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Isotretinoin-Associated Musculoskeletal Adverse Effects: Mechanisms, Clinical Manifestations, Risk Factors, and Monitoring Strategies – A Narrative Review

Authors:

Makary Hejduk

ORCID https://orcid.org/0009-0004-7579-4471

E-mail makaryhejduk@gmail.com

Independent Public Health Care Facility in Myślenice, Poland

Aleksandra Papuga

ORCID https://orcid.org/0009-0003-6851-7102

E-mail amp.papuga@gmail.com

Independent Public Health Care Facility in Myślenice, Poland

Karolina Domańska
ORCID https://orcid.org/0009-0009-1701-7961
E-mail karolina.domanska54@gmail.com
Independent Public Health Care Facility in Myślenice, Poland

Joanna Makowska
ORCID https://orcid.org/0009-0000-6342-8379
E-mail joannamakowska10@gmail.com
Independent Public Health Care Facility in Myślenice, Poland

Jerzy Darmoń
ORCID https://orcid.org/0009-0008-3139-6366
E-mail darmonjerzy@gmail.com
Medical University of Silesia in Katowice, Poland

Maria Windyga
ORCID https://orcid.org/0009-0006-6937-909X
E-mail maria.windyga@poczta.fm
5th Military Hospital with Polyclinic in Kraków, Poland

Anna Sieczka
ORCID https://orcid.org/0009-0003-5509-3486
E-mail asieczka1517@gmail.com
Independent Public Health Care Facility in Myślenice, Poland

Natalia Piegza
ORCID https://orcid.org/0009-0002-9348-0113
E-mail nataliapiegza9@gmail.com
Independent Public Health Care Facility in Myślenice, Poland

Magdalena Grzymek
ORCID https://orcid.org/0009-0000-4337-0261
E-mail magdalena.g2904@gmail.com
The University Hospital in Kraków, Poland

Martyna Więcławek
ORCID https://orcid.org/0009-0006-7956-9962
E-mail martynawieclawek44@gmail.com
The University Hospital in Kraków, Poland

Corresponding Author:
Makary Hejduk, makaryhejduk@gmail.com

Abstract

Background: Oral isotretinoin is highly effective for severe and treatment-resistant acne, but its musculoskeletal safety profile remains incompletely defined.

Aim: This narrative review aimed to summarize current evidence regarding the relationship between isotretinoin therapy and musculoskeletal adverse effects, with particular emphasis on pathophysiological mechanisms, the role of exercise, clinical manifestations, and monitoring strategies.

Methods: PubMed and Google Scholar were searched for English-language articles published from January 2010 to March 2026. Observational studies, case reports, case series, reviews, and guidelines on musculoskeletal outcomes were included.

Results: Isotretinoin-associated musculoskeletal manifestations include low back pain, myalgia, arthralgia, tendinopathy, sacroiliitis, fatigue, asymptomatic creatine kinase elevation, and rare rhabdomyolysis. Most abnormalities appear mild or reversible, but severe muscle injury has been reported, particularly after strenuous exercise. Proposed mechanisms include retinoid-related apoptotic signaling, oxidative stress, mitochondrial vulnerability, and exercise-induced muscle membrane injury, although direct mechanistic evidence remains limited. Creatine kinase elevation is nonspecific and should be interpreted together with symptoms, recent exercise, renal function, hydration status, and aminotransferase patterns.

Conclusions: Although severe muscle complications during isotretinoin therapy are uncommon, clinicians should be aware of potential muscle toxicity, particularly in physically active patients. Individualized monitoring, patient education, and further prospective studies are needed to improve the safety of isotretinoin treatment.

Keywords: isotretinoin; acne vulgaris; creatine kinase; rhabdomyolysis; musculoskeletal injury; low-back pain.

1. Introduction

Acne vulgaris is one of the most common chronic inflammatory skin diseases worldwide, affecting up to 85% of adolescents and young adults [1]. In addition to its cutaneous manifestations, acne is associated with substantial psychosocial burden, including anxiety, depression, reduced self-esteem, and permanent scarring [1,2]. Oral isotretinoin, a systemic retinoid and derivative of vitamin A remains one of the most effective therapeutic options for severe acne and for acne that fails to respond adequately to conventional topical or systemic therapy. Current American Academy of Dermatology guidelines strongly recommend oral isotretinoin for severe acne, acne associated with scarring or psychosocial burden, and acne unresponsive to standard treatment with topical or oral agents [3].

The therapeutic efficacy of isotretinoin is related to its multidirectional effects on the major pathogenic mechanisms of acne, including suppression of sebaceous gland activity, reduction of sebum production, modulation of follicular keratinization, inhibition of *Cutibacterium acnes* proliferation and anti-inflammatory activity [1,4]. Despite its high efficacy, isotretinoin therapy is associated with a broad adverse-effect profile and requires clinical and laboratory monitoring during treatment. Traditional laboratory monitoring has focused mainly on pregnancy prevention, lipid abnormalities, hepatic enzyme elevations, whereas the clinical relevance of creatine kinase (CK) elevation remains less clearly defined [5,6].

The most frequently reported adverse effects of isotretinoin include mucocutaneous manifestations, such as cheilitis and xerosis, as well as laboratory abnormalities, most notably dyslipidemia and elevated liver enzyme levels [1,7]. However, musculoskeletal symptoms are also increasingly reported and include low back pain, arthralgia, myalgia, tendinopathy, sacroiliitis, and, less commonly, laboratory or clinical evidence of skeletal muscle injury [8-10].

