



THE MUSCULOSKELETAL SIDE EFFECTS OF ORAL ISOTRETINOIN: A NARRATIVE REVIEW

ORAL İZOTRETİNOİNİN KAS-İSKELET SİSTEMİ YAN ETKİLERİ: ANLATISAL BİR DERLEME

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ABSTRACT

Introduction: This narrative review aims to summarize the current literature on the musculoskeletal adverse effects of oral isotretinoin, discuss potential mechanisms and clinical implications, and highlight key considerations for clinicians in patient monitoring.

Method: Publications between January 1983 and August 2025 were reviewed through PubMed, Google Scholar, and ScienceDirect. The keywords "isotretinoin", "retinoids", "musculoskeletal system", "sacroiliitis", "spondylarthropathies", "arthritis", "hyperostosis", "osteoporosis", "hypercalcemia", "myalgia", "creatine kinase" and "rhabdomyolysis" were used. Only English-language publications were included. No formal methodological quality scale was applied; instead, study relevance, sample quality, and clinical contribution were considered. Systematic reviews, clinical studies, case series, and case reports were included. The findings were summarized in a narrative manner and evaluated in terms of clinical practice.

Results: Musculoskeletal adverse effects of isotretinoin include axial like symptoms (e.g., inflammatory back pain, sacroiliitis, enthesitis), peripheral arthritis, hyperostosis, premature epiphyseal closure, osteoporosis, hypercalcemia, myalgia, and elevated creatine kinase levels. Back pain, arthralgia, and myalgia are the most common side effects, typically emerging within the first three months of treatment. Sacroiliitis is usually acute, HLA-B27-negative, and resolves after drug discontinuation. Bone effects are primarily observed with prolonged, high cumulative doses, whereas vitamin D metabolism may be affected even in short courses. Muscle involvement is generally mild but may rarely lead to rhabdomyolysis with intensive exercise.

Conclusion: Musculoskeletal side effects of isotretinoin are generally mild and reversible but may mimic spondyloarthropathies or other rheumatologic disorders. Awareness, baseline risk assessment (including vitamin D status), and early recognition are essential to avoid misdiagnosis and unnecessary interventions. Collaboration between dermatology and musculoskeletal specialists is recommended for optimal management.

Keywords: isotretinoin; musculoskeletal system; sacroiliitis; spondylarthropathies; hyperostosis; rhabdomyolysis.

ÖZET

Giriş: Bu anlatısal derlemenin amacı, oral izotretinoinin kas-iskelet sistemi üzerindeki advers etkilerine ilişkin güncel literatürü özetlemek, olası mekanizmaları ve klinik yansımaları tartışmak ve klinisyenler için izlemde dikkat edilmesi gereken temel noktaları vurgulamaktır.

Yöntem: Ocak 1983–Ağustos 2025 arasında yayımlanmış literatür PubMed, Google Scholar ve ScienceDirect veri tabanlarında taranmıştır. Aramalarda "isotretinoin", "retinoids", "musculoskeletal system", "sacroiliitis", "spondylarthropathies", "arthritis", "hyperostosis", "osteoporosis", "hypercalcemia", "myalgia", "creatine kinase" ve "rhabdomyolysis" anahtar kelimeleri kullanılmıştır. Tarama sürecinde yalnızca İngilizce yayımlanmış makaleler değerlendirmeye alınmıştır. Çalışmaların metodolojik kalitesini değerlendirmek için resmi bir ölçek kullanılmamış; bunun yerine çalışmanın konuya uygunluğu, örneklem kalitesi ve klinik katkısı dikkate alınmıştır. Sistemik derlemeler, klinik çalışmalar, olgu serileri ve olgu sunumları dahil edilmiştir. Bulgular önceden belirlenen alt başlıklar altında anlatımsal biçimde sentezlenmiştir.

