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Isotretinoin Therapy and Physical Activity - Implications for Athletes and Physically Active Individuals: A Narrative Review

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Abstract

Background. Isotretinoin is widely used and highly effective in the treatment of severe acne. However, its use is associated with a broad range of adverse effects, some of which may be particularly relevant in physically active individuals. Athletes are often exposed to factors that increase the risk of acne and may therefore be more likely to require systemic treatment. At the same time, the potential impact of isotretinoin on physical performance and training remains unclear.

Aim. The aim of this narrative review was to summarise the current knowledge on the adverse effects of isotretinoin, with a focus on those that may be important in physically active individuals.

Material and methods. A literature search was performed using PubMed and Web of Science databases, including studies published between 2016 and 2026. The search included terms related to isotretinoin, physical activity, exercise, and adverse effects. Only articles published in English were considered, and the results were reviewed and organised thematically.

Results. The findings suggest that isotretinoin may affect several organ systems. Musculoskeletal symptoms, such as muscle and joint pain or increased creatine kinase levels, seem particularly relevant in individuals who engage in regular physical activity. Ocular and mucocutaneous side effects, although usually mild, may still influence comfort during exercise. The relationship between isotretinoin and mental health appears more complex, with most studies indicating a low overall risk, but some patients still reporting mood-related symptoms.

Conclusions. While isotretinoin is an effective treatment, its effects are not limited to the skin and may be more noticeable in physically active individuals. In this group, even mild side effects can affect training and overall well-being. At the same time, there is still a lack of research focused specifically on athletes, which highlights the need for further studies in this area.

Key words: isotretinoin; acne vulgaris; physical activity; athletes; adverse effects

1. Introduction

Skin problems are very common among athletes, although they are often underestimated in everyday clinical practice. Regular physical activity, especially in contact or high-intensity sports, exposes the skin to repeated friction, pressure, heat, and moisture, all of which

can contribute to the development of various dermatological conditions. One of the most typical non-infectious conditions seen in this group is acne, including a specific subtype known as acne mechanica, which results from chronic mechanical irritation caused by sports equipment or tight clothing. While acne in athletes is often mild, in some cases it may become more severe and resistant to standard therapy, requiring systemic treatment such as isotretinoin (1).

At the same time, many athletes, particularly adolescents and young adults, are highly focused on improving their physical performance and body composition. As a result, the use of dietary supplements, especially whey protein, has become increasingly popular. This is due to its benefits in supporting muscle growth. However, at the same time, some studies have shown a positive association between whey protein consumption and risk of acne vulgaris (2).

Together, these factors may result in a higher rate of isotretinoin use among athletes, as it is commonly prescribed for the treatment of acne. Although isotretinoin is highly effective, it is also associated with a wide range of adverse effects that have been widely studied (3). Because of their diversity, some of these side effects may be particularly challenging for physically active individuals, as they can affect skin integrity and overall comfort during exercise. Moreover, certain adverse effects may carry more serious health implications, as suggested by some studies (4).

The aim of this narrative review was to provide an overview of the adverse effects associated with isotretinoin therapy, with a particular focus on those relevant to physically active individuals. Special attention was given to musculoskeletal, psychiatric, mucocutaneous, and ocular side effects, as these may affect physical performance, exercise tolerance, recovery, and overall well-being in athletes. The review also aims to highlight potential risks that may require closer monitoring in this population.

2. Materials and Methods

A literature search was carried out in the PubMed and Web of Science databases. The purpose was to find relevant studies on the effects of isotretinoin therapy, especially adverse effects for physically active individuals.

The search included publications from 2016 to 2026. Additionally, selected landmark studies published before 2016 were included when essential for the conceptual and mechanistic framework of the review. The following keywords and combinations were used: “isotretinoin”,

“13-cis-retinoic acid”, “physical activity”, “exercise”, “athletes”, “myalgia”, “musculoskeletal symptoms”, “muscle strength”, “mental health”, ”rhabdomyolysis” and “adverse effects”.

Only articles published in English were included. Both original research articles and review papers were considered. Studies focused on the systemic use of isotretinoin and its possible impact on musculoskeletal function, muscle strength and mental health were included. Adverse effects on skin and eyes were also considered.

Articles not in English, opinion pieces, conference abstracts, studies with insufficient methodological details, or those without full-text availability were excluded.

Since this review is narrative, no formal quality assessment or meta-analysis was conducted. The chosen studies were analysed and organised thematically.

3. Research results

3.1. Mechanism of Action

Isotretinoin (13-cis-retinoic acid) is a systemic retinoid approved for the treatment of severe recalcitrant nodular acne (5), although it is also frequently used off-label (6). It acts as a prodrug that is intracellularly converted to all-trans retinoic acid. Despite decades of clinical use, its exact mechanism of action remains not fully understood. However, available evidence indicates that its therapeutic effects are multifactorial and target several key pathways involved in acne pathogenesis. Notably, isotretinoin is the only drug that affects all four primary pathogenic factors of acne (7).

