



Biological Factors That May Limit Tendon Adaptation During Rehabilitation in Adolescent Female Runners: A Narrative Review of RED-S and Isotretinoin

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Abstract

Midportion Achilles tendinopathy is commonly managed with progressive loading, but successful rehabilitation depends on the tendon's biological capacity to synthesize collagen, remodel, and adapt to mechanical stress. This narrative review examines why this response may be reduced in adolescent female runners with Relative Energy Deficiency in Sport (RED-S), isotretinoin exposure, or both. Current evidence suggests that RED-S may impair tendon recovery through prolonged low energy availability, hypoestrogenism, reduced insulin-like growth factor-1, increased cortisol, and disrupted protein turnover. Isotretinoin may act through a different pathway, with experimental and limited human evidence indicating possible alterations in tendon structure, biomechanical properties, and musculoskeletal symptoms. Together, these factors may reduce the biological response required for loading-based rehabilitation and help explain persistent symptoms despite appropriate exercise treatment. However, no study has directly examined rehabilitation outcomes in adolescent female runners with midportion Achilles tendinopathy and concurrent RED-S or isotretinoin exposure, and no modified loading protocol has been validated for this population. Standard rehabilitation should therefore remain centered on individualized progressive loading while also assessing energy availability, menstrual function, nutritional status, training load, and medication exposure.

Keywords: Mid-portion Achilles tendinopathy; adolescent female runners; Relative Energy Deficiency in Sport; low energy availability; isotretinoin; tendon rehabilitation

Introduction

Midportion Achilles tendinopathy is a load-related tendon disorder characterized by pain, stiffness, and reduced function in the region approximately 2–6 cm proximal to the calcaneal insertion. It is commonly managed with progressive tendon loading because repeated mechanical stimulation is expected to promote collagen synthesis, restore calf-muscle function, and improve tendon load tolerance (16,17,49). However, this treatment model assumes that the tendon retains sufficient biological capacity to respond to loading through tissue repair and remodeling.

Adolescent female runners represent a particularly important population because they must meet the combined metabolic demands of growth, puberty, and repetitive endurance training. Although Achilles tendinopathy has been extensively studied in adult runners, evidence specific to adolescent female athletes remains limited, and most rehabilitation protocols have been developed and validated in adult populations (16,26). This is clinically relevant because biological and hormonal factors unique to adolescence may influence both injury risk and recovery.

Relative Energy Deficiency in Sport (RED-S) is one factor that may reduce the biological response required for tendon adaptation. RED-S develops from problematic and prolonged low energy availability and may disrupt reproductive function, protein synthesis, metabolism, and tissue repair (1). In adolescent female athletes, reduced insulin-like growth factor-1, increased cortisol, menstrual dysfunction, and hypoestrogenism may impair collagen turnover and limit the tendon's ability to remodel in response to rehabilitation loading (1,9,10,40).

Isotretinoin may represent an additional modifying factor. The drug is commonly prescribed for severe or treatment-resistant acne in adolescents and has been associated with musculoskeletal adverse effects, including tendinopathy and Achilles tendon symptoms (12,13,41–44). Experimental evidence suggests that isotretinoin may alter tendon structure and biomechanical properties, although human evidence remains limited and inconsistent (13,41–44). Isotretinoin has also been associated with menstrual irregularities, which may complicate the distinction between drug-related menstrual changes and RED-S-related hypothalamic dysfunction (48).

Together, RED-S and isotretinoin exposure may reduce the biological response needed for loading-based rehabilitation, potentially helping to explain persistent symptoms despite appropriate exercise treatment. However, no study has directly examined rehabilitation outcomes in adolescent female runners with midportion Achilles tendinopathy and concurrent RED-S, isotretinoin exposure, or both. Their combined effects remain unknown, and no modified loading protocol has been validated for this population.

This narrative review therefore examines why standard tendon-directed rehabilitation may be less effective in adolescent female runners with RED-S, isotretinoin exposure, or both. It first outlines the pathological and clinical features of midportion Achilles tendinopathy, then evaluates how RED-S and isotretinoin may interfere with tendon remodeling, and finally considers the implications for integrated assessment, rehabilitation, and future research.

