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The Female Athlete Triad/Relative Energy Deficiency in Sports (RED-S)

A tríade da atleta feminina/déficit energético relativo no esporte (RED-S)

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Abstract

In a healthy athlete, the caloric intake is sufficient for sports energy needs and body physiological functions, allowing a balance between energy availability, bone metabolism, and menstrual cycle. On the other hand, an imbalance caused by low energy availability due to a restrictive diet, eating disorders or long periods of energy expenditure leads to multi-systemic deregulation favoring the essential functions of the body. This phenomenon, described as the female athlete triad, occurs in a considerable percentage of high-performance athletes, with harmful consequences for their future. The present review was carried out based on a critical analysis of the most recent publications available and aims to provide a global perception of the topic relative energy deficit in sport (RED-S). The objective is to promote the acquisition of more consolidated knowledge on an undervalued theme, enabling the acquisition of preventive strategies, early diagnosis and/or appropriate treatment.

Keywords
- female athlete
- low energy availability
- amenorrhea
- bone health
- menstrual dysfunction

Resumo

Em uma atleta saudável, o aporte calórico é suficiente para a necessidade energética esportiva e para as funções fisiológicas corporais, permitindo um equilíbrio entre disponibilidade energética (DE), metabolismo ósseo e função menstrual. Por outro lado, um desequilíbrio devido à baixa disponibilidade energética (BDE) por dieta restritiva, perturbações alimentares ou grandes períodos de gasto energético conduz a uma desregulação multissistêmica priorizando as funções essenciais do corpo. Este fenômeno, descrito inicialmente como tríade da mulher atleta e, atualmente, como défice energético relativo no esporte (RED-S, na sigla em inglês) tem como pilares a BDE, disfunção menstrual e alterações na densidade mineral óssea (DMO), estando presente em uma percentagem considerável de atletas de alta competição, com consequências nefastas para o seu futuro a curto, médio e longo prazo. A presente revisão foi realizada a partir da análise crítica das publicações mais recentes disponíveis e pretende proporcionar uma percepção global do tema RED-S. O objetivo é promover a aquisição de um conhecimento mais consolidado sobre uma temática subvalorizada, possibilitando a aquisição de estratégias preventivas, diagnóstico precoce e/ou tratamento adequado.

Palavras-chave
- atleta feminina
- baixa disponibilidade energética
- amenorreia
- saúde óssea
- disfunção menstrual

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Definition: Female Athlete Triad versus Relative Energy Deficiency in Sport

The female athlete triad, initially described in 1993 and conceptually defined in 1997 by the American College of Sports Medicine (ACSM), was based on the presence of eating disorders, amenorrhea and osteoporosis. In 2007, 3 new components were defined: low energy availability (LEA), menstrual dysfunction, and changes in bone mineral density.[1–3] Afterwards, it was concluded that the existence of all elements for its diagnosis was not essential, since there is a very high variety in incidence for each one and that it is dependent on the type of sport, which can lead to underdiagnoses. Therefore, since 2014, after meeting the International Olympic Committee (IOC), it was changed for relative energy deficiency in sport (RED-S,) meeting the need for a holistic approach.[4,5]

This new concept allows the identification of energy deficiency as a key to the disruption of several physiological functions of different areas, such as reproduction, bone, endocrine, metabolic, hematological, growth and development, physiological, cardiovascular, gastrointestinal, and immunological, with consequences for the performance and health of the athlete in general.[4,6]

Low Energy Availability

Low energy availability, due to food scarcity or excessive energy expenditure, causes physiological adaptations to ensure life maintenance.[7] Therefore, there are different mechanisms favoring essential processes[8] instead of secondary functions such as growth, development, and reproduction.[9] Energy availability (EA) is calculated by subtracting the energy consumed (kcal) from the energy ingested (kcal) and dividing this value by the free fat mass (kg).[10] It consists of a theoretical concept, difficult to use on a routine basis. However, its knowledge and interpretation are important for a better evaluation of the athletes. The ideal EA should support the basic functions that allow a healthy state and adequate performance,[4] which is believed to be >45 kcal/kg of free fat mass/day.[7] Several authors have attempted to define the threshold beyond which LEA leads to metabolic changes. However, due to the high interpersonal variability, it is only possible to predict that <30kcal/kg of free fat mass/day, there is a high probability of physiological adaptation favoring vital systems.[4,7]

Pathophysiology

The new LEA concept highlights the complexity of this theme, which involves several hormonal pathways. There has been extensive research in this area in an attempt to identify the trigger of pathophysiological changes. However, these appear to result from multiple changes with different influences on different organs and systems.