One of its principal mechanisms of action is a marked reduction in sebaceous gland activity and sebum production. Isotretinoin induces apoptosis in sebocytes, leading to a decrease in gland size and long-term suppression of sebum secretion (8,9). As a result, reduced sebum production limits comedogenesis and creates a less favorable environment for the proliferation of *Cutibacterium acnes* (7), a bacterium considered central to acne development.

In addition, isotretinoin exhibits significant anti-inflammatory properties. It modulates the immune response by reducing the production of inflammatory cytokines in acne patients’ monocytes exposed to *Cutibacterium acnes*. This effect is associated with decreased expression of Toll-like receptor 2 on these cells, which can be observed as early as one week after initiation

of therapy. This effect is believed to persist for at least six months after treatment discontinuation (10). Furthermore, isotretinoin therapy has been associated with reductions in systemic inflammatory markers, including white blood cell count, neutrophil-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio (11).

Beyond its dermatological effects, isotretinoin may influence multiple organ systems, including the musculoskeletal, ocular, neuropsychiatric, renal and others. These systemic effects are reflected in its well-documented adverse effect profile (5). Although the precise mechanisms underlying these effects remain unclear, they highlight the broad, systemic biological activity of isotretinoin.

These effects are particularly relevant in physically active individuals, as the drug's adverse effect profile may negatively influence physical performance and pose an additional challenge to athletic activity.

3.2. Musculoskeletal effects

Musculoskeletal adverse effects are among the most frequently reported systemic complications associated with isotretinoin therapy and include a wide spectrum of clinical manifestations. These include myalgia, arthralgia, low back pain, tendinopathy, and sacroiliitis, with symptoms ranging from mild discomfort to more severe conditions (12,13).

Low back pain is consistently identified as the most common musculoskeletal complaint. In a cross-sectional study including 94 patients treated with isotretinoin, low back pain was reported in 70.2% of patients, myalgia in 53.2%, and arthralgia in 47.9% (14). Similar findings were observed in other studies, where back pain occurred in 41% to 74% of patients, confirming its predominance among musculoskeletal manifestations (12).

Sacroiliitis represents a less common but clinically relevant complication. It was identified in 11.7% of patients in the same cohort and confirmed by radiological findings (14). Evidence from other reports and reviews also supports the occurrence of sacroiliitis as an isotretinoin-associated adverse effect (12,15).

Muscular involvement is also commonly reported. Myalgia is usually mild; however, laboratory abnormalities such as elevated creatine kinase (CK) levels have been documented in a proportion of patients. Sometimes that occurred in the absence of clinical symptoms. CK elevation has been reported in up to 5.6–41% of cases in the literature, indicating muscular

cell damage during treatment (15). In some cases, particularly in physically active individuals undergoing intense exercise, CK elevation can be significant (15,16).

Arthralgia is also a commonly reported musculoskeletal adverse effect of isotretinoin therapy. In a cross-sectional study, joint pain was observed in 47.9% of patients receiving isotretinoin (14). Earlier reports indicate that arthralgia may occur in approximately 20% of treated individuals (18). The symptoms are typically mild to moderate in severity and are usually not associated with objective inflammatory findings or laboratory abnormalities (14).

Additional manifestations include tendinopathy and enthesitis, although these occur less frequently. In clinical studies, tendinopathy was reported in approximately 4.3% of patients, most commonly affecting the Achilles tendon (14).

The exact mechanism is not fully understood, but isotretinoin is believed to induce apoptosis in muscle cells and other tissues, which may contribute to these effects (16).

The onset of musculoskeletal symptoms typically occurs within the first few months of treatment. In clinical observations, the median time to symptom development was approximately 3 months. In most cases, musculoskeletal symptoms improve or resolve after dose reduction or discontinuation of isotretinoin therapy, within the first month (14). Some authors have suggested that supplementation with folic acid and vitamin B12 may alleviate isotretinoin-induced musculoskeletal pain; however, this observation is based on limited clinical data and requires further investigation (19).

3.3. Rhabdomyolysis

Rhabdomyolysis is a serious but rare complication of isotretinoin therapy. Several case reports show it can happen in patients taking isotretinoin, often linked to physical exertion. One report describes a previously healthy teenager who developed acute rhabdomyolysis after intense exercise while on isotretinoin treatment. This case showed high creatine kinase levels and myoglobin in the urine (20). Another report covered a woman who experienced rhabdomyolysis after several months on isotretinoin combined with regular exercise. Her creatine kinase levels exceeded 25,000 U/L (4). Other reports suggest that rhabdomyolysis can also occur soon after starting treatment, even without trauma, and may include signs of muscle inflammation (21). Additionally, there have been cases of significant increases in creatine kinase, some with no clear symptoms. This indicates that rhabdomyolysis can

develop without obvious clinical signs and suggests that muscle injuries related to isotretinoin may often go unnoticed, especially in active individuals (22).