Bulgular: İzotretinoinin kas-iskelet sistemi üzerindeki yan etkileri: aksiyel spondiloartrit benzeri bulgular (inflamatuvar bel ağrısı, sakroiliit, entezit), periferik artrit, hiperostoz, erken epifiz kapanması, osteoporoz, hiperkalsemi, miyalji ve kreatin kinaz yüksekliği şeklinde ortaya çıkmaktadır. Bel ağrısı, artralji ve miyalji en sık görülen yan etkilerdir ve genellikle tedavinin ilk üç ayında ortaya çıkar. Sakroiliit olguları çoğunlukla akut, HLA-B27 negatif olup ilaç kesilmesiyle düzelir. Kemik etkileri genellikle uzun süreli, yüksek kümülatif dozlarla ilişkilidir; kısa süreli tedavilerde ise D vitamini metabolizması etkilenebilmektedir. Kas tutulumu çoğunlukla hafif seyirli olmakla birlikte yoğun egzersizle nadiren rbdomyolize yol açabilir.

Sonuç: İzotretinoinin kas-iskelet sistemi üzerindeki yan etkileri genellikle hafif ve geri dönüşümlüdür; ancak spondiloartrit veya diğer romatolojik hastalıkları taklit edebilir. Yan etkilerin farkında olunması, D vitamini durumu dahil olmak üzere başlangıç risk değerlendirmesinin yapılması ve erken tanı, yanlış tanı ve gereksiz girişimlerin önlenmesi açısından kritik önemdedir. Dermatoloji ile kas-iskelet sistemi uzmanlarının iş birliği, hasta yönetimini optimize eder.

Anahtar kelimeler: izotretinoin; kas-iskelet sistemi; sakroiliit; spondiloartrit; hiperostoz; rbdomyoliz.

INTRODUCTION

Acne vulgaris, a chronic inflammatory skin disease most commonly seen during adolescence, is considered a significant public health problem due to its prevalence and negative impact on quality of life. Topical retinoids, benzoyl peroxide, antibiotics, and hormonal treatments in

appropriate cases are among the first-line options in the management of the disease, according to current guidelines. However, in treatment-resistant cases or in situations where there is a high risk of scarring, systemic isotretinoin has become prominent with a strong recommendation. (1). However, various systemic side effects, particularly

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Submission Date: 22.09.2025 **Acceptance Date:** 31.10.2025
Cite as: Uludogan I, Birtane M. The Musculoskeletal Side Effects Of Oral Isotretinoin: A Narrative Review. Eskisehir Med J. 2025; 6(3): 255-261. doi: 10.48176/esmj.2025.216.

musculoskeletal complications, are an important monitoring issue for clinicians. The aim of this narrative review is to summarize the current literature on the musculoskeletal adverse effects of oral isotretinoin, discuss their potential mechanisms and clinical implications, and highlight key considerations for clinicians in patient monitoring.

Isotretinoin (13-*cis*-retinoic acid) is a retinoic acid derivative and has similar functional properties to vitamin A. Vitamin A deficiency causes hyperkeratosis of the skin and squamous metaplasia of the mucous membranes, and these changes can be reversed by vitamin replacement. Isotretinoin, which has a broader therapeutic index than vitamin A, acts on nuclear DNA, particularly in keratinized epithelium, inhibiting cell proliferation and growth. Since receiving approval for the treatment of severe nodulocystic acne in 1982, data on its clinical use and side effects have been accumulating, and its usage characteristics have become clearer. The immunomodulatory and anti-inflammatory effects of isotretinoin are also well known, and it is still used in the treatment of inflammatory acne, chronic acne, relapses, and acne with a tendency toward excessive scarring that has not responded to conventional treatment.

METHODS:

Literature published between January 1983 and August 2025 was searched in the PubMed, Google Scholar, and ScienceDirect databases. The keywords used were "isotretinoin," "retinoids," "musculoskeletal system," "sacroiliitis," "spondylarthropathies," "arthritis," "hyperostosis," "osteoporosis," "hypercalcemia," "myalgia," "creatine kinase," and "rhabdomyolysis." Only studies published in English were included in the review. No formal methodological quality assessment tool was used; instead, the relevance of the study to the topic, sample quality, and clinical contribution were taken into consideration. Systematic reviews, clinical studies, case series, and case reports were included. The findings were narratively synthesized under predefined subheadings.

What Are the Musculoskeletal Side Effects of Isotretinoin?

