Title:
Relative Energy Deficiency in Sport (RED-S) and Knee Injuries: Current Concepts for Female Athletes

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Abstract
In athletes, a mismatch between caloric intake and energy expended in exercise can result in Low Energy Availability (LEA). LEA can lead to Relative Energy Deficiency in Sport (RED-S), where the athlete suffers from physiological derangements and decreased sport performance. The prevalence of RED-S is higher in females than males.

RED-S more comprehensively describes the syndrome originally known as “Female Athlete Triad” (FAT). FAT encompasses the triad of LEA (with or without disordered eating), menstrual dysfunction and low bone mineral density. RED-S includes other physiological derangements such as poor cardiovascular health, abnormalities of metabolic rate, immunity, and protein synthesis.

Females are already at a higher risk of knee injuries, which has been attributed to a multitude of factors such as hormonal influences, differences in musculoskeletal anatomy and neuromuscular control compared to males. The literature demonstrates an even higher risk of knee injuries in female athletes with symptoms of RED-S. We propose the various factors that influence this risk.

A reduction in anabolic hormones can affect muscle development and tendon repair. A relationship between poor neuromuscular control and knee injury has been established, and this can be further worsened in patients with menstrual dysfunction. Chronic deficiency in nutrients such as collagen and vitamin D can result in poorer recovery from microtrauma in tendon and ligaments. All these factors may contribute to increasing the risk of knee injuries, which may include anterior cruciate ligament tears, patella tendinopathy and patellofemoral pain syndrome.

This review aims to educate sports clinicians to have a high index of suspicion when treating knee injuries in females; to screen and then manage for RED-S if present, for holistic patient care.
Current Concepts

- The prevalence of Low Energy Availability (LEA) and Relative Energy Deficiency in Sport (RED-S) is higher in female athletes than in male athletes.
- Female athletes are at greater risk of knee injuries, such as anterior cruciate ligament tears and patellofemoral pain syndrome.
- Reported contributing factors include differences in hormones, neuromuscular control, and musculoskeletal anatomy.
- RED-S has been associated with hormonal dysfunction as well as further impairment of neuromuscular control, which are factors for knee injuries in female athletes.

Future Perspectives

- The authors propose causative effects of RED-S on knee injuries in the female athlete via three pathophysiological mechanisms.
- RED-S is associated with a reduction in anabolic hormones such as insulin and insulin-like growth factor, and an increase in catabolic hormones like cortisol. This has been shown to be detrimental to the repair of post-exercise microtrauma to muscles and tendon; reduced muscle and tendon strength can result. With the quadriceps and patella tendons heavily involved in lower limb power generation, these athletes are at risk of patellofemoral pain and patella tendinopathy.
- RED-S has been shown to be associated with decreased neuromuscular performance (i.e., lower limb muscular strength and endurance) and reaction time. This impairs landing biomechanics when jumping or running, further increasing the already high risk of injuries such as anterior cruciate ligament tears and patellofemoral pain syndrome.
- RED-S can be associated with deficiencies in nutrients such as vitamin D and collagen. Such nutrients are essential for healing microtrauma to cartilage, tendons and ligaments sustained after intense exercise. The lack of these
nutrients may be associated with impaired tissue repair and greater knee injury risk.

- Future research is needed to establish direct associations between RED-S and these knee injuries. Screening questions such as diet and menstrual history will be important when evaluating female athletes with knee injuries.

Introduction

**What is RED-S**

Relative Energy Deficiency in Sport (RED-S) is a syndrome of impaired physiological functions such as metabolic rate, menstrual function, bone health, immunity, protein synthesis and cardiovascular health. The etiology of RED-S is low energy availability (LEA), which is a mismatch between an athlete’s energy intake (diet) and the energy expended in exercise. This results in inadequate energy to support the body’s baseline physiological functions [3] and can lead to physiological derangements (Fig 1) and decreased sport performance (Fig 2).

