and metabolic profile of athletes with and at risk for the Triad. Recent data also provides support for additional potential consequences of the Triad, such as endothelial dysfunction and related cardiovascular effects, stress fractures, and musculoskeletal injuries. Additional prospective research is needed to evaluate long-term indicators

and consequences of the Triad and identify effective behavioral treatment strategies.

Keywords Energy availability · Functional hypothalamic amenorrhea · Low bone mass · Endothelial dysfunction · Bone microarchitecture · Quantitative computed tomography · Drive for thinness · Dietary restraint · Adolescent athlete · Gut hormones · Bone biomarkers · Resting energy expenditure · Stress fracture · Musculoskeletal injury

Introduction

The Female Athlete Triad (Triad), a condition observed most commonly among athletes participating in leanness sports, is characterized by low energy availability, functional hypothalamic amenorrhea, and osteoporosis [1]. The 2007 American College of Sports Medicine (ACSM) Triad Position Paper first introduced low energy availability (EA), in place of disordered eating, thus, recognizing the existence and consequences of inadvertent energy deficits [1]. Therefore, an energy deficiency, occurring purposefully or unintentionally, can alter activity of the hypothalamic pituitary axes and hormones involved in menstrual function and bone metabolism [2, 3]. The 2007 position paper additionally presented the Triad as a syndrome of 3 interrelated spectrums, including energy availability, menstrual function, and bone mineral density, with each spectrum spanning from a level of optimal health to disease [1]. The aim of the current review is to highlight relevant Triad research published primarily since the dissemination of the 2007 ACSM position paper and note areas where future research may aid in filling current gaps in the literature. Topics discussed include updated Triad and low EA prevalence estimates, information of less studied populations such as adolescent and male athletes, updated assessments and data regarding endocrine factors, recent

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literature highlighting consequences of the Triad, and updated data regarding Triad-related screening, treatment, and prevention.

Updated prevalence estimates

In a recent systematic review of 65 studies in exercising women, Gibbs et al [4] identified updated prevalence estimates of the Triad. To date, 9 studies ($n=991$) have reported the prevalence of all 3 Triad conditions with only a small percentage of athletes (0 %–15.9 %) exhibiting all Triad conditions concurrently [low EA with or without disordered eating (DE) or if EA not measured, DE, menstrual disturbances (MD), and low bone mineral density (BMD.)]. In the review, the authors [4] additionally identified prevalence estimates of 2 concurrent Triad components with estimates of MD and low BMD ranging from 0 %–7.5 % (4 studies; $n=460$); MD and DE from 2.7 %–50.0 % (8 studies; $n=1136$); low BMD and DE from 0.9 %–3.2 % (2 studies; $n=298$); MD and low EA 17.5 % (1 study; $n=80$); and the prevalence of low BMD and low EA 3.75 % (1 study; $n=80$).

Updated individual prevalence estimates of clinical and subclinical menstrual disturbances were also reported. Estimates of primary and secondary amenorrhea in 13 ($n=2216$) and 34 studies ($n=5607$), respectively, ranged from 0 %–56.0 % and 1 %–60.0 % [4]. The range in prevalence of oligomenorrhea was 3.5 %–52.5 % (23 studies; $n=4044$) [4]. Subclinical MD [luteal phase defects (LPD) and anovulation] have been evaluated by few investigators [5–9], despite LPD and anovulation representing the most common MD linked to exercise training [5, 6]. Prevalence estimates in these 4 studies range from 5.9 %–43.0 % ($n=118$) for LPD and 12.0 %–30.0 % ($n=101$) for anovulation.

Gibbs et al [4] found that individual estimates of clinical eating disorders, clinical DE, and subclinical DE ranged from 0 %–48.8 % (17 studies; $n=2869$), 7.1 %–89.2 % (17 studies; $n=2867$), and 2.9 %–60.0 % (6 studies; $n=1363$). To date, 1 prevalence study has determined low EA (<30 kcal/kg lean body mass) in female athletes ($n=80$) compared with sedentary controls ($n=80$) was 6 % vs 4 % [10]. The prevalence of low BMD defined as Z-score ≤ -2.0 ranged from 0 %–15.4 % (8 studies; $n=755$); whereas, the prevalence of low BMD defined as Z-score between -1.0 and -2.0 ranged from 0 %–39.8 % (6 studies; $n=507$).