Among the potential musculoskeletal complications of isotretinoin therapy, creatine kinase elevation is of particular interest because it may represent either a benign laboratory abnormality or a marker of clinically relevant skeletal muscle injury. CK elevation during isotretinoin treatment may occur in asymptomatic patients, in patients with nonspecific myalgia, or in the setting of recent strenuous physical activity. The relationship between

isotretinoin, CK elevation, and exercise remains clinically important but incompletely understood [11–13]. Sayar et al. retrospectively evaluated patients treated with isotretinoin and reported CK elevation in 20.1% of patients. In the same study, marked CK elevation and symptomatic cases were less common than mild or moderate laboratory abnormalities [11].

Although most CK elevations during isotretinoin therapy appear to be mild, transient, or clinically asymptomatic, rare cases of rhabdomyolysis have been reported. Rhabdomyolysis is a potentially serious syndrome caused by skeletal muscle breakdown with release of intracellular contents, including CK and myoglobin, into the circulation. Clinically, rhabdomyolysis may present with myalgia, muscle weakness, dark urine, electrolyte abnormalities, and acute kidney injury [14,15].

The clinical challenge is that the same laboratory signal — an elevated CK level — may reflect very different clinical situations. In an isotretinoin-treated patient, CK elevation may result from physiological post-exercise muscle enzyme release, asymptomatic hyperCKemia, or early rhabdomyolysis. This is particularly relevant for adolescents and young adults, who represent a large proportion of isotretinoin-treated patients and may simultaneously participate in resistance training, endurance sports or other strenuous physical activities [11–15].

Despite growing attention to CK elevation and musculoskeletal symptoms, routine CK monitoring is not universally recommended for all patients receiving isotretinoin [5,6,12,13]. The true incidence of clinically meaningful skeletal muscle injury during isotretinoin therapy remains uncertain because much of the literature consists of observational studies, retrospective analyses, case reports, and expert interpretation rather than large prospective studies. The mechanisms, risk factors, and optimal monitoring strategy also remain incompletely defined [12,13,16]. This narrative review aims to summarize current evidence regarding isotretinoin therapy and the risk of skeletal muscle injury, with particular emphasis on proposed pathophysiological mechanisms, clinical manifestations, the modifying role of exercise, interpretation of CK, and monitoring strategies.

2. Materials and methods

This article was designed as a narrative review focusing on the association between isotretinoin therapy and musculoskeletal adverse effects, with particular emphasis on proposed pathophysiological mechanisms, clinical manifestations, creatine kinase abnormalities, exercise-related risk, rhabdomyolysis, and practical monitoring strategies.

A literature search was performed using PubMed and Google Scholar. The search focused on articles published between January 2010 and March 2026. Older publications were considered only when they provided important background information or were repeatedly cited in more recent literature. The following search terms and combinations were used: “isotretinoin”, “13-cis retinoic acid”, “creatine kinase”, “CK”, “hyperCKemia”, “myalgia”, “myopathy”, “rhabdomyolysis”, “skeletal muscle injury”, “exercise”, “physical activity”, “athlete”, “low back pain”, “sacroiliitis”, “arthralgia”, “tendinopathy”, and “musculoskeletal adverse effects”.

The review included original observational studies, cross-sectional studies, retrospective analyses, case reports, case series, narrative reviews, and clinical guidelines published in English. Studies were excluded if they were unrelated to isotretinoin, did not address musculoskeletal or muscle-related outcomes, or focused exclusively on non-musculoskeletal adverse effects. Relevant articles were first identified through title and abstract screening. Full texts were then reviewed to determine their suitability for inclusion.

Data were extracted and synthesized narratively rather than quantitatively. The evidence was organized thematically around the following areas: musculoskeletal adverse effects of isotretinoin, creatine kinase elevation, exercise as a potential contributing factor, rhabdomyolysis, sacroiliitis and axial symptoms, proposed mechanisms of skeletal muscle injury, interpretation of laboratory abnormalities, and monitoring strategies. Case reports were used primarily to illustrate rare but clinically important complications, whereas observational studies and reviews were used to describe broader patterns of musculoskeletal symptoms and laboratory abnormalities.

3. Results

3.1 Isotretinoin and Musculoskeletal Adverse Effects

Musculoskeletal adverse effects represent an important but often underemphasized component of the safety profile of systemic isotretinoin therapy [8–10,17]. Although mucocutaneous symptoms remain the most common and most predictable adverse effects of isotretinoin, several studies have shown that skeletal muscle, axial skeleton, joints, tendons, and laboratory markers of muscle injury may also be affected during treatment [8–12]. The clinical spectrum is broad and includes fatigue, myalgia, arthralgia, low back pain, inflammatory back pain, sacroiliitis, tendinopathy, elevated creatine kinase levels, and, rarely, clinically significant myopathy or rhabdomyolysis [8-13,17-19]. A recent systematic review including analytical studies, case reports, and case series identified myalgia, low back pain, arthralgia, tendinopathy,

and sacroiliitis as the main musculoskeletal manifestations reported in association with isotretinoin therapy [8].

The frequency of musculoskeletal symptoms varies considerably between studies, probably because of differences in study design, definitions of adverse events, patient selection, isotretinoin dose, treatment duration, and whether symptoms were actively investigated or only spontaneously reported [8,10,17]. In a retrospective study of 200 patients receiving systemic isotretinoin, Acar et al. found that musculoskeletal adverse effects occurred in 49.5% of patients. Low back pain was the most common complaint, whereas sacroiliitis was identified in 2% of the cohort. Mild myalgia was reported in 3% of patients, elevated creatine kinase levels in 18%, and enthesitis in 1% [10]. Özkoca et al. reported lower frequencies in a cross-sectional study, with fatigue in 4.4%, myalgia in 2.8%, and low back pain in 25% of patients [17].