3.4. Muscle strength

Elevated creatine kinase levels and previous findings suggesting a possible myotoxic effect of isotretinoin raise the question of whether the drug may also affect muscle strength. In a prospective controlled study, muscle strength of the hamstrings and quadriceps was assessed in patients treated with isotretinoin and compared with a control group using an isokinetic dynamometer. The results showed no significant differences between the groups at baseline, and no significant changes were observed after six months of treatment. Additionally, no association was found between serum creatine kinase levels and muscle strength parameters. Overall, these findings suggest that isotretinoin does not appear to impair muscle strength during treatment (23).

3.5. Mucocutaneous effects

Cutaneous adverse effects are among the most common and characteristic features of isotretinoin therapy, affecting a large proportion of patients and forming the dominant group of reported side effects. Clinical evidence consistently shows that mucocutaneous symptoms such as dry skin, erythema, scaling and pruritus are not only frequent but, in many cases, expected during treatment. In a large meta-analysis including over 3200 patients, dry skin was reported in approximately 49% of individuals, while erythematous changes and skin fragility affected around 27% (24). Other studies report even higher rates, with xerosis occurring in up to 70% of patients, further highlighting how common these symptoms are in everyday clinical practice (25). Increased susceptibility to sunburn has also been reported during isotretinoin therapy, although it appears less frequently than other mucocutaneous adverse effects. In the same meta-analysis, sunburn was observed in approximately 12% of patients (24).

This may be related to isotretinoin-induced alternations in the epidermal barrier, including reduced sebum production and changes in the stratum corneum, as described in previous studies (24).

3.6. Ocular effects

Ocular side effects are among the most frequently reported systemic complications of isotretinoin therapy. The drug has a noticeable impact on the ocular surface, most commonly leading to symptoms associated with dry eye disease.

One of the main mechanisms involves the meibomian glands, which are responsible for producing the lipid layer of the tear film. Isotretinoin disrupts their function and reduces lipid secretion, which results in faster tear evaporation and instability of the tear film (26). This is believed to happen via suppressed expression of the PPARγ pathway (27). At the same time, it affects conjunctival goblet cells, leading to decreased mucin production and further impairment of tear film quality (28)

Together, these changes disturb the balance of the tear film and contribute to increased osmolarity and irritation of the ocular surface, which are characteristic features of dry eye (29). In clinical practice, this often presents as blepharoconjunctivitis, with inflammation of the eyelids and conjunctiva.

Patients commonly report symptoms such as a gritty or foreign body sensation, eye discomfort, and blurred vision. In one study, these symptoms were reported by a large proportion of isotretinoin users, with blurred vision affecting up to 75.9% of patients. Many individuals also require regular use of lubricating eye drops, which reflects the severity of tear film disruption (30).

In addition, isotretinoin may also influence corneal function. A decrease in corneal sensitivity and changes in corneal nerve structure have been observed, which can weaken protective mechanisms such as blinking and tear secretion, further worsening ocular surface damage (28,29). Less commonly, more complex visual disturbances have also been reported, including impaired visual field and altered colour vision (30). Although these effects are not as frequent, they suggest that isotretinoin may have a broader impact on the visual system.

Overall, large-scale data analyses confirm that isotretinoin is strongly associated with drug-induced dry eye, emphasising the importance of monitoring ocular symptoms during treatment (30).

3.7. Mental health

Concerns about psychiatric side effects have accompanied isotretinoin therapy for many years. Symptoms such as low mood, emotional instability, or even suicidal ideation are among the adverse effects reported by patients, which is also reflected in official drug labelling (34). This has led to ongoing debate and uncertainty in clinical practice, encouraging researchers to take a closer look at the issue. As a result, a wide range of studies have been conducted in an attempt to better understand whether these symptoms are a direct effect of the drug or part of the broader psychological burden associated with acne.

Taken together, the current evidence suggests that the relationship between isotretinoin and psychiatric outcomes is far more nuanced than it was once believed. Large-scale studies provide a reassuring picture at the population level. A recent meta-analysis including over 1.6 million participants showed that the absolute risk of suicide-related outcomes during isotretinoin therapy is very low (below 0.5%), while the risk of depression is relatively modest (around 3.8%). Importantly, isotretinoin was not associated with an increased overall risk of psychiatric disorders, and some data even suggest a reduced risk of suicide attempts following treatment (35). Similar conclusions have been drawn from a retrospective cohort study, where isotretinoin did not increase the incidence of psychiatric outcomes when compared to other acne treatments and, in some cases, was associated with a lower risk (36).