It can be important in the diagnostic process that physicians treating musculoskeletal disorders should be aware of the musculoskeletal system (MSK) side effects of isotretinoin. These effects and side effects can be summarized as follows:

- Effects resembling axial spondyloarthritis (axSpA) (back pain, sacroiliitis, enthesitis, costochondritis)
- Peripheral joint side effects (arthralgia, arthritis)
- Bone tissue side effects (hyperostosis, premature epiphyseal closure, osteoporosis, hypercalcemia)
- Muscle tissue side effects (myalgia, myositis, elevated creatine kinase, rhabdomyolysis)

How Often Are Musculoskeletal Side Effects of Isotretinoin Observed?

The frequency of musculoskeletal side effects during isotretinoin treatment varies considerably across studies. In McLane's analysis of two studies, the incidence of musculoskeletal, connective tissue, and bone disorders was reported to range between 14.3% and 20% (2). More recently, a systematic review published in 2024 analyzed 13 observational studies and found that the most frequently reported symptoms were back pain, myalgia, arthralgia, and sacroiliitis. Among these, back pain was the most prominent, reported in 41–74% of cases, followed by myalgia and arthralgia. Additionally, some studies mentioned fatigue, hip

pain, weakness, and Achilles enthesopathy, although the frequency of these symptoms was not consistently reported across studies (3).

Karaosmanoğlu and Mülkoğlu (2020) reported back pain in 70% of 94 isotretinoin users, myalgia in 53%, arthralgia in 48%, and MRI-confirmed sacroiliitis in 11.7% of cases (4). Furthermore, a large meta-analysis published in 2022 reported musculoskeletal pain in 15–25% and arthralgia in 5–10% of patients. However, it was emphasized that there were significant differences in rates due to heterogeneity in diagnostic criteria, sample characteristics, dosing regimens, and study designs across the included studies (5).

All these differences can be explained by variations in patient populations, daily and cumulative doses used, treatment durations, the way side effects were defined, and heterogeneity in study designs. Therefore, rather than directly comparing the reported rates in the literature, it is important to evaluate them by taking these factors into account. Current evidence suggests that musculoskeletal side effects become more prominent particularly with long-term treatment and higher cumulative doses.

Joint and Axial Involvement: Peripheral Arthritis and Spondyloarthritis (SpA)-like Effects

SpA-like Side Effects

We will refer to three important studies on the subject while examining this topic. In the first study (4), musculoskeletal side effects were compared between a group of nearly 100 patients using isotretinoin and a control group. The median cumulative dose used in the treatment group ($n=94$) was 2400 mg, while the median treatment duration was 3 months. Compared to the 100-person control group, the mean pain score on the Visual Analogue Scale (VAS) was 6 in patients with moderate to severe acne receiving isotretinoin, while it was 4 in the control group ($p=0.03$). The incidence of arthralgia (47.9% vs. 8%), myalgia (53.2% vs. 7%), and back pain (70.2% vs. 10%) was significantly higher in the treatment group than in the control group. In the treatment group, 37.2% of cases with back pain were inflammatory in nature, whereas there were no inflammatory back pain cases in the control group. Sacroiliitis was detected in 11 patients (11.7%) and tendinopathy in 4 patients (4.3%) in the treatment group. No sacroiliitis or tendinopathy was found in the control group. In cases where sacroiliitis was detected on MRI, bilateral sacroiliitis was found in 9 cases and unilateral sacroiliitis in 2 cases. Radiographs were normal in all cases. In the study, the median onset time for musculoskeletal symptoms was around 3 to 3.5 months, and higher cumulative dose was only found to be associated with back pain. The acute phase reaction was within normal limits in all cases of inflammatory back pain. In this study, symptoms dramatically decreased within 1 month and completely recovered by the third month with continued low-dose isotretinoin and the addition of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with low back pain, arthralgia, myalgia, or tendinopathy. In patients diagnosed with sacroiliitis, discontinuation of isotretinoin treatment and NSAID therapy resulted in a dramatic reduction in pain within one month, near-complete recovery by the third month, and full radiological improvement by the sixth month, with all parameters returning to normal.