Low back pain is one of the most frequently reported musculoskeletal complaints during isotretinoin therapy [8–10,17]. Karaosmanoğlu and Mülkoğlu showed that it is a common complication of oral isotretinoin treatment and may present with either mechanical or inflammatory features, with a possible dose-related pattern [9]. This distinction is clinically important because mechanical low back pain is usually associated with posture, physical activity, or nonspecific musculoskeletal strain, whereas inflammatory back pain may be characterized by morning stiffness, nocturnal pain, improvement with movement, and possible sacroiliac involvement. Accordingly, inflammatory symptoms during isotretinoin therapy may raise suspicion of sacroiliitis and require careful clinical evaluation [9–17,19]. However, available studies show some variability in the reported pattern of back pain. For example, Özkoca et al. found that mechanical low back pain was more frequent than inflammatory low back pain among affected patients, and no cases of sacroiliitis were observed in their cohort [17]. These findings suggest that low back pain in isotretinoin-treated patients should not be regarded as a uniform adverse effect, but rather characterized according to pain pattern, severity, duration, functional limitation, and associated inflammatory features [9–17,19].

Myalgia and muscle stiffness are also recognized during isotretinoin therapy, but their clinical significance may range from mild discomfort to possible muscle injury [8,10-12,18]. In many patients, muscle symptoms are nonspecific and may occur without objective weakness or major laboratory abnormalities [10,12]. Acar et al. reported that 3% of patients receiving isotretinoin developed mild muscular adverse effects, such as myalgia and muscle stiffness, which resolved without the need for specific treatment [10].

Creatine kinase elevation is one of the most relevant laboratory manifestations of possible skeletal muscle involvement during isotretinoin therapy [11–13,18]. Slight CK elevation during treatment has often been described as a benign or self-limited finding, especially when it occurs without muscle symptoms, renal impairment, or other signs of rhabdomyolysis [11,12]. In Sayar's retrospective study, only a 16% of patients with elevated CK were symptomatic, and only two patients had CK levels above 1000 IU/L. The same study found that male sex was significantly associated with CK elevation, while a recent history of physical exercise was reported in 29% of patients with elevated CK [11]. These findings support the interpretation that CK elevation during isotretinoin therapy is not always a direct indicator of clinically important drug-induced myotoxicity and may be influenced by sex, physical activity, and other individual factors [11–13].

The relationship between isotretinoin, exercise, and CK elevation is particularly important because young patients treated for acne frequently engage in sports, resistance training, or other strenuous physical activities [11-13,]. Marson and Baldwin described the association between isotretinoin, elevated CK, and exercise as a clinical "conundrum," emphasizing that the correlation is not fully established and that CK interpretation requires attention to intrinsic and extrinsic patient factors [12]. In a later discussion, Marson and Baldwin recommended that dermatologists continue to ask about physical activity and consider the clinical context when interpreting CK elevations during isotretinoin therapy [13]. Tamer et al. evaluated 410 patients treated with systemic isotretinoin and found that median CK levels were similar before and after treatment at three months, while muscle or joint pain developed in 5.6% of patients. Based on these findings, the authors suggested that routine CK evaluation is unnecessary in all acne patients treated with isotretinoin, although symptoms should still prompt clinical attention [18].

Sacroiliitis is an uncommon but clinically important musculoskeletal adverse event reported during isotretinoin therapy [8–10,19]. It may present with inflammatory low back pain, and magnetic resonance imaging (MRI) may demonstrate active inflammatory changes in the sacroiliac joints [9,19]. Aydog et al. presented nine cases of sacroiliitis in patients treated with isotretinoin and reported that sacroiliitis was identified and monitored by MRI. In that case series, symptoms improved after isotretinoin was discontinued and nonsteroidal anti-inflammatory drugs were used, and follow-up MRI showed improvement in some patients. The authors also emphasized that although the association between isotretinoin and sacroiliitis has been described in the literature, the causal relationship is not completely understood [19].

Arthralgia and tendinopathy are additional musculoskeletal manifestations reported during isotretinoin therapy [8-9]. In the systematic review by Almutairi et al., arthralgia was identified in 17% of analyzed cases, while Achilles tendinopathy was reported in eight patients [8]. In the cross-sectional study by Karaosmanoğlu and Mülkoğlu, arthralgia was observed in 49.7% of patients receiving oral isotretinoin, whereas tendinopathy occurred in 4.3% [9]. Although these manifestations are generally discussed less frequently than low back pain or creatine kinase elevation, they remain clinically relevant because they may interfere with physical activity and reduce treatment adherence [8-9].

Bone-related adverse effects are rare during standard isotretinoin treatment for acne, but they remain relevant in selected risk groups [8,20]. In the systematic review by Almutairi diffuse idiopathic skeletal hyperostosis (DISH) was reported in two patients, indicating that retinoid-associated skeletal changes, although uncommon, may occur in isolated cases [8]. Premature epiphyseal closure of long bones has also been reported rarely in pediatric patients treated with isotretinoin, most often after prolonged exposure ranging from several months to years. Importantly, Alazawi et al. indicated that this complication has been described not only with high-dose oncologic regimens but also with therapeutic doses used for acne, underscoring the need to consider potential growth-plate effects in children and adolescents receiving isotretinoin [20].