RED-S is a term that can more comprehensively describe the syndrome originally known as “Female Athlete Triad” (FAT) [4]. FAT only encompasses the triad of LEA (with or without disordered eating), menstrual dysfunction and low bone mineral density whereas RED-S encompasses and covers a greater number of physiological derangements [5].
Fig 1: Health Consequence of Relative Energy Deficiency in Sport (RED-S) showing an expanded concept of the Female Athlete Triad to acknowledge a wider range of outcomes. (*Psychological consequences can either precede or result from RED-S) Adapted from [1],[2]
In most sports, female athletes reportedly consume \(~30\%\) less energy and carbohydrate per kilogram of body weight than male athletes in the same sports [6]. Pasman et al reported that female runners were more dissatisfied with their bodies than males and had greater eating psychopathology than males [7]. Aesthetic sports such as figure skating, gymnastics, and diving tend to tie athletic success to leanness. This can lead to an unhealthy drive for thinness and can increase an athlete’s risk of LEA and subsequent RED-S [3].

LEA, as the etiology of RED-S, has been found to be a risk factor for injury occurrence in distance runners, based on a cross-sectional study by Heikura et al [8]. In their study, the authors found that national and world-class female distance athletes who had physiological symptoms (namely hormone dysfunction, amenorrhea, and low bone density) of LEA had a 4.5-fold higher rate of injury compared to eumenorrheic females.

It is well-established that RED-S is associated with an increased risk of bone stress injuries and fractures in female athletes[1, 9] Stress fractures are most commonly found

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**Fig 2: Potential performance consequences of Relative Energy Deficiency in Sport (RED-S) Adapted from [1],[2]**
in the hip, foot, or tibia amongst triathletes. Pain may be felt in the bone itself, and mild swelling can be present. Bouts of high-intensity training with inadequate recovery can trigger stress fractures. Poor footwear, poor training load management, and muscular imbalances can all be causal factors in stress fracture occurrence [10]. Timely diagnosis via radiological imaging is essential for adequate management of this injury as recovery times can range from weeks to months.

Athletes with Vitamin D deficiency and female athletes with iron deficiency or menstrual disturbances have a higher risk of these stress fractures. Both female and male athletes should pay particular attention to their diet when increasing training load to avoid stress fractures. With a caloric deficit in RED-S, this can cause hormonal imbalances, resulting in reduced bone density. Functional hypothalamic amenorrhea is one of the sequelae of RED-S. Female athletes with oligo or amenorrhea have demonstrated altered bone turnover markers, weaker bones and increased risk for fractures when compared to eumenorrheic peers [11].

Despite this known clinical triad, the relationship between RED-S and its role in the pathophysiology in knee injuries that occur in female athletes has not often been discussed. LEA has been shown to be a risk factor for lower extremity soft tissue injuries such as tendinopathy, and ligament tears in competitive dancers, as reported by Prus et al [12]. Henriksson et al reported that female long distance running athletes with menstrual dysfunction had longer interruptions to their training, due to musculoskeletal injuries than those with regular cycles [13]. In this chapter, we review the clinical and basic science evidence that supports this notion that LEA is a critical risk factor for knee injuries that should be identified and addressed in female athletes.

**Risk factors for knee injuries in female athletes**

Both acute and chronic knee injuries have been shown to be more common in female than male athletes[14, 15]. Females participating in jumping and cutting sports demonstrate a 4 to 6-fold higher incidence of acute knee injury than males participating in the same sports [14]. The incidence of serious acute knee injury is approximately 6-fold higher in female than male athletes [16]. Chronic overuse injuries such as patellofemoral pain syndrome are more commonly reported in females than males (62% females vs 38% males) [15]. While the reason for this continues to be studied, increased injury rates have traditionally been attributed to differences in musculoskeletal anatomy, neuromuscular control and hormones [17].

The differences in pelvic structure and lower extremity alignment result in a larger quadriceps angle, or Q-angle in females, which have been associated with increased risk of patellofemoral pain [18]. Additionally, motor skills and neuromuscular activation of the lower limbs in females are decreased compared to males, especially in the
Premenstrual, or luteal phase. Posthuma et al found that manual dexterity, measured by tests involving manipulation of objects, was worse in women with premenstrual syndrome during the late luteal phase of the cycle compared to those in the early follicular phase [19]. This can lead to further femoral adduction and internal rotation which increases the dynamic quadriceps angle, resulting in greater lateral patellar contact pressures [20] and increased risk of patellofemoral pain.

Dynamic knee valgus is an important risk factor when running, cutting, or landing from jumps, resulting in greater rotatory forces at the tibia-femoral joint, which increases the risk for anterior cruciate ligament (ACL) tears [21]. Female athletes are further at risk due to quadriceps dominance, in which they contract their quadriceps to a much greater degree than the hamstrings compared with male athletes at landing [22]. This decreased hamstring strength and activation can increase the risk of ACL injury. Females also have smaller and narrower femoral intercondylar notches than males, which have also been associated with increased risk of ACL injuries [23].