In the second study (6), 42 cases treated with isotretinoin for acne were compared with 32 cases treated with tetracycline. While no SpA-like findings were observed during treatment in the tetracycline group, SpA-like

symptoms were encountered in 23.1% of patients receiving isotretinoin. Achilles enthesopathy was observed in 3 female patients, unilateral sacroiliitis and Achilles enthesopathy was observed in one case, and inflammatory low back pain in six cases. Discontinuation of the medication and NSAID treatment resulted in normalization in patients within 3 months.

In the third study (7), myalgia was detected in 42.5% of 73 patients using isotretinoin, back pain was observed in 49.3%, inflammatory back pain in 21.9% of cases, and sacroiliitis in 8.2%.

According to a more recent systematic review by Almutairi et al. (2024), which included 13 analytical studies, back pain was reported in 41–74% of patients, inflammatory back pain in 14–20%, and sacroiliitis in 8–11%. Achilles tendinopathy, hip pain, and weakness were inconsistently reported. Most cases were acute, HLA-B27-negative, and resolved upon drug discontinuation. This systematic review provides the most up-to-date prevalence data on SpA-like adverse events in isotretinoin users (3).

Based on this, the following conclusions can be drawn regarding musculoskeletal complaints in patients using isotretinoin: Musculoskeletal complaints usually begin within the first 3 months of use, with arthralgia and myalgia being quite common symptoms. Back pain can occur in up to 50% of cases, inflammatory back pain is seen in 14–20% of cases. Sacroiliitis occurs in 0.5–1% of the general population while it is detected in 8–11% of those using the drug. In these studies, the groups consist only of patients with acne vulgaris; there are no patients with sacroiliitis, fulminant acne, or SAPHO syndrome. In patients using isotretinoin, enthesitis and osteitis are also common, similar to SpA. Unlike SpA, it is more common in women, is generally HLA-B27 negative, presents acutely, and resolves upon discontinuation of treatment. It acts like an acute and temporary SpA (3).

In another non-cross-sectional follow-up study examining the characteristics and prognosis of sacroiliitis in patients using isotretinoin (8), inflammatory back pain was detected in 123 of 513 patients receiving the drug for acne vulgaris (23.98%). Patients diagnosed with inflammatory back pain who are female, have pain above moderate intensity, and have elevated C-reactive protein (CRP) levels are more likely to be diagnosed with radiological sacroiliitis. Once again, the Global Acne Grading System (GAGS) score, pain score, Ankylosing Spondylitis Disease Activity Score (ASDAS) score, and CRP level showed a positive correlation with the severity of sacroiliitis detected on MRI. It was observed that MRI findings improved when the medication was discontinued. The average MRI normalization period was 6.27 months. Unilateral sacroiliitis recovered significantly faster than bilateral sacroiliitis.

In a more recent large cohort study by Zhao et al. (Arthritis Res Ther, 2025), involving 513 patients, inflammatory back pain was reported in 23.98% of cases and MRI-proven sacroiliitis in 8–11%. Female sex, moderate to severe pain, elevated CRP, and higher GAGS scores were identified as predictors of sacroiliitis. The average MRI resolution time after drug discontinuation was 6.27 months, and HLA-B27 positivity was found in 13.4% of cases (9).

There are theories about why isotretinoin causes sacroiliitis. It is thought that it alters the lysosomal membrane structure with detergent-like effects, sensitizing the joint to mild trauma (10). Additionally, isotretinoin has been shown to upregulate matrix metalloproteinases (MMPs), particularly

MMP-2 and MMP-9 in periarticular tissues, which may increase local susceptibility to microtrauma and inflammation (3). Moreover, sacroiliitis has been observed to occur after exercise in some cases. This theory supports the transient nature of sacroiliitis observed after discontinuing medication. Ultimately, metalloproteinases, which are found in excess in joint fluid, may also be responsible for the degeneration of the extracellular matrix. In cases of acne fulminans *Cutibacterium acnes* may induce an interleukin-17 (IL-17) response in CD4⁺ T helper cells, thereby causing sacroiliitis. This may lead to diagnostic difficulties in patients receiving isotretinoin for this disease (11).

