

Female Athlete Triad Treatment Guidelines

Overview

The female athlete triad, first recognized in 1992, is a spectrum disorder with three interrelated components:

1. Low energy availability due to disordered eating, an eating disorder, or inadequate nutrition relative to caloric expenditure
2. Menstrual dysfunction
3. Low bone mineral density

These treatment guidelines provide recommendations based on the 1st (San Francisco, CA, USA) and 2nd (Indianapolis, IN, USA) International Symposia on the Female Athlete Triad. They are intended to guide physicians, athletic trainers, and other healthcare providers in the clinical management of the triad.

List of acronyms used

Below are selected of the acronyms used throughout the handout:

- **BMC:** Bone mineral content
- **BMD:** Bone mineral density
- **BMI:** Body Mass Index.
- **CBT:** Cognitive behavioural therapy
- **COC:** Combined oral contraceptive
- **DE:** Disordered eating
- **DHEA:** Dehydroepiandrosterone
- **EA:** Energy availability
- **ED:** Eating disorder
- **FHA:** Functional hypothalamic amenorrhea
- **FFM:** Fat-free mass
- **IGF-1:** Insulin-like growth factor 1
- **rhIGF-1:** Recombinant human insulin-like growth factor-I
- **RMR:** Resting metabolic rate

Non-pharmacological treatment guidelines for the clinical sequelae associated with the triad

- An optimal treatment approach must address the underlying cause of the triad, that is, low EA.
- Energy status must be normalized primarily through modifications of diet and exercise training, if necessary, with the goal of increasing EA.
- Recommendations should focus on restoring or normalizing body weight as the best strategy for the successful resumption of menses and improved bone health.
- The development of any triad treatment plan should consider the athlete's goals, unique diet and training practices, any coexisting conditions, and a system for monitoring changes.

Specific non-pharmacological recommendations for interventions in athletes with low EA

- Specific treatment recommendations depend on identifying *how* low EA is developed in the athlete. There may be four unique pathways to low EA and, as such, four unique treatment recommendations:
 1. If the cause of low EA is inadvertent undereating, then referral for nutritional education is sufficient. Nutritional education should ideally include a sports dietitian. An exercise physiologist can also complete an assessment of energy expenditure and EA.
 2. If the cause of low EA is DE, the patient should be referred to a physician for nutritional counselling with a sports dietitian.
 3. If the cause for low EA is intentional weight loss without DE, then referral for nutritional education is sufficient.
 4. If the cause of low EA involves clinical ED, treatment should include evaluation and management with a physician, nutritional counselling with a sports dietitian, and referral to a mental health practitioner for psychological treatment. In this case, reversing low EA will not be possible without psychological treatment.

Specific treatment targets of low EA

- Specific treatment targets may include one or more of the following:
 - Reversal of recent weight loss;
 - Return to a body weight associated with normal menses;
 - Weight gain to achieve a BMI of 18.5 kg/m² or 90 percent of predicted weight;
 - Energy intake should be set at a minimum of 2000 kcal/day; or, more likely, a greater energy intake will be required, depending on exercise energy expenditure.
- Recommendations should consider individual preferences and may depend on where the athlete is in the competitive season (reductions in training volume may not be feasible in season; acceptance of reductions in training volume may be better received vs increased energy intake).

- Prescribed changes in energy intake to achieve an increased BMI and/or body weight goal should be gradual, beginning with an approximately 20–30% increase in caloric intake over baseline energy needs, or the amount of energy required to gain approximately 0.5 kg every 7–10 days.

For an athlete consuming 2000 kcal/day, this would represent a gradual increase of 200–600 kcal/day, accomplished over several months. If EA (intake kcal–exercise kcal)/kg of FFM can be reliably estimated, the target should be at or greater than 45 kcal/kg of FFM.

Steps in a plan to increase EA

1. Perform an assessment of baseline energy needs that includes a thorough body weight history including questions about associated changes in menstrual status. Energy intake can be assessed using diet logs and dietary analysis programs.

Energy expenditure can be estimated by measuring or estimating RMR and exercise energy expenditure. RMR can be estimated using one of the several algorithms and multiplying by an activity factor will account for exercise energy expenditure, thereby providing an estimate of total energy expenditure needs.

2. Using the appropriate target for EA, meal plans should be developed that incorporate a variety of factors. Specifically, diet quality, diet variety, food preferences and practical aspects of food availability should be considered. Goals would include achieving an adequate balance of macronutrients and an appropriate intake of micronutrients, particularly calcium, vitamin D, iron, zinc and vitamin K.