Discussion

1. How Does Midportion Achilles Tendinopathy Develop, and Why Does This Matter for Rehabilitation?

1.1 Anatomical and Mechanical Basis

The Achilles tendon is the largest and strongest tendon in the human body and is formed primarily by contributions from the gastrocnemius and soleus muscles, with a possible minor contribution from the plantaris muscle (23). It is composed predominantly of type I collagen arranged within a proteoglycan-rich extracellular matrix and has relatively limited vascularity compared with many other tissues (23). The tendon forms in the distal calf, undergoes approximately 90° of rotation, and attaches to the posterior calcaneus (7,23).

This review focuses specifically on midportion Achilles tendinopathy, which affects the tendon approximately 2–6 cm proximal to the calcaneal insertion (7). This region is clinically important because it is exposed to repeated tensile and shear forces during running and has a relatively limited blood supply, which may reduce its capacity to recover from cumulative mechanical stress. These anatomical and mechanical features help explain why the midportion is particularly vulnerable to overuse injury and why recovery depends on carefully controlled progressive loading rather than rest alone.

1.2 Epidemiology and Relevance to Adolescent Female Runners

Midportion Achilles tendinopathy is one of the most common overuse tendon disorders in physically active populations. The Achilles tendon accounts for approximately 20% of reported tendinopathies, and prospective studies have identified Achilles tendon symptoms in approximately 7% of novice runners during follow-up (8,16). Across recreational running populations, reported prevalence ranges from approximately 6.2% to 9.5%, while higher estimates have been reported in ultramarathon runners (25).

Although the condition is studied predominantly in adults, it also occurs in younger athletes. In adolescent athletes, the population most relevant to this review, pre-participation screening identified Achilles tendinopathy in approximately 1.8% of participants (26). This finding is important because most established rehabilitation protocols have been developed in adults, while adolescent athletes remain

in a period of growth and hormonal development that may influence tendon adaptation and recovery.

Several factors increase the risk of midportion Achilles tendinopathy, including greater cumulative running load, higher weekly mileage, increasing age, and previous running injury (8). Sudden increases in training volume, unfamiliar activity, and changes in footwear or running surface may also increase tendon demand beyond its current capacity (8). In adolescent female runners, these mechanical risks may coexist with low energy availability, menstrual dysfunction, and medication exposure, potentially reducing the tendon's ability to adapt to repeated loading.

1.3 Pathological Changes and Reduced Tendon Capacity

Midportion Achilles tendinopathy develops when repetitive tensile or shear loading exceeds the tendon's capacity to adapt. This imbalance triggers progressive structural and cellular changes (27), including tenocyte proliferation, tendon thickening (16,26), neovascularization (28), expansion of the extracellular ground substance, and thinning and disorganization of collagen fibrils (29).

1.3.1 Dysregulated Matrix Turnover and Angiogenic Signaling

Failed repair in tendinopathy reflects dysregulated matrix turnover and angiogenic signaling — a loss of coordinated regulation... between matrix synthesis, degradation, and vascular ingrowth rather than uniformly increased matrix degradation (51–56). This disrupted regulatory environment may impair collagen remodeling and contribute to the persistent structural disorganization characteristic of tendinopathy, suggesting that the condition reflects more than mechanical overuse alone.

During running, the Achilles tendon repeatedly stores and releases substantial elastic energy. Some of this energy is converted to heat, and inadequate heat dissipation has been proposed as one possible contributor to tenocyte injury and tendon degeneration (45). As these changes accumulate, the tendon may become less effective at tolerating and transmitting force. Tendon stiffness, strength, and force transmission may be altered, although the degree of mechanical impairment varies among patients and disease stages (30). These changes may reduce the

efficiency of force transfer from muscle to bone and contribute to altered motor control (32).

Histologically, tendinopathy is characterized by increased cellularity, expansion of the extracellular matrix, collagen disorganization, and neovascularization (18). Although Achilles tendinopathy is not considered a predominantly acute inflammatory disorder, inflammatory and neurogenic signaling are not completely absent. Mediators such as substance P and calcitonin gene-related peptide may contribute to pain and pathological tendon change (18). Tendon degeneration and inflammatory signaling should therefore be understood as overlapping rather than entirely separate processes (18,33).