Most isotretinoin-associated sacroiliitis cases are HLA-B27 negative, supporting the view that this is not classic SpA but a transient, drug-induced inflammatory phenomenon. The role of HLA-B27 in genetic predisposition has also been discussed. However, the current data are conflicting. A retrospective study reported that only 13.4% of 67 patients who developed sacroiliitis were HLA-B27 positive (9). However, some case reports and small series suggest that HLA-B27-positive individuals may be predisposed to developing sacroiliitis (12). Therefore, it cannot be said that HLA-B27 is an independent risk factor alone; however, more careful clinical monitoring is recommended for patients who test positive.

Achilles tendinopathy and enthesopathy have been described among the musculoskeletal side effects of isotretinoin therapy. In a clinical study, Achilles enthesopathy was observed in several patients receiving isotretinoin, sometimes in association with unilateral sacroiliitis (6). Another series reported cases of Achilles tendon involvement occurring alongside back pain and sacroiliitis during treatment (7). Achilles tendinopathy has also been reported to occur in approximately 9.5% of patients, with a close relationship to isotretinoin dose, and symptoms typically improve after dose reduction or discontinuation (13). Earlier case reports described acute Achilles tendonitis developing within the first months of therapy, which resolved following drug withdrawal (14). These findings indicate that Achilles tendon involvement, although less frequent than back pain or arthralgia, represents a clinically relevant adverse effect that usually improves with appropriate intervention.

In conclusion, it can be said that SpA-like side effects seen in patients using isotretinoin are generally clinical conditions that appear during the first months of treatment, are mostly transient, subside when the drug is discontinued, and must be distinguished from true axial spondyloarthritis.

Peripheral Arthritis

It has been reported as a clinically significant side effect that is rarely seen during isotretinoin treatment. Cases of acute monoarthritis affecting the knee and hip joints in particular have been reported in the literature; in these cases, symptoms generally begin between the first few weeks and the third month of treatment, the synovial fluid often exhibits non-inflammatory characteristics, and autoimmune markers are mostly negative (15). Additionally, cases of arthritis affecting the bilateral wrist and metacarpophalangeal joints, accompanied by unilateral sacroiliitis, have been reported, emphasizing that this condition can mimic rheumatoid arthritis or spondyloarthritis (16). In a more recent case, acute peripheral arthritis symptoms developing around the shoulder, knee, and Achilles tendon completely subsided within two months after discontinuation of isotretinoin and NSAID treatment (17).

Systematic reviews also emphasize that this side effect is rare, but when reported, it is usually rapid in course and improves with discontinuation of the drug (4). Therefore, in cases of acute monoarthritis or oligoarthritis occurring in patients using isotretinoin, this side effect must be kept in mind, especially after septic arthritis has been excluded.

Side Effects on Bone Tissue

The skeletal side effects of isotretinoin use include premature epiphyseal closure, spinal hyperostosis, peripheral bone hyperostosis, and osteopenia. Isotretinoin is suspected to have a hypercalcemic effect.

Premature Epiphyseal Closure

Isotretinoin-induced premature epiphyseal closure is a rare but documented complication, particularly in pediatric populations. Cases have been reported even after 4–6 months of therapy at doses around 0.75–1 mg/kg/day (18). Among pediatric oncology patients treated with high-dose retinoids, growth plate arrest was observed in 3 out of 216 cases ($\approx 1.38\%$) (19). In one reported case, epiphyseal closure led to genu varum deformity (neuroblastoma patient) (20). Mechanistically, retinoids may accelerate endochondral ossification, alter chondrocyte maturation, and affect IGF/GH signaling, leading to early physeal fusion (21). Diagnosis is best made with MRI, which shows physeal edema and irregularity early; radiographs may lag behind. Pain typically resolves after discontinuation, and further growth may resume unless complete fusion has occurred (18).

