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Review paper

Female athlete triad and relative energy deficiency in sport – endocrine changes and treatment in women

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Abstract

Introduction: Female athlete triad (FAT) it is a syndrome of three tightly interrelated components: amenorrhea, eating disorder, and osteoporosis. FAT syndrome has been re-evaluated and re-defined and the International Olympic Committee introduced a new relative energy deficiency in sport (RED-S) syndrome.

Aim: The aim of the study was to review the knowledge on the issues of endocrine changes occurring in FAT and RED-S, and treatment of those conditions on a basis of available literature.

Material and methods: This article was based on a review of the literature search in the electronic databases Medline (PubMed), EBSCO, ClinicalKey, and Willey Online Library, using the terms: 'female athlete triad,' 'relative energy deficiency in sport,' 'FAT and RED-S and endocrine changes,' 'low energy availability (LEA) and endocrine changes,' 'FAT and RED-S and treatment and women'.

Results and discussion: LEA influences abnormal secretion of gonadotropin-releasing hormone (GnRH) and this leads to the disrupted follicle-stimulating hormone (FSH) and luteinising hormone (LH) secretion. Higher ghrelin levels inhibit secretion of GnRH and of adrenocorticotropic hormone (ACTH), growth hormone (GH), FSH and LH. A high peptide YY (PYY) results in a significant suppression of GnRH secretion. Hypercortisolemia occurring in athletes may directly affect reproductive functions. Lack of estrogen contributes both to disrupted mineralization of bones and to endothelial dysfunction.

Conclusions: Low energy levels found in female athletes diagnosed with FAT or RED-S syndrome significantly influence hormonal pathways, disrupting the function of their reproductive system, and this noticeably affects the overall health of sportswomen, influencing endothelial dysfunctions and bone mineral density.

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1. INTRODUCTION

A woman's monthly cycle is a complex physiological process and an indication that the reproductive system is functioning.[1] Menstrual disorders are most often caused by abnormalities at different stages of the hypothalamic-pituitary-ovary system. These abnormalities may result from various gynecological problems, but can also occur in healthy women due to the factors which this system is particularly sensitive to, such as stress, malnutrition, or physical activity exceeding the adaptation capacity of a woman's body.[2]

According to Frisch's[3] theory, menarche occurs when the adipose tissue comprises 17% of overall body weight, with a level of over 22% required to maintain regular menstrual cycles. The chronic limitation of energy availability inhibits reproductive functions and this is defined as functional hypothalamic amenorrhea (FHA), because it suppresses the hypothalamic-pituitary-ovary axis and alters its normal functioning.[4,5] FHA is a reversible disorder of the endocrine system that is characterized by abnormal hypothalamic function leading to secondary amenorrhea in women who previously experienced normal menstruation. The physiology of the hypothalamic-pituitary-ovarian axis is based on the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which in turn stimulates the release the follicle-stimulating hormone (FSH) and luteinising hormone (LH) from the anterior pituitary gland. The level of these hormones has a significant effect on the development of the uterine endometrium. Suppression of any of these links, at any stage, disrupts hormone circulation, shortens the luteal phase and inhibits the menstrual cycle. This reduced LH pulse frequency, described above, occurs regardless of whether energy availability is reduced by diet or exercise, or a combination of the two.[4,6]

Amenorrhea, osteoporosis and eating disorders are the three main components of female athlete triad (FAT) syndrome, which, to a lesser or greater degree, is widespread in many sport disciplines.[7–13] In recent years, FAT syndrome has been re-evaluated and re-defined and in 2014 the International Olympic Committee (IOC) introduced the relative energy deficiency in sport (RED-S) syndrome, which is very broadly described as the consequences, both physical and psychological, of an energy imbalance in the body.[14,15]

2. AIM

The aim of the study was to review the current knowledge on the endocrine changes and treatment of FAT and RED-S in women. This article focused on an attempt to summarize knowledge on various endocrine (hormonal) changes occurring in the human (athlete) body caused by the low availability of energy, which are frequently omitted in scientific publications on FAT and RED-S. Additionally, a brief description of the latest knowledge on FAT and RED-S treatment was presented.