Further research on the prevalence of this interrelated syndrome, both subclinical and clinical outcomes, is warranted to support the advancement of Triad prevention and treatment policies. Additionally, longitudinal studies are needed to identify risk factors for the most pathological presentation of Triad-related clinical conditions.

Triad assessment populations

Adolescents

Triad research has focused primarily on collegiate and young adult athletes. However, because of the importance of consuming adequate nutrition during development, particularly the development and accumulation of bone mineral, recent studies have also targeted the adolescent population. From the 2 studies evaluating the full Triad [10, 11] among competitive athletes representing a variety of sports, the prevalence of disordered eating [utilizing the Eating Disorder Examination Questionnaire (EDE-Q)] ranged from 18.2 %–35.4 %, oligomenorrhea or amenorrhea from 18.8 %–54.0 %, and low BMD ranged from 13.0 %–21.8 %.

In studies among adolescents, investigators have evaluated the relationship between participation in certain sports and low BMD. Barrack et al studied 183 female adolescent athletes, grouped according to sport type, and found that the 90 endurance runner athletes, compared with 93 nonrunner athletes (participating in ball, power, or antigravitational sports) exhibited a significantly higher prevalence (39.8 % vs 10.0 %, respectively) of low BMD, defined as a BMD Z-score of <1.0 at the lumbar spine or total body [12]. The authors also reported that the endurance runner athletes displayed a cross-sectional pattern of suppressed bone mineral accumulation, as no significant differences in bone mineral content (BMC) were found between runners ages 13–14 years compared with those ages 17–18 years [12]. This was in direct contrast to nonrunner athletes who displayed the normal, anticipated pattern of significantly higher BMC values among the older vs younger athletes. This finding of lower bone mass among the adolescent endurance runners compared with nonrunner athletes is consistent with studies among collegiate and young adult populations [13–16] and suggests that BMD deficits identified in collegiate and adult athletes may stem from, not only bone loss in adulthood, but from the failure to optimally accumulate bone mass during the teenage years.

Similar to prior findings in collegiate and young adult athletes, in a study of 93 adolescent endurance runners, oligomenorrhea or amenorrhea, elevated dietary restraint, and participation in 5 or more seasons of endurance running were predictors of low BMD [17]. BMI and lean tissue mass were inversely related to low bone mass [17]. The prevalence of low BMD in this population, defined as a BMD Z-score <1.0 at the total body or lumbar spine, was 39.8 % [15]. Prior researchers have also characterized hormonal and metabolic biomarkers associated with low BMD or amenorrhea. Christo et al reported lower IGF-1 levels among amenorrheic adolescent athletes vs control subjects [18]. Ackerman et al [19] found lower total pulse secretion of

leptin in amenorrheic compared with eumenorrheic adolescent athletes and nonathlete controls. Barrack et al [20] found lower leptin and 25(OH)D₃ levels in younger (ages 14–15 years) athletes with elevated bone turnover. Future longitudinal studies with larger study groups are needed to further confirm associated biomarkers and factors that increase the risk of low bone mass among young athletes.

Studies among adolescents have also evaluated the possibility of “catch-up” bone mass accrual among adolescent athletes with low BMD. A 3-year longitudinal study of 40 adolescent endurance runners found that 13 of 15 runners with low bone mass at baseline also exhibited low bone mass at the 3-year follow-up assessment, despite a 4.8 ± 1.1 kg increase in body weight and an increase in the number of menses in the past year [21]. This finding suggests that even with changes consistent with increases in EA, the group with low bone mass, as a whole, were not able to “catch-up” to their normal peers. However, there have been individual cases where “catch-up” accrual has been documented. Two athletes in the 3-year longitudinal study exhibited a 1.10 unit increase in lumbar spine BMD Z-score, changing their BMD status from “low” to “normal” [21]. Furthermore, 2 recent case studies among adolescent endurance runners with low BMD exhibited an approximate 2-unit increase in lumbar spine BMD Z-score after 6–8 years of gradual weight gain, normal menses, and reduced training [22, 23]. These findings suggest that a consistent increase in EA may promote “catch-up” accrual during young adulthood. Further research is needed to explore effective behavioral treatment options for adolescents with low BMD as well as educational programs geared toward promoting healthy behaviors and optimizing bone mass to allow for regular physical activity and sports participation among those at risk.