Whenever possible, the recommendation should be to increase intake of real foods versus dietary or meal supplements. Dietary recommendations should include incorporation of energy and nutrient-dense foods such as fortified milk drinks and essential fatty acids in the form of fish, healthy oils, nuts avocados and dried fruit. If there is a possibility of gastrointestinal discomfort with high caloric loads, small and frequent meals should be consumed throughout the day, with timing dependent on practice and competition.

Particular attention should be paid to identifying times across the day when dietary energy intake may be particularly low. Adjustments in dietary strategies for increasing EA should also take into account changes across the season in accordance with competition schedules.

A successful treatment plan requires standardized periodic monitoring of body weight. Athletes should be weighed on the same scale and should wear minimal clothing, such as shorts and a t-shirt, to reduce the likelihood of falsifying their weight.

The frequency of weight monitoring depends on the degree to which weight determines health and eligibility to participate in sport. A reasonable frequency is weekly when initiating treatment programs.

Specific recommendations that target ED

- The goals of treatment for exercising women with ED are to normalize pathological eating behaviours, reduce dieting attempts, and alter negative emotions and beliefs associated with food and body image.
- Cognitive behavioural therapy has been demonstrated to be an effective treatment approach for exercising women with ED and may be more beneficial than nutritional counselling alone in some women with amenorrhea, particularly if DE behaviour is present.

Specific recommendations that target low BMD

- In exercising women with low BMD, the focus should be on increasing EA, optimizing weight gain, and resuming menses. Calcium and vitamin D status should also be addressed.
- Weight-bearing exercise is a primary non-pharmacological strategy for increasing and maintaining BMD and geometry across the lifespan.

Recommended time course of non-pharmacological treatment (including follow-up)

- Treatment of the triad conditions by increasing EA will result in the recovery of physiological systems at different rates. Notably, the time to the resumption of menses may vary among exercising women and is dependent on the severity of the energy deficiency and duration of menstrual dysfunction.
- An increase in EA can positively alter metabolic hormone profiles within days to weeks, with concomitant changes in body weight occurring over weeks and months. Weight gain has been observed as a clinically positive outcome associated with the resumption of menses and enhanced bone health in exercising women.
- Recovery of menstrual function with strategies to increase EA can occur within several months but may take longer than one year.
- Improvements in BMD will occur more slowly, often over several years. Whether or not BMD can be restored to levels appropriate for age and training status remains unclear.

Pharmacological treatment strategies for the clinical sequelae of the triad

- Non-pharmacological measures should constitute initial management in female athletes with the triad.
- For the treatment of osteoporosis and/or in athletes with multiple fracture histories, pharmacological management is to be considered if there has been a lack of response to nonpharmacological therapy for at least one year and if new fractures occur during nonpharmacological management.

- Pharmacological management may also be necessary for the psychological treatment of ED and DE, especially if there are significant comorbid conditions.

Strategies for low energy availability, disordered eating, and eating disorders

- Individuals who have unintentional low EA or mild DE may respond well to nutritional education designed to eliminate low EA.
- Individuals with significant DE may benefit from counseling with a mental health practitioner in addition to nutritional education.
- In contrast, individuals who have an ED require intensive interdisciplinary attention and treatment.
- Antidepressant medications, particularly selective serotonin reuptake inhibitors, can be helpful in the treatment of bulimia nervosa.
- Other psychotropic medications can be beneficial in treating comorbid conditions, such as anxiety, depression, and obsessive-compulsive behavior.

Strategies for menstrual dysfunction

- Pharmacological strategies that target menstrual dysfunction are mostly experimental, as are strategies to optimize bone accrual in the adolescent athlete and to optimize BMD in adult athletes and exercising women defined as at least 20 years old.
- When considering pharmacological strategies to address amenorrhea and hypoestrogenemia in athletes and exercising women, it is essential to reiterate that combined oral or non-oral routes of contraceptive therapy do not restore spontaneous menses; indeed, contraceptive therapy simply creates an exogenous ovarian steroid environment that often provides a false sense of security when induced withdrawal bleeding occurs.
- Combined oral contraceptive therapy is not consistently associated with improved BMD in amenorrhoeic athletes and may, in fact, further compromise bone health given first-pass effects on hepatic production of insulin-like growth factor-1 or IGF-1, an important bone trophic hormone.
- Non-pharmacological treatment strategies should be prioritized, particularly focusing on achieving the resumption of menses.