3. MATERIAL AND METHODS

This article is based on a review of the literature search in the electronic databases Medline (PubMed), EBSCO, ClinicalKey, and Willey Online Library using the terms: 'Female Athlete Triad,' 'Relative Energy Deficiency in Sport,' 'FAT and RED-S and endocrine changes,' 'low energy availability and endocrine changes,' 'FAT and RED-S and treatment and women.' A total of 44 the most relevant publications for the topic of the article were included in this review. Inclusion criteria were: studies with humans, article written in English, the presence of keywords. The time framework for search of most important articles on the discussed subjects covered 2020–2022. Summary of the most relevant publications included in review is presented in Table 1.

4. RESULTS AND DISCUSSION

4.1. Endocrine changes caused by low energy availability (LEA)

The energy availability is understood as the amount of energy that remains in the body to maintain all physiological functions after taking into account the energy expenditure needed for physical (sports) activity. The optimal energy availability (EA) for a healthy physiological function is typically achieved at an EA of at leats 45 kcal/kg_{FFM} a day (188 kJ/kg_{FFM} a day).[7] The energy availability threshold, below which clinical consequences for the athlete's health occur, including a disrupted pulsatile release of FSH and LH, is defined as the energy availability of less than 30 kcal/kg_{FFM} a day (125 kJ/kg_{FFM} a day). It's worth noting that this amount of energy approximately corresponds to the average resting metabolic rate (RMR).[16]

The fat mass level affects the secretion of numerous endocrine hormones, such as GnHR, ghrelin, adipokines, peptide YY (PYY), insulin, oxytocin, cortisol, growth hormone (GH), insulin-like growth factor 1 (IGF-1), triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH).[17]

A relationship was found between LEA and the altered pulsatile GnRH secretion. LEA-related abnormal GnRH secretion in the hypothalamus leads to the disrupted secretion of FSH and LH by the pituitary gland, and this results in reduced estradiol and progesterone secretion by ovaries, insufficient folliculogenesis, and, in consequence, no ovulation.[5]

Ghrelin levels reflect the overall energy state of the body and are inversely related to fat mass, i.e., higher ghrelin levels indicate a lower energy status.[18] Ghrelin receptors are located inter alia in the hypothalamus, ovaries and pituitary gland. High levels of ghrelin can suppress the LH and FSH secretion. Therefore, it is thought that it negatively affects secretion of GnRH, adrenocorticotropic hormone (ACTH), and GH.[18]

The reduced adipose tissue content in the body may negatively affect the normal hormonal activity of the adipose tissue. This may be related to the release of endocrine hormones such as adipokines, which in turn affect the hypothalamic-pituitary-ovarian axis (HPO).[19,20] Adipokines, especially leptin,

Table 1. Summary of the most relevant publications included in systematic review.