Male athletes

The 2007 ACSM Triad position paper describes a syndrome of 3 interrelated spectrums (ie, EA, menstrual function, and BMD) among females, with the most severe end of the spectrums describing an athlete with low EA, functional hypothalamic amenorrhea (FHA), and osteoporosis, however, male athletes may also experience similar consequences of low energy availability. Like females, males with known energy deficits, such as those with anorexia nervosa, exhibit low bone mass, with greater deficits associated with a longer duration of low EA. Castro et al [24] reported, among male adolescents with anorexia nervosa (AN), those with AN for >12 months exhibited significantly lower lumbar spine BMD Z-score values compared with those with AN for ≤12 months (-2.08 vs -0.04 , respectively). Additionally, consistent with females, recent evidence suggests that athletes participating in certain sports associated with an

increased risk of developing low EA (eg, distance running) may be more likely to develop low BMD, with other groups of athletes participating in ball and power sports largely exhibiting above-normal BMD values. A recent study by Fredericson et al [25], comparing bone mass of male endurance runners with soccer athletes, found lower hip and lumbar spine BMD among the runners. In addition, 40 % of runners exhibited low bone mass of the lumbar spine (BMD T-score <1.0) [25]. Another study found lower lumbar spine bone mass among adolescent male endurance runners compared with nonendurance runner athletes, competing in soccer, basketball, or volleyball (with 33 % of runners exhibiting low bone mass) [26]. Two reports have shown negative associations between running training volume and lumbar spine BMD [27, 28]. Factors consistent with an energy drain in endurance athletes have also been associated with reductions in osteogenic sex hormones. Several studies have reported significantly lower testosterone levels among male endurance runners compared with nonathlete controls [29–33] as well as reductions in gonadal hormones with increased endurance training [34, 35]. Therefore, like females, males may also experience the metabolic, hormonal, and physiological effects of low EA. Further research, is warranted, as the sample size of existing studies is small (~10–15 per group), few studies have evaluated the prevalence of individual or concurrent Triad components, and there has been minimal exploration of the effects of low EA in males.

Assessments, predictors, and relationships with endocrine factors

Bone microarchitecture

Dual energy x-ray absorptiometry (DXA) is the clinical gold standard method used to measure BMD. However, DXA provides only a 2-dimensional or areal measurement of bone. It underestimates the true BMD of small bones and overestimates BMD of large ones, as it cannot account for bone depth and size. Newer methods of assessing bone are now available and may better predict bone strength and fracture risk [36]. Quantitative computed tomography (QCT) and peripheral QCT (pQCT) provide direct measurement of volumetric BMD and are able to distinguish between cortical and trabecular bone. High-resolution pQCT (HRpQCT) is an even more advanced tool, providing information about cortical and trabecular bone microarchitecture. Various forms of high-resolution CT have been used to demonstrate that girls and women with anorexia nervosa have lower trabecular volume, number, and thickness, greater trabecular separation, and lower cortical thickness than age-matched controls [37].

Ackerman et al [38•] studied endurance running athletes (16 amenorrheic and 18 eumenorrheic) and 16 nonathletes ages 15–21 years. Using HRpQCT, both groups of athletes demonstrated greater total bone area, trabecular area, and cortical perimeter at the weight-bearing tibia compared with nonathletes, but cortical volumetric BMD was lower [38•]. This finding was postulated to be secondary to delayed mineral deposition in the expanding tibia of young athletes. Cortical area and thickness trended lower in amenorrheic athletes. Trabecular number was lower and trabecular separation was higher in amenorrheic athletes compared with the other 2 groups. At the non-weight-bearing radius, trabecular density was lower in the amenorrheic athletes vs the other 2 groups [38•]. In an extension of the above study, cortical perimeter and porosity at the tibia were greater in both groups of athletes than nonathletes, whereas the ratio (%) of cortical to total area was lowest in the amenorrheic athletes [39].