Adaptation to Energy Restriction

Low energy availability leads to a decrease in body fat mass with adaptation of normal adipose tissue activity and activation of different pathways after recognition as an internal stress state (namely activation of the hypothalamic-pituitary-adrenal [HPA] axis and the autonomic nervous system). These changes lead to neuroendocrine adaptations with energy redistribution in favor of vital systems preservation.[11,12] We can, therefore, identify:

- Decrease leptin[13,14]: anorexigenic hormone secreted by adipocytes and regulated by energy state. Negative impact on gonadotropin-releasing hormone (GnRH) secretion.[15]
- Increased ghrelin[13,16,17]: orexigenic hormone secreted by gastric oxyntic cells. Levels inversely related to fat mass. It has an effect on the hypothalamus and on the pituitary gland, negatively affecting the secretion of GnRH, of adrenocorticotrophic hormone (ACTH), of growth hormone (GH), of follicle stimulating hormone (FSH), and of luteinizing hormone (LH).
- Increased peptide YY: increased resistance to ghrelin. Associated with decreased release of GnRH and gonadotropins.[18]
- Decreased oxytocin[19]: apparently suppressive role in activity of the HPA axis and modifies the glucoregulatory response to caloric consumption.[20] It has antidepressant and anxiolytic effects.[21]
- Decreased insulin with increased sensitivity.[22] its decrease has an negative influence on GnRH signaling.
- Decreased insulin-like growth factor 1 (IGF-I): stimulates osteoblast function and bone formation. It mediates several actions by GH and may be responsible for increasing resistance to it.[23–27]
- Resistance to GH, despite its increase[23,24]: pituitary peptide, necessary for muscle and bone anabolism and metabolism of carbohydrates, proteins, and lipids.
- Thyroid function: adaptation due to decreased energy expenditure with a decrease in T3 and thyrotropin-releasing hormone (TRH). Thyroxine and thyroid-stimulating hormone (TSH) without changes/lower limit of normal.[8,28–31]
- Activation of HPA axis: An increase in basal cortisol leads to an increase in its nocturnal pulse amplitude, half-life, and area below the curve in amenorrhea athletes.[32,33] Increase in beta-hydroxybutyrate (ketone synthesized in the liver: carrier of energy to peripheral tissues, activity as an energetic metabolite, cellular signaling functions). Cellular function, regardless of sports practice.[6]

Hypothalamic Amenorrhea

As previously explained, exercise by its own has no suppressive effect on reproductive function. However, it can be the cause of menstrual disruptions by influencing energy availability. According to different studies, it is believed that functional hypothalamic amenorrhea occurs by the combination of different pathways in response to LEA, with a negative influence on GnRH: increased cortisol[34] and corticotropin-releasing hormone (CRH)[35] in response to stress and decreased leptin, with impact directly GnRH (►**Fig. 1**). Therefore, there is a decrease in the GnRH drive with