These pathological changes are directly relevant to rehabilitation. Tendinopathy is not simply a state of excessive matrix breakdown that can be corrected by reducing load. Rather, it reflects poorly coordinated remodeling in which collagen synthesis, degradation, vascular responses, and tenocyte activity are no longer appropriately balanced. Progressive loading is intended to improve tendon strength, load tolerance, and function (17,49) by providing a mechanical stimulus for collagen synthesis and tissue remodeling (20). However, the success of this process depends on the tendon retaining sufficient biological capacity to respond to loading. Low energy availability and hormonal disruption may reduce collagen synthesis and tissue repair (1,9,10,40), while isotretinoin may alter tendon structure and biomechanical properties (13). Therefore, the mechanical stimulus may be appropriate even when the expected adaptive response is reduced.

1.4 Clinical Assessment

Clinical assessment should evaluate pain severity, functional limitations, training exposure, and the athlete's response to tendon loading. The Victorian Institute of Sport Assessment–Achilles questionnaire can be used to assess Achilles-related pain and function, while the Foot and Ankle Ability Measure or Lower Extremity Functional Scale may be used to assess broader activity limitations and participation (16).

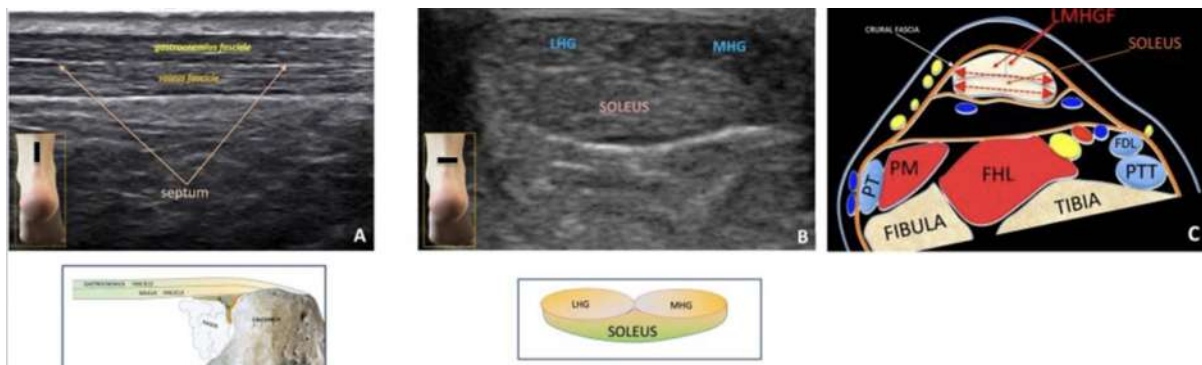
Because this review focuses on adolescent female runners, assessment should extend beyond local tendon symptoms. Menstrual history, recent dietary

changes, and training-load progression should be evaluated to identify possible low energy availability and RED-S (1,3). Current medication use, particularly isotretinoin, should also be documented because it has been associated with musculoskeletal symptoms, tendinopathy, and menstrual irregularities (41–44,48). Considering these factors may help explain persistent symptoms despite apparently appropriate tendon rehabilitation.

1.5 Imaging

Figure 1. Longitudinal ultrasound scan of the Achilles tendon showing its two components: the superficial gastrocnemius fascicle and the deep soleus fascicle, separated by the septum. Reproduced from Salvatore Massimo S, Vita F, Al Khayat SG, Donati D, Ciampi B, Becciolini M, Tedeschi R, Faldini C, Galletti S. Ultrasonographic insights into the complex anatomy and biomechanical dynamics of the Achilles tendon and its fascicles: a pictorial essay. J Ultrasound. 2025.

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1.6 Mechanisms of Pain in Midportion Achilles Tendinopathy

Although midportion Achilles tendinopathy has traditionally been regarded as a degenerative rather than primarily inflammatory condition, patients may still experience substantial pain (33). Symptom severity cannot always be explained by structural degeneration alone, suggesting that neurovascular and biochemical mechanisms also contribute to pain generation.