At the same time, these reassuring findings do not mean that psychiatric symptoms do not occur. Clinical data show that a subset of patients may experience mood changes during treatment. In adolescents, approximately 16% developed new psychiatric symptoms or diagnoses, although most cases were mild and did not require discontinuation of therapy (37). What stands out is that patients with a prior psychiatric history were more likely to report symptoms such as low mood or emotional instability, suggesting that individual vulnerability plays a key role (37).

This picture becomes even more complex when real-world pharmacovigilance data are considered. Analysis of the EudraVigilance database, based on over 33,000 safety reports, found that nearly one-third included neuropsychiatric symptoms, most commonly depression, anxiety, and suicidal ideation. These reports were particularly frequent among adolescents and were more often submitted by patients or caregivers rather than healthcare professionals (38). However, such data should be interpreted carefully, as spontaneous reporting systems tend

to overrepresent more noticeable or concerning symptoms and cannot establish a direct causal relationship.

4. Discussion

This narrative review highlights that although isotretinoin remains a very effective treatment option for severe acne, its use is associated with a wide range of systemic adverse effects that may be particularly relevant for physically active people (3). The findings of this review suggest that musculoskeletal, mucocutaneous, ocular, and psychiatric effects should be carefully considered in this population, as they may influence not only overall health but also physical performance and training capacity.

Musculoskeletal symptoms appear to be among the most clinically relevant adverse effects in the context of physical activity. The relatively high prevalence of myalgia, arthralgia, and low back pain, together with frequently observed elevations in creatine kinase levels, raises concerns about a possible myotoxic effect of isotretinoin. Although current evidence suggests that muscle strength itself is not significantly impaired (23), the presence of subclinical muscle injury and the risk of rare but serious complications, such as rhabdomyolysis, may be particularly important in individuals engaging in intense exercise (4). While available data do not support the need for routine monthly laboratory monitoring in patients receiving standard doses of isotretinoin (39), athletes may represent a specific subgroup requiring closer observation. This is because many of the reported symptoms may overlap with those related to physical training itself, making them more difficult to recognise. As a result, there is a risk that early signs of drug-related toxicity may be overlooked in this population.

Ocular and mucocutaneous side effects, although often considered less severe, can still have a noticeable impact on daily functioning and comfort during physical activity. Changes in the tear film and skin condition may reduce tolerance to environmental factors such as wind, sweat, and friction, which are commonly encountered during exercise, especially outdoors. While these effects are usually manageable, they may still affect adherence to treatment or training routines, particularly in individuals who remain physically active during therapy. In this context, supportive care becomes an important part of managing these symptoms. Simple measures, such as using lubricating eye drops and maintaining proper skin care, including moisturisers and sun protection, can help improve comfort and make the treatment easier

to tolerate. In addition, some evidence suggests that oral omega-3 supplementation in patients receiving isotretinoin may help reduce mucocutaneous side effects (40).

The relationship between isotretinoin and mental health is still not fully clear. While large studies suggest that the overall risk of serious psychiatric outcomes is low (35,36), some patients may still experience mood changes or emotional difficulties during treatment (37). This highlights the importance of an individualised approach, especially in athletes, for whom psychological well-being plays a key role in performance and recovery.

Overall, the available evidence suggests that the effects of isotretinoin in physically active individuals are complex and extend beyond a single organ system. Rather than causing a uniform impairment, the drug appears to influence several areas that, together, may affect an individual's ability to train and perform at their usual level.

This review has several limitations. As a narrative review, it is inherently subject to selection bias and does not include a formal assessment of study quality. In addition, many of the available studies were not conducted specifically in athletic populations, which limits how directly these findings can be applied to this group.

Despite these limitations, this review highlights the importance of taking physical activity into account when evaluating the safety profile of isotretinoin. Clinicians should be aware of the potential impact of treatment on physically active patients and consider appropriate counselling and monitoring.

Further research is needed, particularly prospective studies focused on athletes, to better understand how isotretinoin interacts with physical performance and to identify individuals who may be at higher risk of adverse effects.

5. Conclusion

Although isotretinoin is highly effective, its effects go beyond the skin and may be especially relevant for physically active individuals. In this group, even relatively mild side effects can interfere with training. At the same time, there is still limited research focused specifically on athletes, highlighting an important gap in the literature. More studies in this area could help improve our understanding and better guide clinical practice.

Disclosure

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Declaration of the use of generative AI and AI-assisted technologies in the writing process

In preparing this work, the author(s) used ChatGPT for language improvement and grammatical correction. After using this tool/service, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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