Research	Participants	Mean age ± SD, y	Body mass index (kg/m²) or body mass (kg)	Hormones/Researchers findings
Gordon et al. (2017)	Review: An Endocrine Society Clinical Practice Guideline			FHA is a form of chronic anovulation, proximate cause of this is a functional reduction in GnRH, which results in LH and FSH levels insufficient to maintain full folliculogenesis and ovulatory ovarian function.
Lawson et al. (2013)	45 females: 15 amenorrheic athletes (AA) 15 eumenorrheic athletes (EA) 15 nonathletes (NA)	AA: 20.1 ± 0.4 EA: 18.5 ± 0.4 NA: 19.2 ± 0.3	20.9 ± 0.6 kg/m² 22.3 ± 0.6 kg/m² 21.6 ± 0.6 kg/m²	Nocturnal oxytocin levels were lower in AA and EA than in NA.
Schorr et al. (2015)	60 females 18 anorexia nervosa (AN) 21 normal-weight controls (HC) 21 overweight/obese (OB)	AN: 26 ± 6 HC: 27 ± 7 OB: 30 ± 8	18.2 ± 1.0 kg/m² 22.3 ± 1.4 kg/m² 31.2 ± 4.3 kg/m²	Mean cortisol levels were the highest in AN. Extreme underweight may activate the HPA axis. Hypercortisolemia may contribute to decreased bone mineral density (BMD) and muscle wasting in the setting of caloric restriction.
Ackerman et al. (2012)	59 adolescents and young adult women 21 amenorrheic athletes (AA) 18 eumenorrheic athletes (EA) 20 nonathletes (NA)	AA: 20.0 ± 0.4 EA: 18.7 ± 0.4 NA: 19.1 ± 0.4	20.9 ± 0.4 kg/m² 22.6 ± 0.6 kg/m² 21.7 ± 0.6 kg/m²	Percent of the body fat was associated positively with LH and leptin secretion and inversely with ghrelin. Higher ghrelin and lower leptin secretion in AA related to lower fat mass may contribute to altered LH pulsatility and amenorrhea.
Hoch et al. (2011)	22 elite dancers	23.2 ± 4.7	19.29 ± 1.1 kg/m²	Endothelial dysfunction was correlated with reduced bone mineral dentisity, menstrual dysfunction, and low serum estrogen. Association between athletic amenorrhea and a reduction in brachial artery flow-mediated dilation (FMD). Low FMD was associated with low estrogen concentrations.
Misra et al. (2011)	150 females: 110 girls with anorexia nervosa (AN) 40 normal-weight controls (C)	AN: 16.5 ± 0.2 C: 15.6 ± 0.2	16.9 ± 1.6 kg/m² 21.8 ± 3.7 kg/m²	Estrogen deficiency is an important determinant of low BMD. Physiological estrogen replacement is effective in prospectively halting BMD reductions.
Estour et al. (2010)	252 females: 210 subjects with restrictive-type anorexia nervosa (AN) 42 female controls (C)	AN: 23.1 ± 0.4 C: 23.3 ± 0.7	14.6 ± 0.1 kg/m² 21.4 ± 0.6 kg/m²	Several hormonal parameters were significantly lower in the group of AN compared with controls (IGF-I, free T3, free T4, 17β estradiol, LH, FSH, FTI, mean leptin, and osteocalcin), whereas mean cortisol, CTX (serum carboxy terminal cross-linked telopeptide of type I collagen), median GH level, and SHBG (sex hormone binding globulin) were higher.
Russel et al. (2009) (abstract)	amenorrheic athletes (AA) eumenorrheic athletes (EA)	12–18 years old		PYY was higher in AA than EA (111 ± 52 vs. 61 ± 29 pg/mL, $P < 0.05$), whereas adiponectin did not differ between groups. High PYY levels may be an important factor contributing to low bone density in athletes.
De Souza et al. (2003)	20 females: 10 sedentary (S) 10 excercising (E)	S: 26.6 ± 1.2 E: 28.8 ± 1.3	62.2 ± 5.1 kg 58.1 ± 1.6 kg	Exercising women with amenorrhea exhibit a hypometabolic state. Decrease in total T3, insulin, and leptin in exercising women.
Loucks et al. (2003)	29 healthy, regularly menstruating women	21 ± 1 20 ± 1 22 ± 1	59.7 ± 1.3 kg 59.1 ± 1.2 kg 60.0 ± 1.9 kg	The functionality of the hypothalamic–pituitary–gonadal axis in athletes depends on their state of energy availability. LH pulsatility was unaffected by an energy availability of 30 kcal/kg lean body mass per day, below this threshold LH pulse frequency decreased.

are strongly correlated with energy deficiency and disorders associated with the low body fat mass. In conditions of energy deficiencies, leptin levels in the human body are lower. The low leptin levels resulting from the low adipose tissue content may contribute to the changed GnRH pulsation, and this is reflected by parameters of pulsatile LH secretion.[19,20]

The reduced leptin level was noted in young amenorrheic athletes. It was demonstrated that when women with FHA were administered LH, their ovulation cycle was restored.[21]