Neovascularization is frequently observed in painful Achilles tendons and involves the ingrowth of blood vessels that are uncommon in healthy tendon tissue (34). These vessels can be detected using color Doppler ultrasound and are often found in symptomatic tendons. However, vascular ingrowth does not occur in isolation. Histological evidence

indicates that newly formed vessels are accompanied by sensory nerve fibers, suggesting that neurovascular ingrowth is an organized pathological process (35).

These sensory nerve fibers express pronociceptive neuropeptides, including substance P and calcitonin gene-related peptide, while nearby vascular tissue expresses neurokinin-1 receptors that respond to substance P (35,36). This supports the presence of a local neurovascular signaling pathway that may contribute to pain independently of classical inflammatory processes. Elevated glutamate concentrations have also been identified in painful Achilles tendons compared with healthy tissue, providing further evidence of local biochemical involvement in peripheral pain generation (37).

These mechanisms help explain why rest alone may provide only temporary symptom relief. Reducing

tendon loading may decrease pain provocation, but it does not restore tendon strength or load tolerance and may not resolve ongoing neurovascular or biochemical signaling. Rest also does not address systemic factors that may impair tendon recovery, such as low energy availability, hormonal disruption, or altered tendon tissue properties associated with isotretinoin exposure (1,9,10,13,40). Rehabilitation should therefore combine progressive restoration of tendon load tolerance with assessment and management of biological factors that may contribute to persistent symptoms.

2. Why Female Athletes with RED-S Are at Greater Risk of Achilles Tendinopathy

2.1 Relative Energy Deficiency in Sport (RED-S) and Low Energy Availability

One reason adolescent female runners with RED-S may be at greater risk of Achilles tendinopathy and poorer rehabilitation outcomes is that low energy availability can reduce the metabolic and physiological support required for tendon repair and adaptation. Relative Energy Deficiency in Sport (RED-S) refers to impaired physiological and psychological functioning associated with exposure to problematic low energy availability (1).

Low energy availability occurs when dietary energy intake is insufficient relative to exercise energy expenditure, leaving inadequate energy to support growth, hormonal regulation, metabolism, and tissue repair (1,3). Values below approximately 30 kcal/kg fat-free mass per day have historically been associated with physiological disruption; however, this value should not be interpreted as a universal diagnostic threshold because individual responses vary (1).

Prolonged low energy availability may disrupt reproductive function, bone health, immune function, metabolism, cardiovascular health, and protein synthesis (1,3,9). It may result from intentional dietary restriction or disordered eating, but it can also occur unintentionally when athletes fail to increase energy intake in response to greater training demands, lack sufficient nutritional knowledge, experience appetite changes, or have limited food access (3,9). Body-image concerns, social-media exposure, and pressure to achieve a particular physique or perceived performance advantage may further contribute to restrictive eating behaviors (2).

Disordered eating behaviors, including chronic dieting, binge eating, self-induced vomiting, and laxative misuse, may contribute to low energy availability even when they do not meet the diagnostic criteria for a clinical eating disorder (3). Adolescent female athletes may be particularly vulnerable because they must simultaneously support growth, pubertal development, reproductive maturation, and high training loads (3,9).

Low energy availability has also been associated with increased musculoskeletal injury risk in athletic populations, including lower-extremity injuries in female dancers and other athletes (6,10). These findings are relevant to Achilles tendon rehabilitation because inadequate energy availability may impair protein turnover, collagen synthesis, and tissue repair, thereby reducing adaptation to progressive loading (9,10,40). Therefore, RED-S may increase not only the risk of tendon injury but also the likelihood of persistent symptoms when treatment addresses mechanical loading without correcting the underlying energy and hormonal disturbance.

2.2 Hormonal Mechanisms Linking RED-S to Tendon Injury

A second mechanism involves hormonal adaptation to chronic energy deficiency. During prolonged low energy availability, circulating insulin-like growth factor-1 decreases, which may reduce collagen synthesis and tissue remodeling (9). At the same time, cortisol concentrations may increase, promoting protein breakdown and degradation of structural proteins, including tendon collagen (10). Together, these changes may shift tissue turnover toward a more catabolic state and reduce the tendon's capacity for repair.