Finite element analysis (FEA), an engineering tool, can be applied to HRpQCT images, allowing in vivo estimation of bone strength parameters, such as stiffness and failure load [40], which are associated with fracture risk independent of BMD [41, 42]. FEA was applied to HRpQCT images of amenorrheic athletes, eumenorrheic athletes, and nonathlete controls. Despite greater cortical porosity in the tibias of the eumenorrheic athletes compared with controls, estimated tibial stiffness and failure load were higher than in nonathletes. However, the weight-bearing advantage was lost in the amenorrheic athletes, with no significant difference in stiffness and failure load noted between amenorrheic weight-bearing athletes and controls. At the non-weight-bearing radius, failure load and stiffness were significantly lower in amenorrheic athletes than nonathletes [39]. Larger, prospective studies further exploring bone microarchitecture are needed to find the best predictors of bone strength and fragility in those suffering from Triad.

Psychometric assessments of disordered eating and the triad

In several cross-sectional studies, investigators have evaluated subclinical disordered eating behaviors using the EDE-Q, Eating Disorder Inventory (EDI), and Three Factor Eating Questionnaire (TFEQ) among female athletes and recreational exercising women [14, 43–51]. Findings from recent research suggest that high drive for thinness (DT) or high dietary restraint (DR) as measured by the EDE-Q, EDI, or TFEQ, are indicative of risk for the Triad and are key-stone factors in the development of the Triad and its clinical conditions [14, 43, 47, 48, 52]. Due to the relatively brief and noninvasive method (ie, questionnaire survey) used to measure DR and DT, identifying the significant associations between these variables and clinical conditions of the Triad may facilitate large-scale efforts to screen exercising individuals at risk.

Dietary restraint is the conscious restriction of energy intake in order to achieve or maintain a desired body weight [53]. Several studies have linked high DR with MD, such as FHA, oligomenorrhea, and anovulation [45, 54–57], and lower BMD [43, 45, 56, 58, 59] in exercising women, adolescents, and sedentary women. Recent research by De Souza et al [47] among exercising women also highlights noteworthy relationships between high DT (measured by the EDI) and surrogate markers of low EA, as identified by a ratio of measured compared with predicted resting energy expenditure (mREE/pREE) <0.90. This method of obtaining an indication of low EA is less burdensome than assessing dietary energy intake and exercise energy expenditure over a number of days or weeks, and may be more accurate than self-report or other tools used to measure intake and expenditure. The ratio of mREE/pREE can be used to indicate energy deficiency due to the fact that circulating thyroid hormones and resting metabolism are reduced when energy intake does not match needs over a number of days or weeks. Also, AN patients, known to consume inadequate energy, exhibit mREE/pREE ratios between 0.60–0.80. In addition to relationships between the EDI DT subscale and surrogate markers of low EA, Gibbs et al [48] identified that exercising women with high DT scores, and surrogate markers of low EA are also at higher risk for clinical menstrual disturbances, such as FHA and oligomenorrhea, 74 % vs 38 %, respectively [48].

Therefore, psychometric indicators of eating behavior may be useful in identifying risk for Triad clinical outcomes. Future research is necessary to determine the utility of these psychometric evaluations (ie, DT and DR subscales) in a field setting as noninvasive and feasible methods of assessing risk for the Triad.

Role of appetite-related hormones in the etiology of chronic energy deficiency

Recent evidence from studies of exercising women with FHA highlights the potential role of appetite-related hormones in the etiology of chronic energy deficiency and menstrual disturbances. For example, consistent with patients with AN [60], exercising women with FHA consistently exhibit elevated levels of the orexigenic hormone, ghrelin, and the anorexigenic hormone, peptide YY (PYY) [47, 51, 61], yielding an overall anorexigenic effect. In addition, fasting PYY concentration have been negatively correlated with REE [adjusted for fat-free mass (FFM)] and positively correlated with DT score in women categorized by exercise (exercising vs sedentary) and menstrual status (FHA vs ovulatory). Thus concurrently elevated PYY and ghrelin concentrations, and the subsequent suppressive effect on appetite, may prevent compensatory increases in energy intake in exercising women with FHA.

Interestingly, it appears that the method of the development of low EA (ie, through restricting intake or via increased exercise energy expenditure) may also affect hormone levels, satiety, and hunger. An acute bout of vigorous exercise has been shown to suppress appetite and decrease relative energy intake in both women and men [62, 63] for several weeks [64, 65]. However, in contrast, experimental findings by Hubert et al [66] demonstrated that a diet-induced energy deficit *increased* hunger in healthy women. These results suggest that a lack in initiative to match energy intake to exercise energy expenditure may be physiologically driven, via temporary suppression of ghrelin and increases in PYY postexercise [67]. Thus, these appetite-related hormones may serve as key metabolic signals underlying “inadvertent undereating,” [67] which may increase the risk of developing low EA and subsequent Triad conditions. However, these results are not conclusive [68, 69] and notably, the mechanisms surrounding “exercise-induced anorexia” are complex with currently unknown, potential long-term implications.