Rarely, muscle involvement during isotretinoin therapy may extend beyond nonspecific myalgia or asymptomatic CK elevation to clinically significant myopathy or rhabdomyolysis [12,13,21]. Rhabdomyolysis is a serious condition characterized by skeletal muscle breakdown and release of intracellular contents, including CK and myoglobin, and may lead to acute kidney injury if not recognized and managed appropriately. Fayiga et al. described isotretinoin-associated rhabdomyolysis and emphasized the importance of recognizing CK elevation in the context of potential renal damage [21]. Marson and Baldwin also highlighted that although CK elevation is often benign, severe elevations must be interpreted in relation to symptoms, exercise exposure, and risk of rhabdomyolysis [12,13]. More recently, a case report described isotretinoin-associated myopathy with normal CK levels, suggesting that clinically relevant muscle toxicity may occasionally occur even without CK [22].

Overall, the available literature indicates that musculoskeletal adverse effects of isotretinoin are heterogeneous and usually mild or reversible, but they may occasionally require dose adjustment, treatment interruption, additional laboratory testing, imaging, or specialist referral. Low back pain, myalgia, arthralgia, and fatigue appear to be the most frequent clinical

complaints, whereas sacroiliitis, marked CK elevation, myopathy, and rhabdomyolysis are less common but clinically more consequential [8-13,17-22]. The practical challenge for clinicians is to distinguish common nonspecific symptoms from manifestations that suggest inflammatory disease or skeletal muscle injury [9–13,19-22].

3.2 Pathophysiological Mechanisms of Muscle Injury

The pathophysiological mechanisms responsible for skeletal muscle injury during isotretinoin therapy remain incompletely understood. Current evidence does not support a single, clearly established molecular pathway that could explain the full spectrum of muscle-related adverse effects observed during treatment. Instead, isotretinoin-associated muscle injury appears to be multifactorial and may involve retinoid-related apoptotic signaling, oxidative stress, mitochondrial dysfunction, altered muscle-cell membrane integrity. However, most of these mechanisms remain hypothetical, as direct mechanistic studies in human skeletal muscle from isotretinoin-treated patients are lacking. Therefore, the available explanations should be interpreted as biologically plausible concepts rather than confirmed causal pathways [12,19,22-24].

One of the most frequently discussed mechanisms is apoptosis-related tissue injury. Isotretinoin, or 13-cis-retinoic acid, belongs to the retinoid family and may influence cellular differentiation, proliferation, and apoptosis through retinoid-dependent pathways [23]. Melnik proposed that apoptosis could represent a unifying mechanism explaining both the therapeutic activity and several adverse effects of isotretinoin. According to this hypothesis, isotretinoin may promote pro-apoptotic signaling through intracellular conversion or interaction with retinoid-related pathways, and this effect could theoretically involve tissues beyond sebaceous glands, including skeletal muscle [23]. Melnik also suggested that isotretinoin-induced myalgia may be related to tumour necrosis factor-related apoptosis-inducing ligand-mediated muscle-cell apoptosis, although this remains hypothetical and direct clinical evidence in skeletal muscle is lacking. Interindividual susceptibility may further modify this response, as variability in apoptotic signaling pathways, including retinoic acid receptor-related genetic variation, could help explain why only some patients develop more pronounced muscle symptoms or biochemical evidence of muscle injury [23,24]. Therefore, apoptosis provides a biologically plausible explanation for muscle symptoms and CK release, but it should be interpreted as a

proposed mechanism rather than a proven pathway in isotretinoin-associated myotoxicity [12,23,24].

Oxidative stress has also been discussed as a possible contributor to isotretinoin related CK abnormalities, but the evidence remains indirect [12]. Marson and Baldwin emphasized that the relationship between isotretinoin, CK elevation, and exercise is clinically relevant but not fully defined. In this context, oxidative stress may represent a plausible mechanism by which retinoid exposure could increase muscle vulnerability, particularly when combined with strenuous exercise or other stressors. Nevertheless, there is currently insufficient direct clinical evidence to conclude that oxidative stress is the primary mechanism of skeletal muscle injury during isotretinoin therapy [12].

Another proposed mechanism involves direct cellular stress within skeletal muscle, although this pathway remains hypothetical. In vitro data cited by Drozd et al. suggest that isotretinoin may rapidly reduce mitochondrial membrane potential, promote cytochrome c release into the cytosol, and initiate apoptotic injury resembling mechanisms observed in mitochondrial myopathies [24]. Additional proposed pathways include FoxO hyperactivation, mitochondrial dysfunction, and MMP-2-mediated sarcolemmal instability, which have been discussed as plausible contributors to retinoid-related muscle injury [22]. However, these explanations remain largely mechanistic and speculative, as direct evidence from skeletal muscle tissue in isotretinoin-treated acne patients is still lacking [22,24].

The literature also includes several hypotheses regarding the mechanisms of isotretinoin-associated sacroiliitis. Aydog et al. suggested that isotretinoin may affect immune regulation by altering cytokine balance and may also exert detergent-like effects on lysosomal membranes, potentially contributing to synovial cell degeneration [19]. It has also been hypothesized that isotretinoin may increase cellular susceptibility to minor mechanical trauma that would not normally result in clinically apparent injury [9,19].

Overall, these mechanisms should be viewed as complementary hypotheses rather than established causal pathways, and further clinical and mechanistic studies are needed to define their actual role in isotretinoin-associated muscle and musculoskeletal adverse effects.

