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THE IMPACT OF RELATIVE ENERGY DEFICIENCY IN SPORT (RED-S) ON WOMEN: GYNECOLOGICAL AND HEALTH OUTCOMES - A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: In physically active women, both professional and recreational, proper nutrition is fundamental for maintaining health, performance, and hormonal balance. Adequate energy intake supports bone metabolism, menstrual regularity, and overall physiological function. When energy balance is disrupted—due to restrictive diets, caloric deficits, or intense training—the body activates energy-saving mechanisms that suppress reproductive and skeletal functions. This condition may lead to Relative Energy Deficiency in Sport (RED-S), a multifactorial syndrome involving hormonal, metabolic, skeletal, cardiovascular, and immune disturbances. Despite its serious consequences, the prevalence of RED-S is often underestimated, and awareness among athletes and professionals remains limited.

State of knowledge: The syndrome occurs in both elite and recreationally active women, often remaining undiagnosed. Despite growing scientific interest and expert recommendations, standardized diagnostic criteria and effective screening tools are still lacking, making early recognition and treatment of RED-S challenging.

Aim: The aim of this study was to review current data on RED-S in women, with particular emphasis on its pathophysiology, clinical consequences, diagnostic challenges, and therapeutic strategies.

Materials and Methods: A critical literature review was conducted for the years 2005-2025, including clinical and observational studies, systematic reviews, and expert consensus statements.

Conclusion: RED-S represents a serious threat to women's health and performance, with potential long-term consequences. Early diagnosis and non-pharmacological management—adequate nutrition, training modification, and psychological support—are essential. Pharmacological treatment should be reserved for selected cases. Increasing awareness among healthcare professionals, athletes, and their support teams is crucial for effective prevention, early detection, and management of RED-S.

KEYWORDS

Relative Energy Deficiency in Sport (RED-S), Female Athlete, Menstrual Dysfunction, Bone Mineral Density (BMD), Fertility, Low Energy Availability, Reproductive Health

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Introduction

Relative Energy Deficiency in Sport (RED-S) is a term introduced by the International Olympic Committee (IOC) in 2014, referring to the consequences of chronic low energy availability in athletes. This syndrome encompasses a broad spectrum of metabolic, hormonal, skeletal, immunological, and psychological disturbances, which negatively affect both the health status and physical performance of athletes [1,2,3].

The concept of RED-S represents an extension of the earlier model known as the Female Athlete Triad, defined in 1997, which included disordered eating, amenorrhea, and decreased bone mineral density. In subsequent years, this model was expanded to include additional components such as Low Energy Availability (LEA) and its associated hormonal, metabolic, and psychological disturbances [1,2,3]. In women, the mechanisms associated with RED-S include, among others, suppression of the hypothalamic-pituitary-ovarian (HPO) axis, which may lead to impaired hormonal function [2,4,8]. Low Energy Availability (LEA) occurs when the amount of energy provided by food intake is insufficient to cover the energy expenditure related to training (Exercise Energy Expenditure, EEE) and the basic physiological functions of the body [5,6].

In the scientific literature, Energy Availability (EA) is defined by the following equation:

$$EA \text{ (kcal/kg fat-free mass (FFM)/day)} = \text{Energy Intake (EI; kcal)} - \text{Exercise Energy Expenditure (EEE; kcal)}$$
$$EA \text{ (kcal/kg fat-free mass (FFM)/day)} = \text{Energy Intake (EI; kcal)} - \text{Exercise Energy Expenditure (EEE; kcal)}$$
where EI represents total energy intake, and FFM refers to fat-free body mass (kg) [5,6]. The EA value reflects the amount of energy available for physiological processes after accounting for exercise costs.

Suboptimal EA is defined as 30–45 kcal/kg FFM/day, while low energy availability is defined as <30 kcal/kg FFM/day [6,7]. Chronic energy deficiency can lead to dysfunction of the endocrine, skeletal, cardiovascular, and immune systems [6,7,8]. Despite the growing awareness of Relative Energy Deficiency in Sport (RED-S), there remains a need to gather and systematize evidence regarding its impact on the health of female athletes - particularly on reproductive function, bone mineral density, and the prevalence of menstrual disorders. The present study aims to analyze the available scientific literature to assess the effects of RED-S on women's health, with a particular focus on menstrual disturbances, bone health, reproductive function, cardiovascular and nervous system performance, and thermoregulatory processes, as well as to review current diagnostic strategies and treatment options for this syndrome.