Consequences of the triad

Endothelial dysfunction

Evidence from recent research identifies endothelial dysfunction, a pivotal factor contributing to the development of cardiovascular disease, as another potential consequence of the Triad [70]. Estrogen, which is lower in females with the Triad, stimulates the endothelial nitric oxide (NO) synthase [71] signaling system, thus, promoting NO release. NO promotes vascular smooth muscle cell (VSMC) dilation and has anti-atherosclerotic properties including inhibiting platelet aggregation, smooth muscle proliferation, leukocyte adhesion, and low-density lipoprotein (LDL) oxidation [72].

Previous researchers have reported a 95 % positive predictive value of abnormal brachial dilation in predicting coronary endothelial dysfunction [73]. Various investigators have demonstrated a correlation between exercise-associated amenorrhea (EAA) and brachial artery endothelial dysfunction [74–77]. Hoch et al studied 32 collegiate runners and found that baseline brachial diameters were similar, but that brachial flow-mediated dilation (FMD) was significantly lower in amenorrheic compared with oligomenorrheic and eumenorrheic athletes [74]. Rickenlund et al studied FMD and lipid profiles in endurance athletes with amenorrhea ($n=14$), oligomenorrhea ($n=9$), eumenorrhea ($n=12$), and sedentary eumenorrheic controls ($n=12$). FMD was significantly decreased in the amenorrheic athletes compared with all other groups, and the amenorrheic athletes also had the most unfavorable lipid profile (higher total cholesterol and LDL) compared with the other athlete groups [75]. Yoshida et al

studied 26 teenage volleyball players (12 amenorrheic, 14 eumenorrheic) and 10 eumenorrheic nonathlete controls [76]. As above, FMD was lowest in the amenorrheic athletes. Serum estradiol levels were lower in the amenorrheic athletes compared with the other 2 groups, and levels positively correlated with vascular function. In addition, restored vascular function was associated with increased serum estrogen levels in the amenorrheic athletes who became eumenorrheic in follow-up after quitting strenuous sport activity [76]. In a study of 22 professional ballet dancers, 64 % had decreased FMD (<5 %). FMD results were significantly correlated with serum estrogen and whole-body and lumbar BMD.

Interestingly, Hoch et al demonstrated improvement in FMD in amenorrheic runners and dancers following 4 weeks of folic acid ingestion (10 mg/day), highlighting a potential treatment [78, 79]. However, further work is necessary to better understand the long-term effects of amenorrhea on cardiovascular health and to identify prevention and treatment strategies.

Injury and triad risk factors

Prior studies report relationships between the Triad components and fracture, particularly among groups of athletes with the highest incidence of stress fracture, such as endurance runners and dancers. Runners and/or ballet dancers with a history of fracture have exhibited higher levels of DR [80], restrictive eating [81], or a more prevalent history of anorexia nervosa or bulimia nervosa [82]. Two prospective studies (2–5 years in length) of track and field or cross-country athletes found that menstrual irregularity was a significant independent predictor of stress fracture [81, 83], while several cross-sectional studies found an association between a history of fracture and amenorrhea or oligomenorrhea [82–88]. Previous research evaluating associations between bone mass and stress fracture have yielded conflicting results, with some reports exhibiting lower bone mass among athletes with fracture [83, 89] and others reporting no association [84, 85, 90, 91]. One study by Marx et al observed associations between low bone mass and fracture at sites high in cancellous bone [92].