3.3 Risk factors, timing, and individual susceptibility

The risk of skeletal muscle involvement during isotretinoin therapy appears to be influenced by several patient-related and behavioral factors rather than by drug exposure alone. In the available literature, particular attention has been given to physical activity, age, sex, and

possible genetic susceptibility as variables that may modify the occurrence, severity, or interpretation of muscle-related adverse effects. These factors are especially relevant when interpreting creatine kinase elevation, because CK abnormalities may occur in asymptomatic patients and may also result from recent exercise independently of isotretinoin therapy. Therefore, muscle symptoms and laboratory abnormalities should be evaluated in a broader clinical. However, because most available data come from retrospective analyses, cross-sectional studies, and case reports, these factors should be considered potential risk modifiers rather than definitive predictors of clinically significant muscle injury [9-15,21-25].

Most symptomatic manifestations occur early, usually within the first weeks to the first few months of treatment, whereas structural skeletal changes appear to be more closely related to prolonged exposure. In a cross-sectional study by Karaosmanoğlu and Mülkoğlu, the onset of musculoskeletal symptoms was consistent with previous reports and occurred within the first few months, with a median value of 3 months [9]. Similar observations have been reported in studies and reviews describing early-onset low back pain, myalgia, CK elevation, and inflammatory axial symptoms during isotretinoin therapy [9,10,24]. Therefore, the first months of therapy appear to be the most important period for active clinical questioning about new back pain, muscle symptoms, weakness, or exercise intolerance.

Marson and Baldwin described the relationship between isotretinoin, elevated CK levels, and exercise as a “creatine kinase conundrum,” emphasizing that the available evidence supports only a limited and not fully established association between these variables. They suggested that CK values should not be interpreted in isolation, but rather in relation to recent exercise, symptoms, sex, and other patient-specific factors [12]. In a later publication, the same authors noted that CK elevation may be detected in a substantial proportion of isotretinoin-treated patients, but its clinical significance depends strongly on context [13]. These observations support an individualized approach rather than interpreting every CK elevation as direct evidence of isotretinoin-induced muscle injury [12,13].

Physical activity may act both as a confounder and as a potentiating factor [11–15]. As a confounder, exercise can produce transient CK elevation and muscle soreness independently of isotretinoin, making it difficult to distinguish physiological post-exercise enzyme release from drug-associated myotoxicity [11–13]. As a potentiating factor, strenuous activity may theoretically increase the vulnerability of muscle tissue during isotretinoin therapy and contribute to clinically relevant injury in susceptible patients [11,14,21]. Sayar reported CK elevation in 20.1% of isotretinoin-treated patients, and recent physical exercise was present in

29% of those with elevated CK. In the same study, only 16.2% of patients with CK elevation were symptomatic, suggesting that biochemical abnormalities may occur without clinically significant muscle complaints [11].

The strongest clinical signal supporting exercise as a potentiating factor comes from case reports of rhabdomyolysis occurring during isotretinoin therapy after intense physical activity. Case reports have described rhabdomyolysis after the combination of isotretinoin and intense exercise, including adolescent and young adult patients who developed severe hyperCKemia and myoglobinuria after strenuous training [14,15]. These observations do not imply that all physical activity is unsafe during isotretinoin treatment. Rather, they suggest that high-intensity exercise, competitive sports, military training, resistance training, or sudden increases in training load may increase the likelihood of clinically relevant muscle injury in susceptible individuals. For this reason, patients engaged in regular vigorous exercise may require more detailed counseling, closer symptom review, and selective CK assessment when muscle symptoms, weakness, dark urine, or unexplained transaminase elevation occur [12,14,15,24].

Male sex is one of the most consistently reported factors associated with CK elevation during isotretinoin therapy [11,12]. Sayar retrospectively evaluated 154 patients treated with isotretinoin and found CK elevation in 20.1% of patients, with male sex being a significant risk factor for elevated CK levels [11]. Marson and Baldwin also noted that available evidence suggests that CK elevation during isotretinoin therapy may be more likely in young male patients [12]. Therefore, male sex should not be interpreted as a direct causal factor, but it may identify a group in whom CK elevation is more likely to occur and may require more careful contextual interpretation [11,12].

Age may also influence the pattern of musculoskeletal adverse effects, although findings are not fully consistent [10,11,17]. Acar et al. reported that visual analogue scale scores for musculoskeletal pain correlated with age, suggesting that musculoskeletal symptoms may be more pronounced in older patients within their study population [10]. In contrast, Sayar did not find a significant difference in mean age between patients with and without CK elevation [11]. Özkoca et al. specifically evaluated whether skeletal side effects depended on age, gender, treatment duration, daily dose, and previous isotretinoin exposure, indicating that these variables are clinically relevant to assess, even though not all show consistent associations across studies [17]. These findings suggest that age may be more relevant for symptom burden than for isolated CK elevation [10,11,17].