A third mechanism involves suppression of the hypothalamic–pituitary–gonadal axis. Low energy availability may also suppress hypothalamic gonadotropin-releasing hormone pulsatility, leading to reduced luteinizing hormone and follicle-stimulating hormone secretion and, in some athletes, chronic hypoestrogenism (1). Because estrogen influences musculotendinous protein turnover, sustained disruption of estrogen status may alter tendon collagen metabolism and adaptive capacity (40). Although transient hormonal changes during the menstrual cycle are not equivalent to RED-S-related hypoestrogenism, persistent reproductive dysfunction may reduce the

biological support required for tendon remodeling (39,40).

These hormonal changes are directly relevant to rehabilitation. Progressive loading can provide an appropriate mechanical stimulus, but the expected collagen synthesis and structural adaptation may remain reduced when low energy availability, elevated cortisol, reduced IGF-1, and reproductive dysfunction are not corrected. RED-S may therefore contribute not only to injury development but also to persistent symptoms despite appropriately prescribed loading-based treatment.

Taken together, RED-S may increase susceptibility to Achilles tendon injury and reduce rehabilitation responsiveness by limiting the metabolic and hormonal support required for collagen synthesis, matrix remodeling, and tissue repair. These mechanisms provide a biological explanation for why progressive loading may be less effective when low energy availability and associated endocrine disturbances remain unresolved.

3. How May Isotretinoin Modify Tendon Adaptation and Rehabilitation?

Isotretinoin may represent an additional biological factor... that alters tendon tissue properties and potentially reduces the tendon's ability to tolerate or adapt to rehabilitation loading. Isotretinoin is a synthetic vitamin A-derived retinoid commonly prescribed for severe or treatment-resistant acne and has been associated with musculoskeletal adverse effects, including tendinopathy (12,13).

3.1 Experimental Evidence

Experimental evidence provides biological plausibility for this association. In a rat model, isotretinoin exposure produced histopathological changes and reductions in Achilles tendon biomechanical properties, including measures of tendon strength and elasticity, compared with controls (13). However, the experimental dose was substantially higher than conventional human acne treatment, and species differences limit direct clinical translation.

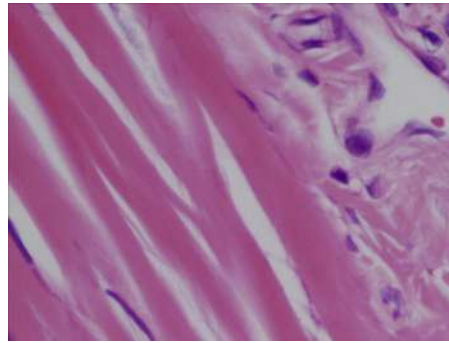
3.2 Human Evidence

Human evidence remains limited and inconsistent. Conventional acne doses have not consistently produced measurable changes in Achilles tendon thickness after short-term treatment (44), while other studies have reported tendinopathy, altered tendon thickness, enthesopathy-related findings, and isolated cases of acute Achilles tendon symptoms during isotretinoin therapy (41–43). More severe complications, including calcific enthesopathy, appear to be associated mainly with prolonged, high-dose retinoid exposure rather than standard acne treatment (11).

3.3 Implications for Rehabilitation

Taken together, the available evidence does not establish isotretinoin as a direct cause of Achilles tendinopathy or rehabilitation failure. However, the reported histological, biomechanical, and clinical findings suggest that isotretinoin exposure may modify tendon capacity in susceptible individuals. In adolescent female runners with persistent symptoms, isotretinoin should therefore be considered a possible contributor to reduced rehabilitation responsiveness rather than an established causal factor.

Figure 2. Increased vascularity in Achilles tendon tissue from an isotretinoin-exposed rat. Hematoxylin and eosin staining, ×400. Reproduced from Beytemür et al. (13) under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) license (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).



4. Treatment

4.1 Standard Management of Midportion Achilles Tendinopathy

Current clinical practice recommends progressive loading rather than complete rest as the foundation of treatment for non-acute midportion Achilles tendinopathy (16,49). Patients may continue recreational activity within pain tolerance while participating in a structured rehabilitation programme, as complete rest is not generally recommended (16,49). Loading-based treatment nevertheless relies on the tendon retaining sufficient biological capacity to respond through collagen synthesis and structural adaptation. Whether this response may be impaired in athletes with RED-S, isotretinoin exposure, or both is examined in Part 2.