Recent research since 2008 has additionally confirmed relationships between Triad components and the development of musculoskeletal injury (including fractures and nonfracture injuries) in most, but not all, studies among adolescent athletes. Rauh et al, in a prospective study occurring over 1 season, found that injured athletes reported significantly higher EDE-Q subscale scores, had a lower lumbar spine BMD, and identified both menstrual dysfunction and low BMD as significant independent predictors of injury incidence [93•]. Thien-Nissenbaum et al [94], in their study among 311 high school athletes, additionally found that meeting criteria for disordered eating, but not menstrual

dysfunction, significantly predicted overuse injury. These studies document relationships between components of the Triad and all musculoskeletal injury, suggesting that conditions consistent with low energy availability may also affect the durability of tissues such as muscle, tendon, and ligaments. Interestingly, Tenforde et al [95], in their retrospective study that evaluated history of overuse injury in 442 female and 306 male adolescent athletes did not observe a relationship between self-reported menstrual dysfunction or disordered eating and injury history. Therefore, further research is necessary to explore these relationships.

Two recent case reports by Okamoto et al [96], and Goolsby et al [97] describe competitive endurance runners age 17 years and 15 years who developed a displaced femoral neck fracture while running on untreated femoral neck stress fractures. Both athletes exhibited either primary or secondary amenorrhea and had a history of strict dieting or a clinical eating disorder, weight loss, and low body weight. Interestingly, BMD levels measured by DXA for both athletes were within the normal range, though the older runner did not have measurements of sites high in trabecular bone such as the hip and spine (only calcaneus). These observations underscore the need to explore microarchitectural aspects of bone and their relationship to fracture and emphasize a devastating potential outcome associated with the Triad.

Female athlete triad: screening and treatment, and prevention

Screening

The Female Athlete Triad Coalition developed 12 questions recommended for inclusion in pre-participation exams (PPEs) [98]. In a study performed by Mencias et al [99], team physicians or athletic trainers at all 347 NCAA Division I universities were contacted to participate in a survey regarding specific Triad questioning used in their PPEs. Two-hundred fifty-seven universities (74 %) participated in the survey, all of which reported requiring PPEs for incoming athletes. However, only 32 % required an annual PPE for returning athletes. Only 9 % had 9 or more of the 12 recommended Triad-related questions as part of their PPEs, and 44 % of the participating universities included 4 items or fewer [99].

The above study illustrated both the lack of annual Triad screening in Division I schools, as well as the incompleteness of Triad questioning when it was performed. However, in 2010, the fourth edition of the PPE history and physical examination form endorsed by the American Academy of Family Physicians, American Academy of Pediatrics, American College of Sports Medicine, American Medical

Society for Sports Medicine, American Orthopaedic Society for Sports Medicine, and the American Osteopathic Academy of Sports Medicine was published. This now serves as the recommended tool for use with PPEs for athletes in middle school through college and addresses 8 of the 12 items recommended by the Female Athlete Triad Coalition position stand. The frequency of its usage has not yet been reported.

Treatment

The primary focus of treatment for the Triad is the modification of diet and exercise behaviors to increase energy availability weight restoration (if needed), subsequent resumption of menses, and ideally improvement of bone metabolism, bone mass, and strength. Because of the number of possible factors leading to low EA (eg, stressors, body image issues, poor nutrition, abnormal eating behaviors, inappropriate training, etc), a multidisciplinary approach, including a team consisting of a primary care and/or sports physician, dietitian, athletic trainer, and psychologist, is recommended [100]. While behavior change therapies, including dietary and exercise modifications, are recommended as the first line of treatment for the Triad, the efficacy of various pharmacological therapies has also been explored. The following paragraphs discuss updated evidence regarding various clinical and experimental pharmacological therapies.

Combined oral contraceptive pills (OCPs), consisting of various doses of ethinyl estradiol and various doses and types of progestones, have been recommended in the past to treat Triad. However, OCP use in amenorrheic athletes and the effects on BMD improvement and stress fracture prevention is controversial, with some studies reporting an increase, some a decrease, and some no change in BMD and stress fracture incidence [101]. These studies are limited by different OCP formulations, small sample size, noncompliance, dropout rates, weight gain, spontaneous resumption of menses in controls, self-reported menstrual status, and undocumented stress fractures. Furthermore, replacing estrogen does not adequately address the fluctuations of other hormones in Triad patients (eg, follicle-stimulating hormone (FSH), luteinizing hormone (LH), leptin, ghrelin, insulin-like growth factor-1 (IGF-1), triiodothyronine (T3), growth hormone (GH), cortisol, etc).