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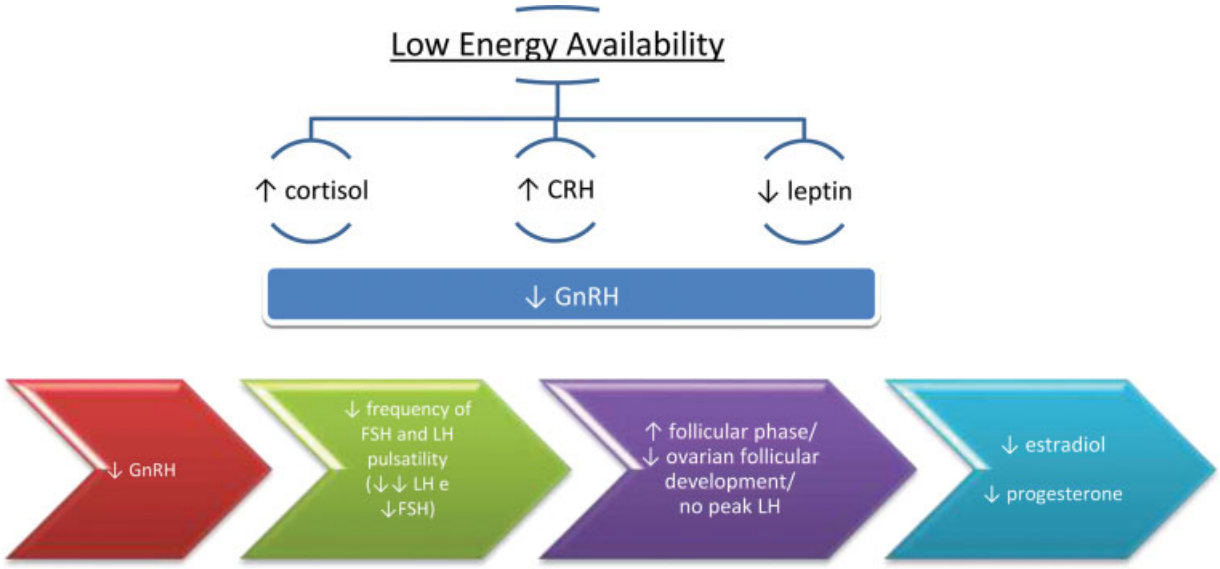

Figs. 1 and 2. Influence of low energy availability on the menstrual cycle.

reduction in frequency of FSH and LH pulsatility,[22,30,36] leading to changes in folliculogenesis and ovulatory function, resulting in lower estradiol and progesterone levels (►**Fig. 2**).[37]

It is important to emphasize that there is a wide spectrum of possible menstrual patterns, namely ovulatory eumenorrhea, subclinical menstrual dysfunctions, and amenorrhea.[34] A higher rate of amenorrhea occurs in sports whose lean phenotype is imposed (gymnastics, running, among others). The prevalence of hypothalamic amenorrhea can be as high as 69%, compared with 2 to 5% in the general population.[37–39]

Bone Metabolism

Bone development is negatively affected by LEA, with a decrease of different elements such as estrogens (inhibition of osteoclasts and growth of osteoblasts), IGF-1 (stimulation of osteoblastogenesis and promotion of bone formation), leptin (proliferation of osteoblasts) and T3 (proliferation of osteoblasts and promoting bone formation). Decrease in bone formation and bone turnover are the main consequences of changes in bone metabolism. This combination leads to loss of normal repair mechanisms for minor and major lesions, resulting in a higher risk of fracture.[40–43] In amenorrhea athletes, there is a decrease in bone mineral density (BMD), volumetric bone density, and strength associated with abnormal bone microarchitecture.[44–47] Even in weight-bearing exercises with theoretical benefit in BMD, changes are described mainly when associated with restrictive eating habits and low weight.[48,49]

Other Consequences

Cardiovascular: increase in total cholesterol, triglycerides, LDL and HDL.[50] Impairment of endothelial function and increased vascular resistance[51–53] associated with increased central fat.[54] Amenorrheic athletes can have lower heart rates and systolic blood pressure, due to disruptions of the normal renin-angiotensin-aldosterone response.[4] In more severe LEA states, severe bradycardia, hypotension, valve abnormalities, pericardial effusion, and arrhythmias can occur.[4]

Sports performance: impaired recovery with change in muscle mass and function[55]; interference in the glycogen reserve and protein synthesis.[56] The literature in this area is scarce, with only one study confirming a 10% decrease in the swimming speed of 400 m in athletes with amenorrhea versus eumenorrhea.[57]

Bone metabolism: Because it occurs mostly in adolescence, there is a proven risk of loss of bone mass with potential inability to reach the bone peak, which in 90% of individuals is reached by age of 18.[6]

Diagnosis

The diagnosis of RED-S does not imply the existence of concrete clinical or laboratory changes. It consists of an active search for athletes at risk due to insufficient energy availability, either due to low input or excessive expenditure.