It is hypothesized that chronic low energy availability in female athletes leads to hormonal dysfunction, decreased bone mineral density, and reduced fertility, while early identification and appropriate nutritional and training interventions may help to minimize these consequences.

Pathophysiology

Low Energy Availability (LEA) results in a reduced amount of body fat, triggering metabolic and hormonal adaptations aimed at conserving energy [5]. There is a decrease in leptin, an anorexigenic hormone secreted by adipocytes; its reduced level signals insufficient energy intake, which may suppress pulsatile GnRH secretion, leading to decreased levels of LH and FSH, and consequently to reduced ovarian stimulation [9,10,11].

At the same time, an increase in ghrelin levels is observed [9,11] - an orexigenic hormone produced by gastric cells, whose concentration is inversely proportional to fat mass. Elevated ghrelin exerts an inhibitory effect on the hypothalamus and pituitary gland, reducing the secretion of GnRH, ACTH, GH, FSH, and LH, thereby further affecting reproductive function, metabolism, and hormonal homeostasis [12,13]. High levels of peptide YY (PYY) further increase ghrelin resistance, reducing the release of GnRH and gonadotropins [14].

Within the hypothalamic-pituitary-adrenal (HPA) axis, activation and elevated basal cortisol levels are observed, leading to a wide range of effects: menstrual disturbances, bone and muscle loss, immune suppression, psychological disorders, and reduced athletic performance [10,15]. Energy deficiency also contributes to a decrease in oxytocin levels [16], which under normal conditions inhibits HPA activity and exerts antidepressant and anxiolytic effects [17]. A reduction in caloric intake also lowers insulin levels, while simultaneously increasing insulin sensitivity, which likewise suppresses GnRH signaling. The level of insulin-like growth factor 1 (IGF-1) also decreases: IGF-1 is responsible for stimulating osteoblasts and bone formation, as well as mediating the effects of growth hormone (GH)[10]. Despite elevated GH levels, GH resistance is observed, disrupting muscle and bone anabolism and the metabolism of carbohydrates, proteins, and lipids [19]. Under conditions of energy deficiency, the concentrations of T3 and TRH decrease, while T4 and TSH remain within the normal range or at its lower limit [10,20].

Menstrual disorders

The primary mechanism leading to menstrual disturbances in RED-S is the suppression of the hypothalamic-pituitary-ovarian (HPO) axis, typical of functional hypothalamic amenorrhea (FHA) [1,2]. Low Energy Availability (LEA) reduces pulsatile secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus, leading to decreased levels of pituitary hormones: LH and FSH [1,21]. As a result, ovarian stimulation is insufficient, causing reduced production of estrogens and progesterone. Clinically, this hormonal state manifests as menstrual cycle disturbances, including both lengthened cycles (oligomenorrhea) and complete absence of menstruation (amenorrhea) [1,22].

This mechanism is modulated by various metabolic and hormonal signals, including decreased leptin levels, increased cortisol, and changes in insulin and IGF-1, which further suppress HPO axis function [1,2,23]. Prolonged estrogen deficiency leads to secondary health consequences, such as reduced bone mineral density and an increased risk of stress fractures [1,22,23].

The prevalence of menstrual disturbances among active women depends on sport discipline, training intensity, age and nutritional status. Systematic reviews and studies indicate a wide prevalence range: depending on the study, from a few percent up to 50-60% in selected groups, particularly in sports emphasizing a lean physique (e.g., gymnastics, long-distance running). Differences arise from variations in definitions, retrospective periods, and research methods[24,25].

Bone metabolism

Chronic low energy availability (LEA), a central feature of Relative Energy Deficiency in Sport (RED-S), leads to profound disturbances in bone metabolism, including both reduced bone formation and increased bone resorption [1,2]. This process results from complex hormonal, metabolic, and mechanical interactions. A key pathophysiological factor is the decrease in estrogen levels due to suppression of the hypothalamic-pituitary-ovarian (HPO) axis [1,26]. Estrogen deficiency removes their protective antiresorptive effect on bone tissue, resulting in osteoclast activity predominating over osteoblasts and accelerated bone loss [26].