In a report from 2011, Misra et al randomized 110 girls with AN (ages 12–18 years) to either a transdermal patch with a physiologic replacement dose of estradiol along with cyclic oral progesterone, or placebo. Both spine and hip BMD improved in the treatment vs the placebo group over the 18-month trial [102]. The transdermal delivery of estrogen may be beneficial to bone partially because of the lack of suppression of endogenous IGF-1. A similar study is now

being conducted in amenorrheic athletes. Sienkiewicz and colleagues studied 20 strenuously exercising young women with hypoleptinemia (<5 ng/mL) and amenorrhea of at least 6 months. Eleven were randomized to recombinant methionyl human leptin (metreleptin) and 9 were randomized to placebo for 9 months. Metreleptin significantly increased lumbar bone mineral content (BMC) and lumbar spine BMD trended higher at 9 months in the entire sample (intention-to-treat analysis) [103]. Unfortunately, 1 common side-effect of metreleptin is weight-loss, requiring dosing adjustments during treatment. This pilot study is promising, but longer, larger trials are needed, with the feasibility of metreleptin dosing changes addressed [103].

Bisphosphonates are antiresorptive agents, used in postmenopausal osteoporosis, that inhibit osteoclast function. Low EA and amenorrhea can both increase bone loss and suppress formation, therefore, since bisphosphonates act by inhibiting bone resorption, they do not address the issue of reduced bone formation. Additionally, long-term effects of bisphosphonates on the BMD of Triad patients are unknown, and bisphosphonates are not recommended in this population secondary to the long half-life of these drugs (up to 10 years) and their potential teratogenic effects [101].

Prevention

Knowledge of the Triad is an important component of prevention. Of 180 female exercisers (ages 18–40 years) in Australia, only 10 % could name all 3 components of the Triad, and 45 % did not think amenorrhea could affect bone health. Twenty-two percent of those in lean-build sports reported that they would do nothing if they were amenorrheic. Interestingly, participation in lean-build sports, a history of amenorrhea, and a history of stress fracture were all correlated with not taking action to correct the amenorrhea [104]. In an American study of 103 female high school track athletes, ≥ 90 % provided incorrect answers about consequences of bone loss and the link to menstrual irregularity [105]. Thus, improving athletes' knowledge and attitudes regarding the Triad is paramount.

Recently, several athlete-focused disordered eating prevention programs have been evaluated. During an 8-week program known as ATHENA, coaches and peers led sessions with high school athletes. These sessions addressed depression, self-esteem, healthy norms, societal pressures to be thin, and steroid use. Athletes who underwent the ATHENA program reported less diet pill use and positive improvements in diet habits and exercise self-efficacy compared with those who only received educational pamphlets. In up to 3 years of follow-up, athletes in ATHENA showed reductions in marijuana and alcohol use, but unfortunately

not in eating pathology [106]. Other notable methods are cognitive dissonance-based prevention (DBP), where participants discuss and actively confront the thin-ideal standard of female beauty through various activities in order to create cognitive dissonance, and the healthy weight prevention intervention (HWI), where participants are encouraged to make small lifestyle changes in dietary and exercise habits to maintain a healthy weight. Becker et al compared an athlete-modified DBP (AM-DBP) and an athlete-modified HWI (AM-HWI) program in a study of 157 female collegiate athletes [107]. Both interventions reduced thin-ideal internalization, dietary restraint, bulimic pathology, shape and weight concern, and negative affect at 6 weeks, and bulimic pathology, shape concern, and negative affect at 1 year. There was also an increase in students spontaneously seeking medical consultation for female athlete triad [107]. Larger studies with longer follow-up periods are needed.

Conclusions

A number of recent findings related to the Female Athlete Triad have emerged, particularly related to the epidemiology of the Triad among adult and adolescent athletes, microarchitectural aspects of bone, physiological, and injury consequences associated with the Triad, pharmacological treatment, and prevention programs geared toward improving body image and reducing the occurrence of high risk behaviors. Future prospective investigations evaluating the development and progression of the Triad are needed to better understand Triad predictors and long-term consequences. Additional studies addressing the efficacy of behavioral strategies are needed to aid in the development of additional evidence-based treatment recommendations.

Conflict of interest Michelle T. Barrack declares that she has no conflict of interest. Kathryn E. Ackerman declares that she has no conflict of interest. Jenna C. Gibbs declares that she has no conflict of interest.

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