Genetic susceptibility may represent a patient-specific factor influencing the risk of isotretinoin-associated musculoskeletal symptoms, although current evidence remains limited. Alzoubi et al. noted that selected polymorphisms in proteins involved in cell-death pathways have been associated with symptomatic arthralgia, while Melnik's mechanistic model suggests that interindividual differences in apoptosis-related signaling may contribute to variable tissue responses to isotretinoin. However, these findings should be interpreted as preliminary and hypothesis-generating rather than as established predictors of muscle or joint toxicity [23,25]

3.4 Monitoring strategies

Monitoring during isotretinoin therapy traditionally focuses on pregnancy prevention, lipid abnormalities, and hepatic enzyme elevations, whereas routine creatine kinase monitoring is not recommended for all patients [5,6,27]. Lee et al. showed that clinically significant laboratory abnormalities during isotretinoin therapy are uncommon in standard acne patients, and Xia et al. reached Delphi consensus that alanine aminotransferase and triglycerides should be checked before treatment and at peak dose, without supporting broad monthly laboratory testing [5,6]. Barbieri et al. similarly reported that frequent laboratory testing often has limited clinical utility [27]. These findings support a risk-adapted rather than universal approach to monitoring [5,6,27].

The available monitoring recommendations do not fully address skeletal muscle injury, because CK is not consistently included as a routine parameter in isotretinoin protocols [6,12,21]. Marson and Baldwin emphasized that the relationship between isotretinoin, CK elevation, and exercise remains clinically uncertain, but they suggested that baseline CK testing may be considered in selected patients, particularly those with high levels of physical activity [12]. Fayiga et al. argued that CK monitoring may be useful for identifying patients at risk of rhabdomyolysis and renal injury, especially when muscle symptoms or marked biochemical abnormalities occur [21]. Therefore, CK testing should not be viewed as mandatory for every patient, but rather as clinically appropriate in selected contexts [12,21].

For patients without muscle symptoms, high-intensity exercise exposure, or previous CK abnormalities, routine CK monitoring during isotretinoin therapy is not clearly supported by current evidence [5,6,12,18]. Tamer et al. found no significant difference between median CK levels before treatment and after three months of systemic isotretinoin therapy and concluded that routine CK evaluation is unnecessary in all acne patients treated with isotretinoin [18]. This conclusion is consistent with the broader trend toward reducing unnecessary laboratory testing

during isotretinoin treatment in low-risk patients. Nevertheless, clinicians should continue to ask about new muscle symptoms at follow-up visits, because CK may become relevant if symptoms or risk factors develop during therapy [12,18,21].

A targeted CK assessment appears reasonable in patients with muscle symptoms, unexplained weakness, high-intensity exercise exposure [12,21]. CK should also be considered when aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations occur without a clear hepatic explanation, particularly if gamma-glutamyl transferase (GGT) remains normal or the patient reports muscle symptoms or recent exercise [16,26]. Maden et al. found that changes in ALT and AST during isotretinoin therapy were more frequently associated with CK, while GGT remained unaffected, suggesting that some aminotransferase elevations may have a muscular rather than purely hepatic origin [16]. Webster et al. similarly noted that AST and ALT may fail to distinguish liver from muscle abnormalities during isotretinoin therapy [26]. These observations support adding CK and GGT in selected patients with unexplained aminotransferase elevations [16,26].

Rhabdomyolysis requires prompt recognition because skeletal muscle breakdown may lead to myoglobinuria, electrolyte disturbances, and acute kidney injury. In such cases, evaluation should include not only CK, but also creatinine, electrolytes, and urinalysis to exclude rhabdomyolysis and its renal complications. Case reports indicate that isotretinoin-associated rhabdomyolysis has occurred particularly in the context of physical exercise. Therefore, training history should be a regular component of assessment in patients with elevated CK or muscle symptoms [14,15,21].

Monitoring should also include non-muscular musculoskeletal manifestations. Low back pain during isotretinoin therapy may be mechanical, inflammatory, or related to sacroiliitis [9,19]. Patients presenting with persistent low back or hip pain, particularly when inflammatory features are suspected, may require targeted evaluation for sacroiliac involvement. MRI appears useful in this setting, as case series have confirmed sacroiliitis by magnetic resonance imaging during isotretinoin therapy [19,28].

Overall, current evidence supports a selective and individualized approach to monitoring of musculoskeletal safety during isotretinoin therapy. Routine CK testing in all patients is not clearly supported, but CK assessment is reasonable in patients with muscle symptoms, intense physical activity, previous CK abnormalities, unexplained AST or ALT elevation, suspected rhabdomyolysis, or special risk factors. This strategy may reduce unnecessary laboratory testing

in low-risk patients while improving recognition of clinically significant muscle injury in higher-risk groups [12,16,19,21].

4. Limitations and Future Directions

The current evidence on isotretinoin-associated musculoskeletal adverse effects remains limited and heterogeneous. Most available data come from retrospective studies, cross-sectional analyses, case reports, and narrative reviews rather than large prospective trials. Therefore, the true incidence of clinically meaningful skeletal muscle injury during isotretinoin therapy is still uncertain [8–13,17–22].

A major limitation is the lack of standardized definitions. Studies differ in how they define myalgia, hyperCKemia, inflammatory back pain, sacroiliitis, and rhabdomyolysis. CK thresholds are also inconsistent, which makes it difficult to distinguish mild, transient laboratory abnormalities from clinically relevant muscle injury [11–13,18,21]. In addition, physical activity is not always assessed in detail, despite being an important confounder. Exercise may independently cause muscle soreness and CK elevation, and many studies do not report training intensity, timing of exercise before blood sampling, hydration status, or supplement use [11–15].

Mechanistic evidence is also insufficient. Proposed pathways, including apoptosis, oxidative stress, mitochondrial dysfunction, and increased susceptibility to microtrauma, remain biologically plausible but largely hypothetical. Direct studies in skeletal muscle tissue from isotretinoin-treated patients are lacking [12,19,22–24].