Simultaneously, there is a reduction in insulin-like growth factor 1 (IGF-1) levels and relative growth hormone (GH) resistance, leading to impaired osteoblastogenesis and reduced synthesis of bone matrix [27]. Additionally, low leptin levels, characteristic of energy deficiency and low fat mass, weaken the anabolic effects of this hormone on bone tissue [1,2].

These changes are further amplified by metabolic adaptations to LEA, such as decreased triiodothyronine (T3), increased cortisol, and reduced insulin levels, which further limit the synthesis of structural bone proteins and enhance catabolism [28,29]. Biochemical studies in women with RED-S show reduced levels of bone formation markers (osteocalcin, P1NP) alongside increased resorption markers (CTX, DPD) [27,28,29].

Clinically, this manifests as an increased incidence of stress fractures [27,28]. Young women during adolescence are particularly vulnerable, as energy deficiency during the period of peak bone mass formation may lead to irreversible reductions in bone mineral density, increasing the risk of osteopenia and osteoporosis in adulthood [22,26,27,29].

Reproductive function

Studies indicate that intensive recreational physical activity can impact female reproductive function. Analysis of NHANES (USA) data showed that women engaging in moderate-intensity recreational exercise for more than 5.8 hours per week were at a higher risk of infertility, with each additional hour of activity above this threshold increasing the risk by 4% [30]. Furthermore, a meta-analysis including over 700,000 women confirmed that high levels of physical activity, particularly recreational, can significantly affect reproductive health, highlighting the need to maintain a balance between exercise and energy availability [31].

While regular physical activity provides numerous health benefits for women, excessive exercise combined with inadequate energy intake can lead to reproductive dysfunction. The key mechanism is Relative Energy Deficiency in Sport (RED-S), which disrupts the hypothalamic-pituitary-ovarian (HPO) axis. This results in reduced secretion of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and estradiol, leading to anovulation, cycle lengthening, or secondary amenorrhea [11,14].

Nervous system

Low Energy Availability (LEA), a central feature of RED-S, also affects cognitive function and mental health in athletes [32,33]. Studies indicate that chronic energy deficiency leads to impaired concentration, slowed decision-making processes, weakened working memory, and difficulty processing information [32,34]. These mechanisms are partially related to glucose deficiency, the brain's primary fuel, as well as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and decreased levels of anabolic and mood-regulating hormones such as leptin, insulin-like growth factor 1 (IGF-1), and oxytocin [33,34].

Cardiovascular system

In the cardiovascular system, numerous metabolic and hemodynamic changes are observed, including elevated levels of total cholesterol and LDL and HDL fractions [35,36]. Additionally, endothelial dysfunction and increased vascular resistance may occur, often associated with central fat accumulation [35,37,38].

Low energy availability in athletes can lead to iron-deficiency anemia, reducing physical performance and increasing the risk of injuries and overuse [39]. Typically, athletes with menstrual disturbances in the context of RED-S present with lower resting heart rate and blood pressure. Prolonged or severe LEA may further impair cardiovascular function, including bradycardia and hypotension, due to the body's energy-conserving mechanisms [1,40,41].

Thermoregulation

Athletes with chronic energy deficiency (Low Energy Availability, LEA) may experience reduced resting body temperature, increased susceptibility to hypothermia, and decreased exercise tolerance in extreme thermal conditions [33,32]. The mechanisms underlying these disturbances include metabolic adaptations, such as decreased thyroid hormone levels and reduced resting metabolic rate [33,34].

Diagnosis

There are no specific diagnostic tests for RED-S, and diagnosis is primarily based on excluding other causes of symptoms, as well as a detailed clinical history and assessment of the athlete's functioning [33,34].

The clinical history should include information on dietary habits and changes, body weight fluctuations, type and intensity of physical activity, training hours, sleep quality, stress levels, mood changes, menstrual cycle regularity, occurrence of stress fractures, and substance abuse [33,32]. A family history of eating disorders and reproductive problems is also important, as it may increase the risk of RED-S [34,2].