Peptide YY is released by intestinal cells in response to calorie intake.[22–24] A high level of PYY, found in women who practice sports professionally, results in a significant suppression of GnRH secretion. It was demonstrated that the PYY levels are increased in women with EA and in athletes with amenorrhea.[23] Considering the above facts, a hypothesis was proposed that PYY may play a possible role in FHA produc-

tion, contributing to resistance to ghrelin, and reducing GnRH regulation, thus disrupting normal release of gonadotropins.[22]

In states of energy deficiency, the levels of insulin and glucose in the body of female athletes are likewise reduced, which also adversely affects the secretion of LH. Furthermore, in female athletes with defects in the luteal phase a lower insulin level and increased sensitivity to it were observed versus the control group without disrupted ovulation; lower leptin and T3 levels were also found in that group.[25]

It was demonstrated that women with menstrual cycle disrupted by LEA are characterized by lower oxytocin secretion (especially at the night-time) when compared to women menstruating regularly. Due to the fact that oxytocin is a hormone secreted mainly by the hypothalamus and stored in the posterior pituitary, it is assumed that it is involved in inhibiting the activity of the hypothalamus-pituitary-adrenal (HPA) axis and modifying a glucoregulative response to calorie intake.[26–28]

Cortisol is a catabolic hormone secreted by the adrenal cortex in response to chronic physical training, hunger, glycogen depletion, and stress.[29–31] For cortisol, it was demonstrated that extreme underweight and overweight alike activate the HPA axis, resulting in higher cortisol levels.[30] It was demonstrated that cortisol levels measured in urine of women with the disrupted menstrual cycle were higher than in the control group. Hypercortisolemia may directly affect reproductive functions or be a biomarker for stress and reproductive dysfunctions in athletes with amenorrhea.[29–31]

GH is a peptide secreted by the pituitary gland and it is stimulated by hormones such as ghrelin. Certain biological effects of GH are strongly mediated by the IGF-1, a peptide produced in the liver. In women with LEA, an increased GH secretion and a reduced IGF-1 level were observed.[32]

Thyroid hormones, T3, T4, and TSH, also play an important role in reproduction, and both their surplus and deficiency may inhibit reproductive functions. Women with FHA had a decreased T3 level, but variable T4 and TSH levels.[33] It was observed that the hypothalamus–pituitary–thyroid axis adjusts to LEA by reducing its energy expenditures. Therefore, low T3 levels may be a useful marker for low energy levels in the human body.[33]

Menstrual disorders with estrogen deficiency predispose women to osteoporosis. It does not develop immediately after the onset of menstrual disorders in female athletes, but there is a direct correlation between the duration of amenorrhea and a decrease in BMD.[34–36] Estrogen has a protective effect on the bone mass and plays an important role in the regulation of BMD, as it limits bone resorption, stimulates calcitonin and promotes renal calcium retention. The absence of a monthly cycle contributes to the initiation of the osteoporosis process. The most critical period for bone growth in women occurs within 2 years after the first menstruation, and bone development peaks around 20–25 years of age. Therefore, impaired bone growth caused by lack of estrogen, together with the downregulated mineralization of the bones at that age, may lead to a greater risk of developing osteoporosis in the future. A decrease in BMD, in turn, causes an increased risk of falls and stress fractures among athletes.[34–36] Research carried out by Loucks[37] showed that with the low energy availability and a lack of estrogen, the rate of bone resorption increases and the rate of bone formation decreases within 5 days of reducing the energy availability to less than 30 kcal/$kg_{lean\ mass}$ a day in exercising women.