Future research should focus on prospective studies with standardized symptom assessment, baseline and follow-up CK measurements, detailed exercise history, and clear documentation of isotretinoin dose and treatment duration. Particular attention should be given to physically active adolescents, athletes, young men, and patients with previous CK abnormalities or unexplained transaminase elevation. Further studies should also clarify when CK testing and imaging for suspected sacroiliitis are clinically justified.

Until stronger evidence is available, routine CK monitoring in all patients cannot be recommended. A selective, risk-based approach appears more appropriate, with CK assessment reserved for patients with muscle symptoms, intense physical activity, unexplained AST or ALT elevation, previous CK abnormalities, or symptoms suggestive of rhabdomyolysis [12,16,19,21]. This approach may help balance patient safety with avoidance of unnecessary laboratory testing.

5. Conclusions

Isotretinoin remains one of the most effective systemic treatments for severe and treatment-resistant acne, but its musculoskeletal safety profile should not be overlooked. Available evidence indicates that musculoskeletal adverse effects during isotretinoin therapy are heterogeneous and may include low back pain, arthralgia, myalgia, tendinopathy, sacroiliitis, creatine kinase elevation, and, rarely, clinically significant myopathy or rhabdomyolysis.

Most musculoskeletal symptoms and CK abnormalities appear to be mild, transient, and reversible. However, the clinical interpretation of these findings may be challenging. Current evidence does not support routine CK monitoring in all patients treated with isotretinoin. Additionally, CK elevation should not be interpreted in isolation, but rather in relation to symptoms, recent exercise, sex, transaminase abnormalities, and the overall clinical context. Further prospective studies are needed to clarify risk factors, mechanisms, and optimal monitoring strategies.

Author contributions:

Conceptualization: Makary Hejduk, Jerzy Darmoń, Aleksandra Papuga, Magdalena Grzymek

Formal analysis: Makary Hejduk, Natalia Piegza, Karolina Domańska, Martyna Więcławek

Investigation: Makary Hejduk, Anna Sieczka, Jerzy Darmoń, Maria Windyga, Karolina Domańska, Aleksandra Papuga, Joanna Makowska, Magdalena Grzymek

Writing rough preparation: Makary Hejduk, Anna Sieczka, Maria Windyga, Natalia Piegza, Joanna Makowska, Magdalena Grzymek, Martyna Więcławek

Writing review and editing: Makary Hejduk, Jerzy Darmoń, Maria Windyga, Anna Sieczka, Natalia Piegza, Karolina Domańska, Aleksandra Papuga, Martyna Więcławek

Supervision: Makary Hejduk

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References

1. Eichenfield DZ, Sprague J, Eichenfield LF. Management of Acne Vulgaris: A Review. *JAMA*. 2021;326(20):2055-2067. https://doi.org/10.1001/jama.2021.17633
2. Layton AM, Bettoli V, Delore V, Puentes E, Tan JKL. The Burden of Acne Vulgaris on Health-Related Quality of Life and Psychosocial Well-Being Domains: A Systematic Review. *Am J Clin Dermatol*. 2026;27(1):17-47. https://doi.org/10.1007/s40257-025-00983-3
3. Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2024;90(5):1006.e1-1006.e30. https://doi.org/10.1016/j.jaad.2023.12.017
4. Melnik BC. Acne Transcriptomics: Fundamentals of Acne Pathogenesis and Isotretinoin Treatment. *Cells*. 2023;12(22):2600. Published 2023 Nov 10. https://doi.org/10.3390/cells12222600
5. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS. Laboratory Monitoring During Isotretinoin Therapy for Acne: A Systematic Review and Meta-analysis. *JAMA Dermatol*. 2016;152(1):35-44. https://doi.org/10.1001/jamadermatol.2015.3091
6. Xia E, Han J, Faletsky A, et al. Isotretinoin Laboratory Monitoring in Acne Treatment: A Delphi Consensus Study. *JAMA Dermatol*. 2022;158(8):942-948. https://doi.org/10.1001/jamadermatol.2022.2044
7. Rajput I, Anjankar VP. Side Effects of Treating Acne Vulgaris With Isotretinoin: A Systematic Review. *Cureus*. 2024;16(3):e55946. Published 2024 Mar 11. https://doi.org/10.7759/cureus.55946
8. Almutairi RR, Almutairi AG, Alhallafi AF, et al. Isotretinoin musculoskeletahl side effects: a systematic review. *Dermatol Reports*. 2024;16(4):9845. Published 2024 Apr 12. https://doi.org/10.4081/dr.2024.9845
9. Karaosmanoğlu N, Mülkoğlu C. Analysis of musculoskeletal side effects of oral Isotretinoin treatment: a cross-sectional study. *BMC Musculoskelet Disord*. 2020;21(1):631. Published 2020 Sep 25. https://doi.org/10.1186/s12891-020-03656-w
10. Acar EM, Şaş S, Koçak FA. Evaluation of musculoskeletal adverse effects in patients on systemic isotretinoin treatment: A cross-sectional study. *Arch Rheumatol*.