The International Olympic Committee (IOC) developed the IOC RED-S Clinical Assessment Tool (IOC RED-S CAT), which enables a comprehensive assessment of risk, symptoms, and severity of RED-S [2]. In 2023, an updated version, IOC RED-S CAT2, introduced a three-step diagnostic process and a four-level risk classification system based on a "traffic light" approach: green (low risk), yellow (moderate risk), orange (elevated), and red (high risk)[42,43].

The IOC RED-S CAT2 includes three main stages:

1. Initial Screening - identification of warning signs and symptoms potentially indicative of RED-S.
2. Severity/Risk Stratification - assessment of symptom severity and assignment of the corresponding risk level (green-red).
3. Final Diagnosis and Treatment Plan - decision made by a physician in collaboration with a multidisciplinary team (dietitian, coach, psychologist) [42,43].

Validation studies indicate that IOC RED-S CAT2 effectively classifies athletes according to health risk. Those assigned to the orange and red categories show more frequent amenorrhea, stress fractures, reduced hormone levels (T3, testosterone), and lower bone mineral density (BMD) compared to those in the green category [42,43].

Menstrual disturbances are one of the earliest warning signs of developing RED-S in women. Amenorrhea or irregular menstrual cycles (oligomenorrhea) result from low energy availability, which suppresses the hypothalamic-pituitary-ovarian axis and reduces reproductive function [1,44].

In cases of scant or absent menstruation lasting more than three months, functional hypothalamic amenorrhea (FHA) should be considered, which is diagnosed in the absence of anatomical or organic pathology [45]. FHA results from reduced pulsatile GnRH secretion, leading to decreased LH, FSH, and estradiol [45,46]. This hormonal disruption causes hypoestrogenism, which may present as delayed sexual maturation, breast atrophy, and vaginal mucosal atrophy. Predisposing factors include low energy availability, excessive stress, intense physical activity, and insufficient rest [45,46].

FHA diagnosis is clinical and requires exclusion of other causes of secondary amenorrhea, such as polycystic ovary syndrome (PCOS), hyperprolactinemia, ovarian failure, or thyroid disorders [45,46]. Initial evaluation should include pregnancy testing (hCG), as well as measurement of thyroid-stimulating hormone (TSH), free T4 (FT4), prolactin, follicle-stimulating hormone (FSH), estradiol, and anti-Müllerian hormone (AMH) [45].

Even a short-term period of LEA (a few days to weeks with energy intake <30 kcal/kg fat-free mass) can lead to rapid hormonal and metabolic changes, including reductions in LH, estradiol, T3, basal metabolic rate (RMR), and alterations in protein and collagen metabolism, affecting recovery and bone health [47].

Bone mineral density (BMD) assessment is recommended for patients with menstrual disturbances (primary or secondary amenorrhea, oligomenorrhea ≥ 6 months), low BMI (<17.5 kg/m²), significant weight loss (>5-10% within a month), minor stress or post-traumatic fractures, or eating disorders. The Z-score is preferred over the T-score, as it accounts for age and sex. Measurements may cover different skeletal sites, with the spine most commonly assessed in adolescent and young women with amenorrhea [48,49,50].

Menstrual disturbances may appear long before other RED-S symptoms, such as osteopenia or reduced physical performance [1]. Therefore, monitoring menstrual cycles and implementing early dietary and training interventions are crucial to prevent further health consequences and restore energy balance [44,47].

Treatment

Non-pharmacological treatment

The etiology of Relative Energy Deficiency in Sport (RED-S) is multifactorial and includes excessive training load, rapid weight loss, chronic stress, and an inadequately balanced diet [51,52]. Therefore, effective management requires a multidisciplinary approach involving physicians, dietitians, physiotherapists, and sports psychology specialists [53,54].

The cornerstone of treatment is the restoration of energy balance, which involves optimizing caloric intake, selecting appropriate macronutrients, monitoring nutritional status, and adapting training to the body's capacity. The result is the restoration of the hypothalamic-pituitary-ovarian axis [51,52].