Strategies for replacement of gonadal steroids

- Oral oestrogen–progesterone combination pills are not an effective strategy to increase BMD in low-weight conditions such as anorexia nervosa (in adults and adolescents).
- Pharmacological treatment that aims to restore regular menstrual cycles with COC does not normalize metabolic factors impairing bone health and will, therefore, likely not result in the reversal of low BMD in the athlete with triad disorders.
- Transdermal oestradiol administration, when given in replacement doses, does not suppress IGF-1 and, therefore, warrants further investigation as an alternative to COC therapy in the amenorrhoeic female athlete with the triad.

- Vaginal oestradiol administration also circumvents hepatic first-pass metabolism, and a vaginal oestrogen-progesterone combination contraceptive ring is now available.
- There is no data available on testosterone administration in amenorrhoeic athletes and exercising women.

Strategies for normalizing gonadotropin pulsatility and secretion

- Few studies have examined the impact of administering metreleptin to women with FHA. Although metreleptin improved ovulatory status and increased BMC in women with FHA, the women sustained significant weight loss and reductions in fat mass, even when doses of the drug were carefully titrated.
- Low IGF-1 is an important contributor to low BMD in amenorrhoeic athletes and exercising women, particularly in those who are low-weight. In adolescents and adults with anorexia nervosa, administering recombinant human IGF-1 (rhIGF-1) increases the levels of surrogate bone formation markers.

Strategies for bone mineral density

- Data are lacking regarding the efficacy of pharmacotherapy in treating low BMD with or without a fracture history in female athletes.
- While pharmacological therapy is recommended in postmenopausal women and men \geq age 50 years with osteoporosis, the threshold for pharmacological treatment in young female athletes with low BMD, stress fractures, and/or impaired bone accrual is less clear.
- Athletes with triad risk factors who sustain bone stress injuries may have a delay in return to sports.
- Treating or not treating with pharmacological therapies does not depend on BMD Z-scores alone but also on additional risk factors such as fracture history, genetics, and cumulative triad risk factors, which have been associated with an increased risk for low BMD and bone stress injury and the rate of bone loss with non-pharmacological management.
- Caution should be exercised when considering FDA-approved postmenopausal treatment strategies for use in premenopausal women and children, including Triad athletes and exercising women. Bisphosphonates have a very long half-life and should be used with extreme caution in women of childbearing age because of concerns about teratogenicity.

Pharmacological treatment considerations

Athletes and exercising women who should be targeted for pharmacological therapy

- Non-pharmacological therapy is the mainstay of treatment for all athletes with one or more components of the triad.
- There is no evidence at this time to *unequivocally recommend* pharmacological therapy in athletes with female athlete triad disorders due to the lack of evidence-based research in this population.

- Pharmacological therapy may be considered in an athlete with:
 - BMD Z-scores ≤ -2.0 with a clinically significant fracture *AND* lack of response to at least 1 year of non-pharmacological therapy (a mainstay of treatment).
 - BMD Z-scores between -1.0 and -2.0 with a clinically significant fracture history and \geq two additional Triad risk factors *AND* lack of response to at least a year of non-pharmacological therapy.
- Transdermal oestradiol replacement with cyclic progesterone may be considered in young athletes ≥ 16 and < 21 years of age with FHA to prevent further bone loss during this critical window of optimal bone accrual if they have:
 - BMD Z-scores ≤ -2.0 without a clinically significant fracture history and at least one additional Triad risk factor *AND* lack of response to at least 1 year of non-pharmacological therapy.
- Lack of response to therapy has been defined as:
 - A clinically significant reduction in BMD Z-scores after at least 1 year of non-pharmacological therapy; or
 - Occurrence of new clinically significant fractures during non-pharmacological treatment over 1 year.
- Further research is warranted to assess the outcomes of pharmacological management and potential risks in this population.
- There are no current treatments approved by the FDA for this specific population.
- Further research on pharmacological treatment alternatives is needed in this higher-risk group of athletes with low BMD and fracture history, as well as those with low BMD without a fracture history.

Therapy that can be offered

Increasing EA and optimizing energy status

- All athletes and exercising women, particularly those who are considered candidates for pharmacological therapy, should be counseled regarding lifestyle and behavioral changes to increase EA and optimize energy status.
- Non-pharmacological management should continue, even if pharmacological therapy is prescribed.