Exercise rehabilitation has the strongest evidence supporting its use in Achilles tendinopathy (17,49). Its aims are to reduce pain and restore calf-muscle strength, endurance, tendon load tolerance, and lower-limb function. Although the optimal loading dose remains uncertain, rehabilitation generally involves progressively increasing tendon demand within an individual's tolerance (17). Loading does not produce adaptation automatically; rather, it provides a mechanical stimulus that may initiate mechanotransduction, collagen synthesis, and tissue remodeling (20).

Several loading approaches are widely used in clinical practice, including the Alfredson eccentric loading programme, the Silbernagel combined concentric–eccentric model, and Heavy Slow Resistance (HSR) training (17,18,22). Although these programs differ in exercise selection, frequency, and progression, no single loading mode has consistently demonstrated clear superiority. For example, eccentric and HSR programs have produced similarly favorable long-term

clinical outcomes (22). This suggests that several forms of progressive loading can be effective, but it does not establish why some patients fail to improve. Adherence, load progression, individual variability, and systemic factors affecting tendon adaptation may all influence treatment response.

The Alfredson protocol is one of the most extensively studied loading programs and consists of eccentric heel-drop exercises performed twice daily for 12 weeks (18). The original study reported substantial clinical improvement, while subsequent research comparing loading strategies has shown that treatment responses vary among patients (18,22). Long-term ultrasound follow-up has demonstrated reduced tendon thickness and a more normal tendon structure after eccentric training (19). However, structural improvement on imaging does not necessarily correspond directly with symptom resolution in every patient.

Adjunctive treatments may also be incorporated into conservative management. Eccentric loading has been associated with reduced neovascularization, although the mechanisms and clinical significance of this change remain uncertain (15). Extracorporeal shockwave therapy may provide additional pain relief in some patients, particularly when combined with exercise rehabilitation, but treatment responses vary (16).

4.2 Why Tendon-Directed Rehabilitation Alone May Fail

4.2.1 Mechanical Loading Requires a Biological Response

All current rehabilitation protocols share a common assumption: mechanical loading will stimulate collagen synthesis and tendon remodeling. However, in adolescent female runners with RED-S, isotretinoin

exposure, or both, this response may be impaired. Rehabilitation may therefore provide an appropriate mechanical stimulus while the physiological response required for adaptation is reduced or delayed. This offers one possible explanation for persistent symptoms despite appropriate adherence and load progression, although it has not yet been tested directly in this population.

4.2.2 Relative Energy Deficiency in Sport (RED-S)

As discussed in section 2, RED-S may impair tendon adaptation through several complementary mechanisms. Chronic low energy availability suppresses hypothalamic GnRH secretion, leading to reduced estrogen production and impaired collagen turnover within tendon tissue (1,40). At the same time, circulating IGF-1 decreases while cortisol concentrations increase, creating a catabolic environment characterized by reduced collagen synthesis and increased protein degradation (9,10). Together, these hormonal changes diminish the biological substrate required for tendon remodeling.

Low energy availability may also coexist with inadequate intake of protein and micronutrients involved in connective tissue health, further limiting recovery and tissue regeneration (10). Under these circumstances, increasing rehabilitation intensity may not improve outcomes and could instead increase mechanical demand on a tendon whose biological response to loading is reduced or delayed.

4.2.3 Isotretinoin

As discussed in Section 3, isotretinoin may modify tendon adaptation through effects on tendon structure and biomechanical properties. Experimental evidence from a rat model demonstrated histopathological changes and reductions in elastic modulus, yield force, and ultimate tensile force following isotretinoin exposure (13). Human evidence is more limited and includes reported clinical tendinopathy, tendon-thickness changes, and isolated cases of acute Achilles tendon symptoms during therapy (41–44). These findings make it biologically plausible that some patients receiving isotretinoin may respond differently to progressive loading. However, no clinical study has established a narrower safe loading range or a specific modified rehabilitation protocol for isotretinoin-treated athletes.