It is recommended to increase body weight by 5-10% or 1-4 kg through appropriate nutrient intake, which typically requires increasing daily caloric intake by 300-600 kcal, distributed evenly throughout the day, with emphasis on protein and carbohydrates [48].

Subsequently, systematic monitoring of hormonal function, bone density, and overall health parameters is necessary to assess the effectiveness of interventions and prevent long-term complications [10,55].

Supplementation with calcium and vitamin D is an important component of preventing and treating these complications. The doses of vitamin D and calcium are determined individually based on laboratory results and deficiencies. Studies have shown that administration of 1300 mg of calcium per day (up to 1500 mg/day in cases of deficiency) and 800-2000 IU of vitamin D allows achievement of serum 25(OH)D levels >75-100 nmol/L, which reduces the risk of stress fractures and supports bone recovery [56,57].

Due to the long half-life and potential teratogenic effects in future pregnancies, the use of bisphosphonates is not recommended in young female athletes [56].

Pharmacological treatment

Pharmacological treatment should be considered only after failure to restore menstruation within 6-12 months of non-pharmacological therapy, especially if the athlete demonstrates persistent decreases in bone mineral density (BMD) [3,58].

In young athletes with amenorrhea or oligomenorrhea, combined oral contraceptives (COCs) are often used as an adjunct to "induce" normal menstrual cycles [59]. However, current scientific evidence does not clearly support a beneficial effect of COCs on bone health in women with RED-S [60,61]. Their use may mask the return of natural hypothalamic-pituitary-ovarian axis function and hinder identification of the primary cause of the disorder; therefore, COCs should not be considered a standard method for restoring menstruation or preventing bone mass loss in this patient group [62,63].

Confirming the lack of indication for oral estrogen use, several studies have demonstrated their ineffectiveness in restoring bone mineral density and providing protective effects on bone tissue [64,65]. This phenomenon is explained by the first-pass hepatic effect, which reduces insulin-like growth factor 1 (IGF-1) production, consequently weakening its anabolic effect on bone [64,65].

Furthermore, when COCs are used as the sole intervention, it should be noted that if the energy deficit is not corrected, bone loss may continue despite the presence of exogenous hormones [64,65].

In cases of persistent amenorrhea despite non-pharmacological treatment, short-term administration of transdermal estradiol (E2) combined with cyclic oral progestogen can be considered [58,65]. It should be emphasized, however, that transdermal E2 does not provide effective contraception; therefore, patients should be informed about the need for additional contraceptive measures [65].

Unlike oral estrogens, transdermal estradiol does not reduce insulin-like growth factor 1 (IGF-1) levels, which plays a key anabolic role in bone metabolism [66]. This is explained by bypassing the first-pass hepatic effect characteristic of oral therapy [64,66].

Studies have shown that transdermal E2 increases bone mineral density (BMD) in both women with anorexia nervosa and athletes with secondary amenorrhea [67,68]. This therapy therefore represents a safer and more effective alternative to oral estrogens in treating hypogonadism associated with RED-S.

Promising experimental therapies in RED-S

In addition to standard non-pharmacological and hormonal interventions, experimental therapies are emerging in research that may support bone health and reproductive function in women with RED-S.

In patients with severe bone loss or delayed fracture healing, temporary treatment with teriparatide, a recombinant parathyroid hormone analog, can be considered [69]. It should not be used in young adults with

open growth plates. Data indicate improvements in bone density and accelerated healing, but evidence in athletes with RED-S remains limited [70,71,72].

Recombinant leptin (metreleptin) shows potential for restoring hypothalamic-pituitary-ovarian axis function, improving BMD, and enhancing metabolic markers. However, its use is associated with appetite and weight loss, and therefore it remains experimental [10,73,74].

Conclusion and future directions

RED-S represents a significant health concern in physically active women, causing hormonal disturbances, decreased bone mineral density, an increased risk of fractures, as well as adverse metabolic and cardiovascular effects. Its prevalence is likely underestimated, as diagnosis is often delayed due to limited awareness of the symptoms. Therefore, it is crucial to raise awareness among healthcare professionals, athletes, and their families to enhance vigilance for RED-S, enabling more effective prevention, early identification of the condition, and implementation of appropriate treatment.

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