Hormonal fluctuations have also been explored in relation to the increased risk of knee injury in female athletes. Estrogen receptors are present in fibroblasts in the ACL, and the binding of estrogen to these receptors has been shown to cause a decrease in synthesis of collagen precursors [24]. This may result in reduced tensile strength of the ACL [25]. Wojtys et al found an increased incidence of ACL injury in women during the ovulatory phase of the menstrual cycle, when a surge in estrogen production occurs [26].

Relaxin is a hormone produced by the corpus luteum and placenta which helps loosen ligaments in the female pelvis to prepare for delivery [27]. Relaxin receptors have been identified on the ACL of females and not males. Dragoo et al found that the serum relaxin concentrations for female athletes with ACL tears was significantly higher than that for those without ACL tears [28]. Oral contraceptive pills, specifically those with high progestin-to-estrogen ratios, may alter relaxin levels and benefit female athletes by reducing their ACL injury risk [29]. While the relationship between hormones and ACL injury risk has been identified, further studies are needed to apply this into clinical practice guidelines.

In addition to ligaments, estrogen receptors are also found in tendons [24]. Increased estrogen levels can attenuate the tendon hypertrophy response and collagen synthesis rate in women both at rest and after exercise [30]. These changes can reduce the mechanical strength and stiffness of the tendon [31] which may predispose to injuries such as patella tendinopathy. In addition, lower tendon stiffness has been reported in
women, leading to a worse adaptation to mechanical loading and a reduced tendon hypertrophy response after habitual training, predisposing to tendon injuries [32].

This review proposes a causative effect of how RED-S potentiates knee injuries in female athletes via a combination of hormone imbalance, nutrient deficits, and further impaired neuromuscular control, which requires further investigation.

Hormonal dysfunction

Hormonal dysfunction is a hallmark of LEA. Anabolic hormones such as insulin and insulin-like growth factor are reduced [9]. This results in reduced glycogen and protein synthesis [33] and impaired repair of muscle microtrauma post-exercise. Cortisol levels are also elevated in LEA, promoting a catabolic state that causes proteolysis of muscle tissue [34, 35]. Lower insulin levels also accelerate breakdown of muscle proteins to sustain blood glucose. These effects can be detrimental to muscle strength and performance.

Quadricep weakness is a driving risk factor for patellofemoral pain syndrome [36]. A catabolic state induced by hormone dysfunction from RED-S will predispose female athletes to patellofemoral pain due to this impaired muscle repair function. Reduced protein synthesis can also negatively affect repair and adaptation of tendon tissue [37] after microtrauma, predisposing to conditions like patella tendinopathy.

Neuromuscular Performance

Female athletes in sports involving running, cutting, and jumping are, at baseline, already at higher risk of aberrant landing biomechanics compared to male athletes; a ten-fold increased risk of such injuries. RED-S can further compromise this by negatively affecting neuromuscular control of the lower limb due to hormonal imbalance, further increasing risk of acute knee injuries such as ACL tears.

Amenorrhea, as a physiological manifestation of RED-S, is associated with reduced neuromuscular performance. Tornberg et al reported a decrease in reaction time and knee muscle strength (specifically the quadriceps and hamstrings assessed using isokinetic dynamometry) in elite endurance athletes with menstrual dysfunction in contrast to eumenorrheic endurance athletes [38]. A negative effect on muscle protein synthesis, and hence muscle strength, due to LEA is implied by reduced anabolic hormones and a potential increase of cortisol in more severe or prolonged LEA.
Tornberg et al reported that the adverse performance effect of RED-S in female athletes with functional hypothalamic amenorrhea could be due to decreased neuromuscular control compared to their eumenorrheic counterparts. This adverse effect on performance is of particular concern in sports like gymnastics or dance where neuromuscular skills are crucial and yet where RED-S is most prevalent. This puts such athletes at increased injury risk.

Estrogen has also been reported to enhance the activity of endothelium-derived relaxing factor (nitric oxide) in the macrocirculation, promoting vasodilation. RED-S causes functional hypothalamic amenorrhea and results in a hypoestrogenic state. This may result in reduced perfusion and impaired aerobic metabolism in skeletal muscle, further impacting neuromuscular performance of female athletes with RED-S [39].