4.3 Potential Combined Effects of RED-S and Isotretinoin

When RED-S and isotretinoin exposure coexist, they may affect tendon recovery through potentially distinct pathways: RED-S may reduce anabolic and collagen-remodeling capacity, while isotretinoin may alter tendon tissue properties. Furthermore, because isotretinoin has been associated with menstrual irregularities (48), distinguishing drug-induced menstrual dysfunction from RED-S-related hypothalamic amenorrhoea may present an additional diagnostic challenge.

Emerging clinical evidence also suggests that hormonal status may influence rehabilitation outcomes. In a retrospective cohort of runners treated with extracorporeal shockwave therapy for Achilles or hamstring tendinopathy, female athletes using oral contraceptives were less likely to achieve clinically meaningful improvement than non-users, including within the Achilles subgroup (50). Although oral contraceptive exposure is not equivalent to RED-S-related hypoestrogenism, this finding provides indirect evidence that sex-hormone status may be associated with treatment response; causation cannot be inferred from this observational study.

4.4 Proposed Integrated Management

Taken together, these findings suggest that treatment should target both the tendon and the systemic factors limiting its capacity to adapt. Mechanical loading should remain the foundation of rehabilitation, consistent with current clinical guidelines discouraging complete rest (16,49). However, progression should be guided by symptom and functional outcomes, including VISA-A scores, heel-raise performance, running tolerance, and side-to-side performance, rather than fixed timelines alone, as systemic factors may substantially delay biological adaptation.

For athletes with RED-S, restoring adequate energy availability through increased dietary intake, reduced exercise expenditure, or both should occur concurrently with rehabilitation. Management may require a multidisciplinary team that includes a sports medicine physician, registered sports dietitian, physical therapist, mental health professional, and, where appropriate, the athlete's coach (1,3). Addressing low energy availability should be

considered a core component of management because it may restore the physiological conditions needed for tissue recovery and adaptation.

Where isotretinoin use is identified, persistent or worsening tendon symptoms should prompt communication with the prescribing dermatologist or physician, who can determine whether any modification of isotretinoin therapy is appropriate (41,43). Athletes should not alter or discontinue isotretinoin independently. Because evidence guiding rehabilitation during isotretinoin therapy remains limited, clinicians should exercise caution when progressing high-load rehabilitation programs.

The integrated management approach proposed in this review represents a synthesis of current evidence rather than an established clinical guideline. Future prospective studies are required to determine whether addressing systemic biological factors alongside progressive loading improves outcomes in adolescent female runners with midportion Achilles tendinopathy.

Conclusion

The evidence reviewed suggests that rest-based rehabilitation alone is unlikely to be sufficient for some adolescent female runners with midportion Achilles tendinopathy because tendon recovery depends on both mechanical loading and adequate biological capacity for adaptation. Although progressive loading remains the cornerstone of treatment, successful rehabilitation requires normal collagen synthesis, tissue remodeling, and hormonal regulation. When these biological processes are impaired, mechanical unloading or appropriately prescribed loading may fail to produce the expected tendon adaptation.

The literature reviewed indicates that RED-S may reduce tendon adaptation through prolonged low energy availability, hormonal disruption, reduced IGF-1, elevated cortisol, and chronic hypoestrogenism, all of which may impair collagen synthesis and tissue repair. In contrast, isotretinoin appears to influence tendon biology through different mechanisms, with experimental studies demonstrating histopathological and biomechanical changes and human studies reporting tendinopathy, altered tendon morphology, and isolated cases of Achilles tendon symptoms. Together, these findings suggest

biologically plausible mechanisms by which tendon responsiveness to rehabilitation may be reduced.

Despite these findings, important gaps remain. No prospective clinical study has directly investigated rehabilitation outcomes in adolescent female runners with both RED-S and isotretinoin exposure. Likewise, no study has established whether correcting low energy availability or modifying isotretinoin therapy improves tendon adaptation during rehabilitation. Current evidence is therefore based largely on indirect associations, animal studies, observational research, and biological plausibility rather than direct clinical trials.

Future research should prospectively examine how energy availability, menstrual function, isotretinoin exposure, and progressive loading interact during rehabilitation. Until stronger evidence becomes available, clinicians should assess systemic biological factors alongside tendon loading when managing adolescent female runners with persistent midportion Achilles tendinopathy. Such an integrated approach may improve rehabilitation outcomes beyond tendon-directed treatment alone.

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