2021;37(2):223-229. Published 2021 Dec 24. https://doi.org/10.46497/ArchRheumatol.2022.8645

11. Kılıç Sayar S. Elevated Serum Creatine Kinase Levels in Acne Vulgaris Patients Treated with Isotretinoin A Retrospective Single-Center Study. Turk J Dermatol. 2021;15(1):1-4. https://doi.org/10.4103/tjd.tjd_2_21
12. Marson JW, Baldwin HE. The creatine kinase conundrum: a reappraisal of the association of isotretinoin, creatine kinase, and rhabdomyolysis. *Int J Dermatol*. 2020;59(3):279-283. https://doi.org/10.1111/ijd.14758
13. Marson JW, Baldwin HE. Elevated creatine kinase levels, exercise, and isotretinoin for acne. *JAAD Case Rep*. 2022;21:133-135. Published 2022 Jan 22. https://doi.org/10.1016/j.jdcr.2021.07.044
14. Dasgupta K, Lim P, Reedstorm H. A Common Drug With a Dangerous Side Effect: Acute Rhabdomyolysis Caused by the Synergistic Effect of Isotretinoin and Exercise in an Adolescent. *Cureus*. 2020;12(10):e10929. Published 2020 Oct 13. https://doi.org/10.7759/cureus.10929
15. Raneses E, Schmidgal EC. Rhabdomyolysis Caused by Isotretinoin and Exercise in an Otherwise Healthy Female Patient. *Cureus*. 2022;14(6):e25981. Published 2022 Jun 15. https://doi.org/10.7759/cureus.25981
16. Maden S. Alterations in Alanine Transaminase, Aspartate Transaminase, Gamma-Glutamyl Transpeptidase, and Creatine Kinase in Acne Patients Undergoing Isotretinoin Treatment: A Retrospective Evaluation of Laboratory Tests. *Cureus*. 2024;16(3):e57296. Published 2024 Mar 30. https://doi.org/10.7759/cureus.57296
17. Özkoca D, Caf N, Alacagöz Yılmaz NN, Uzunçakmak TK, Özdil A, Atsü AN. Skeletal Side Effects of Systemic Isotretinoin Treatment: Do They Depend on Age, Gender, Treatment Duration, Daily Dose and Isotretinoin-Naiveness?. *Dermatol Pract Concept*. Published online April 1, 2023. https://doi.org/10.5826/dpc.1302a121
18. Tamer F, Farajsoylu L, Adisen E. Should Serum Levels of Creatine kinase be Evaluated in Patients with Acne Vulgaris Treated with Systemic Isotretinoin?. Romanian Journal of Military Medicine No.5 / 2024, Vol. CXXVII, Published September. 2025. https://doi.org/10.55453/rjmm.2024.127.5.3
19. Aydog E, Ozturk G, Comert A, Tasdelen N, Akin O, Kulcu DG. Sacroiliitis during isotretinoin treatment: Causal association or coincidence?. *North Clin Istanb*. 2018;6(1):75-80. Published 2018 Aug 7. https://doi.org/10.14744/nci.2018.93798

20. Alazawi S, Hendriksz T. Analysis of the effects of isotretinoin on the premature epiphyseal closure in pediatric populations: a literature review. *J Osteopath Med*. 2021;122(1):45-53. Published 2021 Oct 11. https://doi.org/10.1515/jom-2021-010
21. Fayiga FF, Reyes-Hadsall SC, Sebastiany LC, Arutyunyan S, Wong A, Duarte AM. Isotretinoin Associated Rhabdomyolysis: Monitoring Creatine Kinase and Educating Patients. *Skin Appendage Disord*. 2021;7(6):493-498. https://doi.org/10.1159/000517831
22. Mahyar M, Jahanbazi R, Khorram A, Shahramirad S, Vataniman M. Isotretinoin-Associated Myopathy With Normal Creatine Kinase (CK) Levels: EMG-Based Diagnosis at Low Dose-A Case Report. *Clin Case Rep*. 2025;13(10):e71210. Published 2025 Oct 7. https://doi.org/10.1002/ccr3.71210
23. Melnik BC. Apoptosis May Explain the Pharmacological Mode of Action and Adverse Effects of Isotretinoin, Including Teratogenicity. *Acta Derm Venereol*. 2017;97(2):173-181. https://doi.org/10.2340/00015555-2535
24. Drozd, M., Czarnota, J., Dobrzyński, M., Skubel, T., Sokół, D., Dudek, I., & Piecewicz-Szczęsna, H. (2020). Impact of oral isotretinoin therapy on musculoskeletal system and physical activity in patients with acne. *Journal of Education, Health and Sport*, *10*(8), 372–382. https://doi.org/10.12775/JEHS.2020.10.08.045
25. Alzoubi KH, Khabour OF, Hassan RE, Qarqaz F, Al-Azzam S, Mhaidat N. The effect of genetic polymorphisms of RARA gene on the adverse effects profile of isotretinoin-treated acne patients. *Int J Clin Pharmacol Ther*. 2013;51(8):631-640. https://doi.org/10.5414/CP201874
26. Webster GF, Webster TG, Grimes LR. Laboratory tests in patients treated with isotretinoin: occurrence of liver and muscle abnormalities and failure of AST and ALT to predict liver abnormality. *Dermatol Online J*. 2017;23(5):13030/qt7rv7j80p. Published 2017 May 15.
27. Barbieri JS, Shin DB, Wang S, Margolis DJ, Takeshita J. The clinical utility of laboratory monitoring during isotretinoin therapy for acne and changes to monitoring practices over time. *J Am Acad Dermatol*. 2020;82(1):72-79. https://doi.org/10.1016/j.jaad.2019.06.025
28. Kocak O, Kocak AY, Sanal B, Kulan G. Bilateral Sacroiliitis Confirmed with Magnetic Resonance Imaging during Isotretinoin Treatment: Assessment of 11 Patients and a Review of the Literature. *Acta Dermatovenerol Croat*. 2017;25(3):228-233.