Female runners with symptoms of RED-S demonstrated a lower neuromuscular performance with significantly reduced hamstring and quadricep muscular strength and endurance compared to eumenorrheic athletes [38]. This leads to faulty landing biomechanics and patella maltracking when jumping or running and would predispose them to conditions such as patellofemoral pain syndrome. The lack of muscle strength and endurance also increases the risk for overuse patella tendinopathy.

Hormonal imbalances and a functional hypothalamic amenorrhea state in RED-S lead to poor neuromuscular control [38] and hence a higher risk of knee injury, likely ACL tears. A hypoestrogenic state resulting in reduced muscle perfusion [39]; and a hypoinsulinemic, hypercortisolic state resulting in increased muscle proteolysis [34, 35] are likely contributing factors.

**Nutrient Deficiencies**

Between 15-62% of the female athletic population exhibit disordered eating behaviours [40]. With a reduced energy intake, nutrient intake is also reduced by the same relative amount. LEA is often accompanied by low macronutrient and micronutrient intakes [41]. Matt et al [42] found that female endurance runners with low energy availability also exhibited below-recommended intakes of nutrients such as calcium, vitamin D, and potassium.

A study done on collegiate distance runners found that more than 50% of the female runners did not meet the recommended daily allowance for calcium, vitamin D and potassium [43]. The reported prevalence of vitamin D deficiency in elite athletes was 30% in adults and 39% in adolescents [44]. Female athletes have been shown to have a consistently lower intake of vitamin D [45].
Vitamin D deficiency is associated with patellofemoral-related complaints in female athletes [46]. Low vitamin D levels and its detrimental influence on quadriceps strength are therefore risk factors for patellofemoral pain syndrome [36]. Vitamin D supplementation has also been shown to improve hamstring and quadriceps strength [47]. The greater the muscle strength, the lower the injury incidence. This been demonstrated in female athletes such as dancers [48] and ski racers [49].

Vitamin D is also important in tendon health. The degradation of collagen within tendons is aided by upregulating matrix metalloproteinases (MMPs). Vitamin D downregulates MMPs, potentially playing a role in preventing tendinopathy [50]. It has been shown that Vitamin D supplementation improves tendon enthesis health and strength [51].

Collagen is a component of the extracellular matrix of hyaline articular cartilage and tendons. Collagen supplementation reduces joint pain in athletes and increases the length of pain-free strenuous exertion [52]. It has been shown that the consumption of 10g of hydrolyzed collagen in a randomized, double-blinded, placebo-controlled study in athletes decreased knee pain from standing and walking [53].

Collagen consumption is important for collagen synthesis in tendons. Shaw et al. [54] demonstrated that subjects who consumed 15 g of gelatin showed twice the collagen synthesis, compared to placebo. This is crucial in post-exercise tissue repair and injury prevention. A dietary lack of collagen intake in RED-S may predispose to patellofemoral pain syndrome and patella tendinopathy.

Vitamin C plays a role in the hydroxylation of proline and lysine, both of which are essential in creating collagen helix formation and crosslinks in tendons [55]. An intake of 1mg/kg bodyweight of Vitamin C a day is essential for collagen cross-link formation [56]. Vitamin C deficiency can predispose to patella tendinopathy from impaired cross-linking in the tendon.

It has also been suggested that a lack of dietary collagen and vitamin C can predispose to ACL tears. Nyland et al suggested that non-contact ACL injuries are a result of cumulative ACL microtrauma. Proper nutrition with glycine-rich collagen peptides, or gelatin-vitamin C supplementation in combination with healthy sleep, and adjusted sports training periodization with increased recovery time may therefore potentially improve ACL extracellular matrix collagen deposition homeostasis, decreasing sudden non-contact ACL rupture incidence likelihood in youth and adolescent athletes [57].
Finally, it has been shown in martial arts and power athletes that caloric restriction and decreases in glycogen stores seen in RED-S are associated with poor performance, decreased vigour, while increasing muscle fatigue and tension [51].