The diagnosis requires a low threshold of suspicion and an approach based on a detailed medical history that should include questions about diet, dietary changes, weight fluctuations, exercise, training hours, sleep changes, stress, mood, cycle menstruation, fractures, and substance abuse. It is also important to address psychosocial issues such as the need for social approval, the claim to perfectionism, ambitions and expectations, which are more marked in athletes with amenorrhea. Family history of eating and reproductive disorders should also be explored.[34] In order to standardize screening and follow-up, the IOC created the RED-S clinical assessment tool (CAT), which should be part of the annual health assessment of the athlete and/or whenever there is evidence of eating disorder, menstrual dysfunction (secondary amenorrhea > 6 months or primary amenorrhea > 16

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years), history of stress fracture, significant weight loss, change in height in relation to the target family height in adolescents, deficient performance, or evident mood change.[6,58]

Frequently, the first manifestation results in dysregulation of the menstrual cycle or in amenorrhea, and a functional etiology must be considered in the presence of oligomenorrhea and/or in the presence of amenorrhea for > 3 months.[6,34]

Functional hypothalamic amenorrhea is characterized by the absence of menstrual cycles or by irregular cycles associated with estrogen deficiency due to insufficient stimulation or suppression of the hypothalamic-pituitary-ovary (HPO) axis in the absence of anatomical or organic pathology.[34]

As it is an exclusion diagnosis, it is crucial to consider the main causes of amenorrhea, such as drugs, intracranial prolactinoma/tumor, Kallmann Syndrome (anosmia and hyposmia), thyroid pathology, chronic pathology, and congenital pathology (i.e., imperforate hymen, Mullerian abnormalities/androgen insensitivity syndrome [AIS]).[59–63] To complement this study, a complete physical examination with search for excess androgens signs is essential, and the need for gynecological evaluation and imaging studies should be considered.[29,64–66]

In hypothalamic functional amenorrhea, bradycardia, orthostatic hypotension, BMI < 18.5 kg / m2, parotid hypertrophy and/or signs of tissue hypoperfusion[65] are frequently accompanied by signs of hypoestrogenism, namely delayed puberty, breast atrophy, and vaginal atrophy.[6]

Complementary Diagnostic Tests

The initial study of amenorrhea includes the evaluation of hCG levels (to exclude pregnancy), FSH, prolactin and TSH. Some authors also recommend in the initial assessment the search of Free T4 (FT4), LH, estradiol and anti-Müllerian hormone (AMH).[34]

Additional studies depend on clinical suspicion. In chronic disease or eating disorder: blood count, liver and kidney function, electrolyte Panel, calcium, magnesium, phosphorus, glycemia, erythrocyte sedimentation rate, and C-reactive protein should be requested[34]; in the presence of signs of hyperandrogenism, total testosterone, DHEA-S, and 17OH-progesterone should be considered.[67,68]

Expected results in functional amenorrhea are decreased LH or low normal, normal FSH (usually higher than LH) and E2 < 50pg/ml. The acute response after GnRH stimulation is preserved. Thyroid stimulating hormone, FT4, and testosterone are usually at the lower limit of normal.[30,31,34,69] Anti-Müllerian hormone does not change, and there seems to be no interference in the ovarian reserve.[70]

Bone mineral density assessment should be considered when menstrual dysfunction (6–12 months of amenorrhea/oligomenorrhea, primary amenorrhea), low BMI (< 17.5 kg/m2) or significant weight loss (> 5–10% of body mass within 1 month), in the presence of minor stress/post-trauma fracture, or in the event of an eating disorder. It is advisable to use the Z-Score scale in preference to T-Score, as the first is adapted to age and gender. Any location in the skeleton can be assessed; however, the spine is the most consensual in adolescents and young women with amenorrhea.[6,44,45,71–74]

The interpretation of densitometry in athletes must follow specific criteria, with BMD being considered lower than expected when Z-score> -1; low BMD if Z-score between -1 and -1.9 with risk factors (nutritional deficiencies, hypoestrogenism or stress fractures), and osteoporosis when Z-score < -2 with risk factors.[2,3,49]

Treatment

Due to the multifactorial etiology of female athlete triad - stress, weight loss, excessive exercise, and poor nutrition - a multidisciplinary team is essential for its approach.[2,3]

Nonpharmacological

Nonpharmacological treatment is always the first line of treatment, allowing resolution of most cases. As it is based on LEA, the aim is to restore normal balance with an individualized and dynamic nutritional, psychological, and sports plan that will allow the reestablishment of the hypothalamic-pituitary-ovary axis.[4] The increase of 5 to 10% of body weight or of 1 to 4 kg of weight with appropriate nutritional supply – 300 to 600 kcal caloric increase – distributed throughout the day and with protein and carbohydrate consumption preference.[6]

Vitamin Supplementation

Calcium and vitamin D have shown important benefits in decreasing the risk of stress fractures, as well as in their recovery, with supplementation recommended.[75,76] A daily dose of 1,300 mg of calcium (up to ,1500 mg/day) and of 800-1,000 IU of vitamin D (to achieve blood 25[OH]D concentration > 75-100 nmol/L)[2,77,78] is recommended. The use of bisphosphonates should still be avoided, especially in young athlete women, considering its long half-life and its potential teratogenic effect in future pregnancies.

Pharmacological

Pharmacological treatment has a crucial role in selected cases. However, it should only be considered after failure in reestablishing menstruation after between 6 and 12 months of nonpharmacological therapy associated with a proven decrease in BMD. In presence of a young athlete with amenorrhea or oligomenorrhea, combined oral contraception is often used as an adjunct to normalize menstrual cycles. Despite the success in most cases, its use for this purpose is not recommended, as it may cover a possible physiological normalization and give false confidence to the athlete.[4] Corroborating the nonindication for its prescription, several studies report the lack of efficacy of oral estrogens in the recovery of BMD/bone protective effect.[79,80] This

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is justified by their hepatic "first-pass effect," with potential suppression of liver production of IGF-1 impairing its bone trophic effect.[6,81] Currently, when it is necessary to initiate hormone replacement, the most accepted approach consists of transdermal estradiol therapy (E2) (which does not affect IGF-I secretion) associated with a cyclic oral progestative for a short period.[34] Nevertheless, it is always important to remind athletes that this has no contraceptive effect.[82] For contraceptive purposes, there is no contraindication for any method, although if there is a preference for combined contraceptive, we can offer the vaginal or transdermal route to avoid hepatic "first-pass effect". The only method that allows the perception of normal recovery are nonhormonal methods, such as nonhormonal intrauterine devices.

Investigational Therapy

Recombinant parathyroid hormone: can be weighted for short periods of time when BMD is very low or in cases of delayed fracture healing.[34] It is contraindicated in adolescents or young adults with open growth plates. It has shown improvement in BMD and faster recovery.[83,84]

Recombinant leptin: a promising therapy showing increased frequency and levels of LH pulse, improved follicular development, ovarian volume, E2 levels, increased T4, FT4, IGF-I, IGF-binding protein 3, bone alkaline phosphatase, and osteocalcin. However, decreased appetite and significant weight loss have been reported.[85] Similar results can be achieved with metreleptin regarding weight loss and fat mass.[86]

Recovery after Treatment

Nonpharmacological therapy can restore menstrual cycles to normal in months. However, some athletes may maintain folliculogenesis and altered follicular dynamics for years, with decreased gonadotropins and sex steroid hormones. In these cases, a luteal phase defect may occur with long menstrual periods associated with premenstrual spotting or short cycles due to decreased progesterone secretion.[87,88] Regarding bone metabolism, results can take several years to appear. Regardless of the positive correlation between increasing BMD and menstrual reestablishment, in many cases a full recovery is not achieved.[89]

Conclusion

Relative energy deficiency in sport consists of a low energy availability status mainly affecting young athletes, with potentially harmful and irreversible consequences on their health. Its prevalence is underestimated due to lack of and late diagnosis due to deficient knowledge of signs and symptoms. It is crucial and urgent to promote dissemination among different professionals, extending to athletes and their families, in order to increase alertness to this condition, allowing its prevention, early diagnosis, and adequate treatment.

Contributors

All authors were involved in the design and interpretation of the analyses, contributed to the writing of the manuscript, and read and approved the final manuscript.

Conflict to Interests

The authors have no conflict of interests to declare.

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