It was demonstrated that female athletes with amenorrhea not only have a lower BMD, but also impaired bone architecture, reduced estimated bone strength, and higher ratio of fractures when compared to athletes with the normal menstrual cycle.[38]

The components of FAT do not have to occur simultaneously for a woman to actually suffer from negative health effects of this syndromes.[7–13] FAT in combination with a chronic hypoestrogenic state leads to many secondary physiological and clinical health consequences. Sex hormones not only affect fertility and body composition, but also have a significant impact on the cardiovascular system. Studies[39,40] showed that estrogen is an important regulator of the cardiovascular system. Although the word 'triad' suggests that there are three components of this disorder and for years it has been described as such by researchers of this syndrome, today, the possibility of a tetrad is being considered. This is because an understanding of the pathophysiology of amenorrhea in women has resulted in increasingly frequent descriptions of a fourth element of FAT, which is as silent as osteoporosis and affects the endothelium of blood vessels. It has been shown that the disappearance of the menstrual cycle and the associated lack of estrogen are often accompanied by dysfunction and disorders in the vascular endothelium, an unfavorable lipid profile, and premature cardiovascular disorders in athletes. Intensive training may lead to the impaired vascular function in healthy people, with particular emphasis on the causal role that reactive oxygen species play in this impairment. Coronary and peripheral vessels are known to contain estrogen receptors, so estrogen can play a regulatory role in the vasomotor function. Endothelial cells have also been shown to contain estrogen receptors, and in response to estrogen stimulation they secrete nitric oxide, which is responsible for vasodilation.[39,40] Therefore, a lack of estrogen results in reduced vasodilation. Researchers[39,40] demonstrated a correlation between FAT and vascular endothelial dysfunction. Disruptions in the monthly cycle linked to practicing sport are pathophysiologically similar to the amenorrhea associated with the menopause. In both cases, a reduction in the estrogen level may impair the vascular endothelial function and result in arterial dilatation disorders, which are a precursor to cardiovascular diseases.[39,40]

4.2. FAT prevention and treatment

The treatment of FAT requires a multidisciplinary team, including doctors, psychologists, nutritionists, coaches and parents, to tackle the problem. The overall goal of FAT treatment is to restore a positive energy balance, i.e. to increase the overall energy availability to at least 30–45 kcal/kg_{FFM} a

day in combination with calcium and vitamin D supplementation, and to reduce caloric expenditure in order to restore the menstrual cycle and strengthen BMD.[41–43] While there is no clearly approved optimal daily dose of calcium for female athletes, ACSM recommends 1000–1300 mg of calcium, at least 600 IU of vitamin D, and iron supplementation (18 mg a day) to maximize bone mineral build-up.[41–43] As a rule, the normal monthly cycle is restored when energy intake (by eating) and availability increase, especially during periods of increased energy expenditure (training), which clearly indicates the causal role of LEA in the induction of FHA, as well as its importance in reversing menstrual disorders associated with practicing sport.[41–43]

Certainly, a qualified sports nutritionist can accurately determine the caloric deficit and develop a diet plan with suggested changes in order to improve the energy balance. Coaches and trainers, however, are the ones responsible for recognizing the first symptoms of FAT in their athletes, especially when they are young girls, in whom FAT may have the greatest impact on health disorders. Typically, the athlete has not purposefully caused the energy imbalance in their body, so usually the woman willingly cooperates with the team trying to correct the problem. The key to success, therefore, is education concerning correct nutrition and nutritional advice on energy needs, as well as information on the person's current demand for calcium and vitamin D. Amateur sportswomen, without professional support, should be taught to be aware of the first symptoms of FAT. [41–43]

Most importantly, however, for treatment to be effective, women affected by FAT must be as much a committed part of the team as the professionals caring for them, so the athletes themselves must be willing to change their eating habits. Often, young female athletes are reluctant to admit to behavior that may reflect their fear of weight gain or body image problems, so overcoming the psychological component of this attitude is important.[41–43] It is recommended to conduct diagnostic tests for FAT in every woman athlete with a history of menstrual disruptions or a recent bone fracture, especially stress fractures. Their monthly cycles, eating behavior and training load should be analyzed. It is also helpful to professionally define their current energy balance. According to the American College of Sports Medicine (ACSM)[44], every athlete suspected of having FAT who has oligomenorrhea lasting longer than 6 months, plus eating disorders and bone stress fractures, should have a densitometry test. The prevention and early diagnosis of FAT disorders are of key importance to ensure the timely initiation of treatment, which, considering the number of unfavorable symptoms of FAT, is relatively simple and easy to implement.

FAT and RED-S are two issues that every sports doctor, physiotherapist, trainer and athlete should know about, as, unquestionably, so should the women undertaking physical activity and exercising both on a professional and on an amateur basis. The persistent low energy availability can compromise health, causing many medical complications in the skeletal (injuries, stress fractures, potentially irreversible bone loss), endocrine, cardiovascular (endothelial dysfunction), reproductive, and central nervous (depression, anxiety, low self-esteem) systems and in the lipid profile, and, consequently, leads to a decrease in sports performance.[14,15]

6. CONCLUSIONS

LEA influences abnormal secretion of GnRH and this leads to the disrupted FSH and LH secretion. Higher ghrelin levels accompanying LEA inhibit secretion of GnRH and of ACTH, GH, FSH and LH. A low leptin level resulting from LEA may also contribute to changed GnRH pulse frequency. A high PYY level accompanying LEA results in a significant suppression of GnRH secretion.

In women with LEA, the increased GH secretion and the decreased IGF-1 levels were observed, as well as reduced T3 and variable T4 and TSH levels. Hypercortisolemia occurring in athletes may directly affect reproductive functions. Lack of estrogen contributes both to disrupted mineralization of bones and to endothelial dysfunction.

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References
1 Gray SH. Menstrual disorders. *Pediatr Rev.* 2013;34(1):6–17. https://doi.org/10.1542/pir.34-1-6.
2 George ChA, Leonard JP, Hutchnson MR. The female athlete triad: a current concepts review. *SAJSM*. 2011;23(2):50–55. https://doi.org/10.17159/2078-516X/2011/v23i2a543
3 Frisch RE. The right weight: body fat, menarche, and fertility. *Nutrition*. 1996;12(6):452–453. https://doi.org/10.1016/s0899-9007(97)85084-8.
4 Javed A, Kashyap R, Lteif AN. Hyperandrogenism in female athletes with functional hypothalamic amenorrhea: a distinct phenotype. *Int J Women's Health*. 2015;13(7):103–111. https://doi.org/10.2147/ijwh.s73011.
5 Gordon CM, Ackerman KE, Berga SL, et al. Functional hypothalamic amenorrhea: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;102(5): 1413–1439. https://doi.org/10.1210/jc.2017-00131.
6 Cadegiani FA, Kater CE. Hormonal aspects of overtraining syndrome: a systematic review. *BMC Sports Sci Med Rehabil*. 2017;9:14. https://doi.org/10.1186/s13102-017-0079-8.
7 Horn E, Gergen N, McGarry KA. The female athlete triad. *R I Med J*. 2013;97(11):18–21.
8 Williams NI, Statuta SM, Austion A. Female athlete triad future directions for energy availability and eating disorder research and practice. *Clin Sports Med*. 2017;36(4): 671–686. https://doi.org/10.1016/j.csm.2017.05.003.

9 De Souza MJ, Koltun KJ, Etter CV, et al. Current status of the female athlete triad: Update and future directions. *Curr Osteoporos Rep.* 2017;15(6):577–587. https://doi.org/10.1007/s11914-017-0412-x.

10 Beals KA, Meyer NL. Female athlete triad update. *Clin Sports Med.* 2007;26(1):69–89. https://doi.org/10.1016/j.csm.2006.11.002.

11 Daily JP, Stumbo JR. Female athlete triad. *Prim Care Clin Office Pract.* 2018;45(4):615–624. https://doi.org/10.1016/j.pop.2018.07.004.

12 Matzkin E, Curry EJ, Whitlock K. Female ahlete triad: past, present, and future. *J Am Acad Orthop Surg.* 2015;23(7):424–432. https://doi.org/10.5435/jaaos-d-14-00168.

13 Hoch AZ, Lal S, Jurva JW, Gutterman DD. The female athlete triad and cardiovascular dysfunction. *Phys Med Rehabil Clin N Am.* 2007;18(3):385–400. https://doi.org/10.1016/j.pmr.2007.05.001.