RED-S and LEA have been reported to be associated with ligamentous injuries of the knee, including the ACL. Scheid et al found that a high drive for thinness amongst female athletes, aged 18 to 22 years, from basketball, volleyball, track/cross-country/triathlon, and football was associated with knee injuries such as quadriceps strain, cruciate and collateral ligament tears. A high drive for thinness is a proxy indicator of LEA [58].

Poor nutritional intake, as is seen in LEA, increases the likelihood of sudden non-contact ACL rupture in youth and adolescent athletes [57]. Reduced intake of glycine-rich collagen peptides, or vitamin C, may affect repair of ACL microtrauma, predisposing to complete ACL tears [57].

Rauh et al's prospective cohort studies showed that high school female athletes with physiological derangements were 3 times more likely to develop chronic overuse injuries of the knee, such as patellofemoral pain syndrome and patella tendinopathy [59, 60]. These cohorts included distance runners with derangements such as disordered eating, oligomenorrhea/amenorrhea, and low bone mineral density, which are all indicators of RED-S.

In addition, Oxfeldt et al showed that LEA in females can lead to impairments in myofibrillar and sarcoplasmic muscle protein synthesis. This has negative consequences for both tendon and muscle adaptations in female athletes [37]. This implicates LEA as a potential risk factor for patella tendinopathy.

RED-S may result in deficiencies of nutrients such as vitamin D and collagen. Such nutrients are essential for healing microtrauma to cartilage, tendons and ligaments sustained after intense bouts of exercise. Lack of those nutrients may be associated with impaired tissue repair and greater knee injury risk in the long term. Table 1 summarises how RED-S potentiates knee injuries.

How to screen for and treat RED-S

Screening for RED-S oftentimes is opportunistic as the female athlete may present not for RED-S symptoms but for a musculoskeletal injury. The clinician should have a high index of suspicion for the symptoms of RED-S. Menstrual history should be asked for, specifically oligomenorrhea and amenorrhea. Frequent reporting of illness--most
commonly upper respiratory symptoms, and injury--especially bone stress injuries, are also red flags [61-63].

Coaches should also be educated and be aware of signs of RED-S including decreased performance, undertaking of excessive or obligatory exercise beyond that recommended for training or performance [64], or exercising whilst injured despite medically-prescribed activity restriction. They should be mindful of their athletes exhibiting abnormal behaviours related to diet and eating, such as self-restriction of food intake unnecessary for health sport performance or appearance [61, 65], excessive weighing or refusal to weigh [66], use of laxatives or diuretics, and evidence of vomiting unrelated to illness or due to purposeful purging [64]. Athletes who frequently self-criticise about their body weight, size and shape, as well as claiming to feel fat despite being thin [61, 66], may also be at risk of RED-S.

The Low Energy Availability in Females Questionnaire [67], or LEAF-Q, is a useful screening tool for LEA as a proxy for RED-S. It is for female athletes only and has a high sensitivity (78%) and specificity (90%). The International Olympic Committee also has a RED-S Clinical Assessment Tool and a return to sport model which practitioners may use to aid in the athlete’s return to training and competing [68].

If an athlete is suspected to have RED-S and not already seeing a medical provider, the coach or team manager should speak with the athlete (or parent if a youth) and encourage the athlete to seek consultations with a sports medicine physician or team doctors for further evaluation [9]. Communication should be done privately away from other athletes and in a manner that preserves the athlete’s dignity [9].

Treatment of RED-S will involve the sports medicine physician invoking a multidisciplinary team including sport dietician, exercise physiologist, athletic trainer, sport psychologist and endocrinologist. Treatment should focus on increasing energy intake and/or decreasing energy output. Intake of vitamins and nutrients should follow established guidelines, and regular assessments of bone mineral density should be done [68]. High impact exercise should be avoided due to the risk of developing stress injuries.

**Conclusion**

RED-S is associated with hormonal derangement, neuromuscular compromise, and nutrient deficiencies, all of which are associated with increased risk of knee injuries in female athletes. Medical practitioners and coaches should have a high index of suspicion to identify and address RED-S. Management of RED-S will require a multidisciplinary team effort with a sports medicine physician lead.
Table 1: Types of Knee Injury and Possible Causative Factors in RED-S

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<td>Decreased endurance performance</td>
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<td>Increased injury risk</td>
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<td>Decreased training response</td>
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<td>Impaired judgement</td>
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Fig 2: Potential performance consequences of Relative Energy Deficiency in Sport (RED-S) Adapted from [1],[2]
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: