Premenopausal osteoporosis is not an infrequent cause of referral for clinical evaluation in younger women. Patients typically sustain one or more low-trauma fractures in unexpected circumstances. Further evaluation leads to bone density testing and basic laboratory assessment. There are many potential secondary causes of bone loss that may lead to fracture in younger women, but the female athlete triad is an increasingly recognized cause in those who participate in intense athletic activity, usually while still in school or while at university, but sometimes after university in women in the third decade who continue to pursue intense physical activity. The triad may be seen in ballet dancers, long-distance runners, or other athletes who restrict caloric intake to enhance performance.

The female athlete triad classically includes restrictive eating, amenorrhea, and osteoporosis [1]. Restrictive eating leads to low energy availability, as does intense physical activity during training or competition [2]. Low energy availability may be associated with disordered eating or an eating disorder, but not always. Patients with the triad consequently have a low body mass index (BMI). This may lead to delayed menarche, and oligomenorrhea or amenorrhea associated with functional hypothalamic amenorrhea evidenced by low serum estradiol and gonadotropins [3], which leads to increased bone turnover and rapid bone loss. Patients typically have low bone mineral density (BMD) that eventually leads to stress reaction or fracture, commonly in the lower extremities [4,5].

According to the Female Athlete Triad Coalition [1], risk factors leading to the female athlete triad include at least one of the following “high risk” triad risk factors: DSM-5-diagnosed eating disorders; BMI ≥ 17.5 kg/m², body weight of < 85% expected weight, or weight loss of > 10% in one month; menarche at ≥ 15 years; current or past history of < 6 menses over 12 months; two or more stress reactions or fractures, one high-risk stress reaction/fracture, or a low-energy non-traumatic fracture; or a bone density Z-score < −2.0. It may also be diagnosed with at least two “moderate risk” triad risk factors, including: disordered eating for ≥ 6 months; BMI between 17.5 and 18.5 kg/m², body weight of 85–90% expected weight, or recent weight loss of 5–10% in one month; menarche between 15 and 16 years; 6–8 menses over 12 months; one prior stress reaction/fracture; or BMD Z-score between − 1.0 and − 2.0. It may also be diagnosed with ≥ 1 nonperipheral or ≥ 2 peripheral, long-bone traumatic fractures if there are ≥ 1 moderate or high risk triad risk factors. The Coalition issued a Cumulative Risk Assessment for the Female Athlete Triad in its 2014 paper, to give a more objective way of determining an individual athlete’s risk using risk stratification and evidence-based risk factors.

Treatment of this condition begins with first recognizing the disorder. Patients not likely to have this disorder include female athletes who do not practice dietary restriction, have a BMI > 18.5, or body weight ≥ 90% expected weight, or those not losing weight, with menarche at age < 15 years, > 9 menses in 12 months, BMD Z-score > −1.0, and no history of stress reaction/fracture.

Patients with the female athlete triad benefit from increased caloric intake, decreased physical activity, or both, as long as they are willing to do this. Target body weight should ideally be ≥ 90% of ideal body weight for height. Achieving these goals usually will cause menses to resume and bone density to increase [6]. Cognitive behavioral therapy is recommended for those with irregular eating behavior or a distorted body image who may be resistant to gaining weight or reducing exercise [7]. Baseline bone density should be rechecked after one year to make sure this is improving as expected. Menstrual function should resume with weight regain and reduced physical activity, but if it does not, hormone therapy may be considered [8]. In adolescents and younger women, physiologic 17-beta estradiol may be used transdermally if menses have not resumed after 6–12 months, in combination with cyclic progesterone for endometrial protection. Oral contraceptives with progesterone may be used in older women without contraindications.

Bisphosphonates or denosumab are usually not given to premenopausal women due to risk to future pregnancies, unless hormone therapy is contraindicated or has been found to be ineffective in preventing fractures [9]. Teriparatide or abaloparatide could be used for up to two years in premenopausal women with very low BMD and fractures not responding to hormone therapy or with delayed fracture healing, but this is off-label and may not be covered by insurance [10]. After stopping these anabolic agents, bisphosphonate or denosumab would typically be given to prevent the rapid bone loss that will otherwise occur.Raloxifene is not used in premenopausal women because it may cause bone loss. There is no published experience with romosozumab or calcitonin in this setting.

It is important for clinicians to recognize secondary causes of bone loss in premenopausal women that will limit acquisition of peak bone density before the late third or early fourth decade, and that may cause bone loss after achievement of peak bone density. Unlike many of the more familiar secondary causes, the female athlete triad may be completely prevented or treated initially with nonpharmacological therapy, including reduced physical activity and weight regain with adequate nutrition. If these interventions are successful, peak bone density is likely to be achieved, and osteoporosis and fractures prevented. In patients resistant to weight regain or increased calorie
intake, physiological hormone therapy may be added. If these interventions do not work adequately, then women with the female athlete triad may be treated with the less frequently used pharmacologic therapy as described. Starting pharmacologic therapy early in life may consign patients to longer exposure to agents that were initially intended only for postmenopausal women, with the attendant risks.

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References

[1] M.J. De Souza, A. Nativ, E. Joy, et al., Expert panel, 2014 Female athlete triad coalition consensus statement on treatment and return to play of the female athlete triad: 1st international conference held in San Francisco, California, May 2012 and 2nd international conference held in Indianapolis, Indiana, May 2013, Br. J. Sports Med. 48 (2014) 289, https://doi.org/10.1136/bjsports-2013-093218.

[2] M.P. Warren, N.E. Perirotto, The effects of intense exercise on the female reproductive system, J. Endocrinol. 170 (2001) 3–11, https://doi.org/10.1677/joe.0.1700003.

[3] L. Falsetti, A. Gambra, L. Barbetti, C. Specchia, Long-term follow-up of functional hypothalamic amenorrhea and prognostic factors, J. Clin. Endocrinol. Metab. 87 (2002) 500–505, https://doi.org/10.1210/jc.87.2.8195.

[4] D.R. Weber, A. Boyce, C. Gordon, et al., The utility of DXA assessment at the forearm, proximal femur, and lateral distal femur, and vertebral fracture assessment in the pediatric population: 2019 ISCD Official Position, J. Clin. Densitom. 22 (2019) 567–589, https://doi.org/10.1016/j.jocd.2019.07.002.

[5] N.J. Crabtree, A. Arabi, L.K. Bachrach, et al., International Society for Clinical Densitometry. Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD pediatric official positions, J. Clin. Densitom. 17 (2014) 225–242, https://doi.org/10.1016/j.jocd.2014.01.003.

[6] C.M. Gordon, K.E. Ackerman, S.L. Berga, et al., Functional hypothalamic amenorrhea: an Endocrine Society Clinical Practice Guideline, J. Clin. Endocrinol. Metab. 102 (2017) 1413–1439, https://doi.org/10.1210/jc.2017-00131.

[7] V. Michopoulos, F. Mancini, T.L. Loucks, S.L. Berga, Neuroendocrine recovery initiated by cognitive behavioral therapy in women with functional hypothalamic amenorrhea: a randomized, controlled trial, Fertil. Steril. 99 (2013) 2084–2091, https://doi.org/10.1016/j.fertnstert.2013.02.036.

[8] M. Mira, D.K. Katzman, N.M. Estella, et al., Impact of physiologic estrogen replacement on anxiety symptoms, body shape perception, and eating attitudes in adolescent girls with anorexia nervosa: data from a randomized controlled trial, J. Clin. Psychiatry 74 (2013) e765–e771, https://doi.org/10.4088/JCP.13m08365.

[9] K.K. Miller, E. Meenaghan, E.A. Lawson, et al., Effects of risedronate and low-dose transdermal testosterone on bone mineral density in women with anorexia nervosa: a randomized, placebo-controlled study, J. Clin. Endocrinol. Metab. 96 (2011) 2081–2088, https://doi.org/10.1210/jc.2011-0380.

[10] P.J. Fazel, L.S. Wang, K.K. Miller, et al., Teriparatide increases bone formation and bone mineral density in adult women with anorexia nervosa, J. Clin. Endocrinol. Metab. 99 (2014) 1322–1329, https://doi.org/10.1210/jc.2014-4105.

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