14 Mountjoy M, Sundgot-Borgen J, Burke L, et al. IOC consensus statement on relative energy deficiency in sport (RED-S): 2018 update. *Br J Sports Med.* 2018;52(11):687–697. https://doi.org/10.1136/bjsports-2018-099193.

15 Sim A, Burns SF. Review: questionnaires as measures for low energy availability (LEA) and relative energy deficiency in sport (RED-S) in athletes. *J Eat Disord.* 2021;9(1):41. https://doi.org/10.1186/s40337-021-00396-7.

16 Loucks AB, Kiens B. Wright HH. Energy availability in athletes. *Sport Sci.* 2011;29(Suppl 1):7–17. https://doi.org/10.1080/02640414.2011.588958.

17 Elliott-Sale KJ, Tenforde AS, Parziale AL, et al. Endocrine effects of relative energy deficiency in sport. *Int J Nutr Exerc Metab.* 2018;28(4):335–349. https://doi.org/10.1123/ijsnem.2018-0127.

18 Ackerman KE, Slusarz K, Guereca G, et al. Higher ghrelin and lower leptin secretion are associated with lower LH secretion in young amenorrheic athletes compared with eumenorrheic athletes and controls. *Am J Physiol Endocrinol Metab.* 2012;302(7):800–806. https://doi.org/10.1152/ajpendo.00598.2011.

19 Corr M, De Souza MJ, Toombs RJ, Williams NI. Circulating leptin concentrations do not distinguish menstrual status in exercising women. *Hum Reprod.* 2011;26(3):685–694. https://doi.org/10.1093/humrep/deq375.

20 Donoso MA, Munoz-Calvo MT, Barrios V, Hawkins F, Argente J. Increased circulating adiponectin levels and decreased leptin/soluble leptin receptor ratio throughout puberty in female ballet dancers: Association with body composition and the delay in puberty. *Eur J Endocrinol.* 2010;162(5):905–911. https://doi.org/10.1530/eje-09-0874.

21 Chou SH, Chamberland JP, Liu X, et al. Leptin is an effective treatment for hypothalamic amenorrhea. *PNAS.* 2011;108(16):6585–6590. https://doi.org/10.1073/pnas.1015674108.

22 Scheid JL, Williams NI, West SL, VanHeest JL, De Souza MJ. Elevated PYY is associated with energy deficiency and indices of subclinical disordered eating in exercising women with hypothalamic amenorrhea. *Appetite.* 2010;52(1):184–192. https://doi.org/10.1016/j.appet.2008.09.016.

23 Russell M, Stark J, Nayak S, et al. Peptide YY in adolescent athletes with amenorrhea, eumenorrheic athletes and non-athletic controls. *Bone.* 2009;45(1):104–109. https://doi.org/10.1016/j.bone.2009.03.668.

24 Scheid JL, De Souza MJ. Menstrual irregularities and energy deficiency in physically active women: The role of ghrelin, PYY and adipocytokines. *Med Sport Sci.* 2010;55:82–102. https://doi.org/10.1159/000321974.

25 De Souza, MJ, Van Heest J, Demers LM, Lasley BL. Luteal phase deficiency in recreational runners: Evidence for a hypometabolic state. *J Clin Endocrinol Metab.* 2003;88(1):337–346. https://doi.org/10.1210/jc.2002-020958.

26 Lawson EA, Donoho DA, Blum JI, et al. Decreased nocturnal oxytocin levels in anorexia nervosa are associated with low bone mineral density and fat mass. *J Clin Psychiatry.* 2011;72(11):1546–1551. https://doi.org/10.4088/jcp.10m06617.

27 Lawson EA, Ackerman, KE, Estella NM, et al. Nocturnal oxytocin secretion is lower in amenorrheic athletes than nonathletes and associated with bone microarchitecture and finite element analysis parameters. *Eur J Endocrinol.* 2013;168(3):457–464. https://doi.org/10.1530/eje-12-0869.