Calcium and vitamin D

- Calcium-rich foods should be recommended, with optimal calcium intake between 1000 and 1300 mg/day.
- Vitamin D status should be optimized. The recommendation is an intake of 600 IU of vitamin D for adolescents and adults up to age 70. Higher doses may be needed if they are deficient or insufficient in vitamin D. It is recommended that vitamin D levels be maintained between 32 and 50 ng/mL.

Oestrogen administration in female athletes with FHA or prolonged oligomenorrhoea who have failed non-pharmacological management

- In athletes and exercising women with FHA and prolonged amenorrhea of hypothalamic origin who meet the criteria for pharmacological therapy, a reasonable option is estrogen administration with cyclic progesterone after ruling out other causes of amenorrhea. It is also essential to consider the contraceptive needs of the athlete. Before starting therapy, a thorough history and examination should be conducted to rule out contraindications for oestrogen therapy.
- COC therapy containing 20–35 µg of ethinyl oestradiol may maintain BMD in those with very low BMD measures, although data are not definitive. Most of the studies in adolescents and adults with anorexia nervosa and in amenorrhoeic athletes suggest that COC therapies are not effective in increasing BMD or in reducing stress fractures, although they are effective for contraceptive needs when used in recommended doses.
- Transdermal oestradiol (100 µg of 17β oestradiol) with cyclic progesterone maintains BMD Z-scores in adolescents with anorexia nervosa and is a consideration for low-weight, amenorrhoeic athletes who meet the criteria for pharmacological intervention. Athletes who are symptomatic with this dose for oestrogen-related side effects such as nausea, bloating, and breast tenderness may be started on a lower dose of the transdermal patch (50 µg) and the dose increased to 100 µg after 1 month.
- Cyclic progesterone is necessary in those on transdermal oestradiol to avoid deleterious effects of unopposed oestrogen on the uterine lining, and 200 mg of micronized progesterone or 5–10 mg of medroxy progesterone acetate is recommended for 12 days of every month.
- Of importance, the combination of transdermal oestradiol and cyclic oral progesterone in the described doses has unproven contraceptive efficacy, and other contraceptive methods are necessary if contraception is desired.
- If oestrogen replacement is considered in an athlete with a known or family history of thrombophilic disorders, it is recommended to consult with a hematologist to assess whether tailoring the oestrogen dose, route and regimen to minimize risk is an option, with the full-written informed consent of the patient. If oestrogen replacement is instituted, management should include ongoing follow-up with a hematologist.
- Testosterone, DHEA, leptin, or rhIGF-1 replacement is not recommended at this time in athletes who meet the criteria for pharmacological therapy due to a lack of studies in the female athlete population and potential adverse effects.

When should pharmacological options other than oestrogen be considered as options for treatment?

Pharmacological options other than oestrogen replacement/COC

- In rare instances, pharmacological management other than oestrogen replacement/COC therapy can be considered when athletes meet the criteria for osteoporosis and, have failed non-pharmacological therapy (with recurrent fractures), and meet one of the following criteria
 - Contraindications to oestrogen;

- Lack of response to oestrogen replacement after ≥ 18 –24 months in a compliant patient;
 - Eumenorrhoeic athletes/exercisers (not hypoestrogenic) who meet the criteria for therapy;
 - Athletes with multiple debilitating fractures and significant morbidity.
- For the last two indications, patients should undergo a complete metabolic work-up, and genetic testing may be considered depending on the patient's and her family's history.
 - Other pharmacological options include bisphosphonates and teriparatide, which are effective strategies for treating postmenopausal osteoporosis and osteoporosis in special populations, but for whom data are limited, that is, in younger women, including female athletes. If such options are considered, the athlete/exerciser should be referred to an endocrinologist or an expert in metabolic bone diseases for further management, and treatment should be implemented *only* in conjunction with the endocrinologist or expert in metabolic bone disorders.
 - Teriparatide is administered once daily as a subcutaneous injection and is bone anabolic. While this is a promising agent in adult athletes and studies are ongoing, data regarding its efficacy in a younger population are lacking at this time.
 - Bisphosphonates are effective in increasing BMD in adult women with anorexia nervosa, but should be considered in athletes who meet criteria for pharmacological intervention with options other than oestrogen replacement, *only when no other* strategy is effective or when other strategies are contraindicated.
 - Reproductive-age women taking bisphosphonates should be prescribed birth control measures and counseled at length regarding the very long half-life of these medications and potential teratogenic effects on the fetus should pregnancy occur. If bisphosphonate therapy is prescribed, a time limit for these ongoing treatments, as in adults, should be considered due to the potential risks of prolonged therapy.

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