28 Lawson EA, Ackerman KE, Slattery M, Clarke H, Misra M. Oxytocin secretion is related to measures of energy homeostasis in young amenorrheic athletes. *J Clin Endocrinol Metab.* 2014;99(5):E881–E885. https://doi.org/10.1210%2Fjc.2013-4136.

29 Schaal K, Van Loan MD, Casazza GA. Reduced catecholamine response to exercise in amenorrheic athletes. *Med Sci Sports Exerc.* 2011;43(1):34–43. https://doi.org/10.1249/mss.0b013e3181e91ece.

30 Schorr M, Lawson EA, Dichtel LE, Klibanski A, Miller KK. Cortisol measures across the weight spectrum. *J Clin Endocrinol Metab.* 2015;100(9):3313–3321. https://doi.org/10.1210/jc.2015-2078.

31 Ackerman KE, Patel KT, Guereca G, Pierce L, Herzog DB, Misra M. Cortisol secretory parameters in young exercisers in relation to LH secretion and bone parameters. *Clin Endocrinol.* 2013;78(1):114–119. https://doi.org/10.1111/j.1365-2265.2012.04458.x

32 Misra M, Miller KK, Herzog DB, et al. Growth hormone and ghrelin responses to an oral glucose load in adolescent girls with anorexia nervosa and controls. *J Clin Endocrinol Metab.* 2004;89(4):1605–1612. https://doi.org/10.1210/jc.2003-031861.

33 Estour B, Germain N, Diconne E, et al. Hormonal profile heterogeneity and short-term physical risk in restrictive anorexia nervosa. *J Clin Endocrinol Metab.* 2010;95(5):2203–2210. https://doi.org/10.1210/jc.2009-2608.

34 Williams NI, Mallinson RJ, De Souza MJ. Rationale and study design of an intervention of increased energy intake in women with exercise-associated menstrual disturbances to improve menstrual function and bone health: The REFUEL study. *Contemp Clin Trials Commun.* 2019;14:100325. https://doi.org/10.1016/j.conctc.2019.100325.

35 Richard N, Palmer C, Adams HP. Female athlete triad: Low energy availability, menstrual dysfunction, altered bone mineral density. *Physician Assist Clin*. 2018;3(3): 313–324. https://doi.org/10.1016/j.cpha.2018.02.001.

36 Misra M, Katzman D, Miller KK, et al. Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. *J Bone Miner Res*. 2011;26(10):2430–2438. https://doi.org/10.1002/jbmr.447.

37 Loucks AB, Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly menstruating women. *J Clin Endocrinol Metab*. 2003;88(1):297–311. https://doi.org/10.1210/jc.2002-020369.

38 Papageorgiou M, Dolan E, Elliott-Sale KJ, Sale C. Reduced energy availability: Implications for bone health in physically active populations. *Eur J Nutr*. 2017;57(3):847–859. https://doi.org/10.1007/s00394-017-1498-8.

39 Lanser EM, Zach KN, Hoch AZ. The female athlete triad and endothelial dysfunction. *AAPM&R*. 2011;3(5):458–465.

40 Hoch AZ, Papanek P, Szabo A, Widlansky ME, Schimke JE, Gutterman DD. Association between the female athlete triad and endothelial dysfunction in dancers. *Clin J Sport Med*. 2011;21(2):119–125. https://doi.org/10.1097/jsm.0b013e3182042a9a.

41 Klein DA, Paradise SL, Reeder RM. Amenorrhea: A systematic approach to diagnosis and management. *Am Fam Physician*. 2019;100(1):39–48.

42 Lebrun CM. The female athlete triad: What's a doctor to do? *Curr Sports Med Rep*. 2007;6(6):397–404.

43 Berz K, McCambridge T. Amenorrhea in the female athlete: What to do and when to worry. *Pediatr Ann*. 2016;45: e97-e102. https://doi.org/10.3928/00904481-20160210-03.

44 Thomas DT, Erdman KA, Burke LM. American College of Sports Medicine Joint Position Statement. Nutrition and Athletic Performance. *Med Sci Sports Exerc*. 2016;48(3):543–568. https://doi.org/10.1249/mss.0000000000000852.