Hyperostosis

One of the most typical skeletal findings of vitamin A hypervitaminosis is appendicular skeletal hyperostosis, and this involvement often resembles diffuse idiopathic skeletal hyperostosis (DISH) (22). Differential diagnosis may be necessary between axial spondylitis, SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis)syndrome, DISH, and retinoid-related hyperostosis for skeletal lesions that occur in some patients receiving retinoid therapy. In retinoid hyperostosis, cervical spine involvement is particularly predominant, whereas in DISH, spinal involvement is reported to be asymmetric and mostly prominent on the right side and is also seen more frequently in the older age group (23). In SAPHO syndrome, involvement of the anterior chest wall is typically present and frequently includes the sternoclavicular joint (24). In retinoid hyperostosis, growth and enlargement may also occur in long bones (e.g., clavicle), but enthesopathy findings are generally not observed (25). Therefore, careful analysis of hyperostosis patterns is important in distinguishing possible retinoid-induced lesions from other hyperostotic and inflammatory spondyloarthropathies.

To summarize retinoid-related hyperostosis: It begins at the earliest 6 months, bone spurs are exceedingly small and have no clinical significance. Short-term use of low doses of medication is not risky in this regard. Rather, the cumulative dose effect of short-term use is blamed. After the third to fifth year of treatment, hyperostosis occurring in the anterior spine particularly in the anterior longitudinal ligament (ALL) and, more rarely, in the posterior longitudinal ligament (PLL) may subsequently extend to the peripheral bone enthesal regions. It is generally an asymptomatic radiological condition and laboratory tests are normal. NSAIDs are used in treatment. Physicians dealing with musculoskeletal disorders should be cautious in this regard and should also take a history regarding the medications used.

Osteoporosis

Excessive dietary intake of vitamin A has been associated with reduced bone mineral density and an increased risk of hip fracture in large epidemiological studies. In a cross-sectional and nested case–control study conducted in Sweden involving 175 controls and over 1,000 hip fracture cases, Melhus et al. demonstrated that for every 1 mg increase in daily retinol intake, the risk of hip fracture increased by 68%. Women with an intake greater than 1.5 mg/day had a 10–14% reduction in femoral neck and lumbar spine bone mineral density (BMD) and a twofold higher risk of hip fracture compared to those with an intake below 0.5 mg/day (26).

In contrast, a Danish population-based cohort study including 2,016 perimenopausal women found no association between vitamin A intake and BMD or fracture risk, likely reflecting the lower average vitamin A intake in Denmark compared to Sweden and the United States (27).

In patients treated with isotretinoin, which is a vitamin A derivative, similar skeletal effects are theoretically expected; however, clinical studies have yielded mixed results. A systematic review reported that in three clinical studies comprising a total of 70 patients, no significant loss of lumbar or femoral BMD was detected during isotretinoin treatment (3).

Hypercalcemia

Hypercalcemia associated with isotretinoin therapy has been rarely reported in humans but is clinically relevant. The earliest report dates back to 1983, when a patient receiving oral isotretinoin for severe acne developed hypercalcemia that resolved after discontinuation of the drug (28). Subsequently, individual case reports have documented hypercalcemia in pediatric patients undergoing isotretinoin treatment, including a 12-year-old neuroblastoma patient who developed significant hypercalcemia during therapy (29). Another case described hypercalcemia in association with osteoblastic bone lesions induced by 13-cis-retinoic acid, suggesting that retinoids may affect bone remodeling pathways (30).

More robust evidence was provided by Hoernberg et al. (2021), who retrospectively analyzed 350 pediatric patients with high-risk neuroblastoma receiving 13-cis-retinoic acid. They found that 22.3% developed hypercalcemia, with grade 3–4 hypercalcemia in 10.6%, most commonly during the first treatment cycle. Risk factors included single kidney status after nephrectomy and recent myeloablative chemotherapy. Proposed mechanisms involve increased osteoclastic activity, inhibition of osteoblastic alkaline phosphatase, and alterations in vitamin D and parathyroid hormone metabolism. Most cases were managed successfully with temporary treatment interruption, hydration, and loop diuretics, without the need for permanent discontinuation of therapy (31).

Vitamin D metabolism

Isotretinoin, a derivative of vitamin A, has various biological effects on both bone and vitamin D metabolism. Vitamins A and D regulate gene expression through nuclear receptors — the vitamin D receptor (VDR) and the retinoid X receptor (RXR), which form a heterodimer; therefore, molecular cross-talk between these two vitamins is possible (32). In a randomized, double-blind, crossover clinical study in healthy subjects, Johansson and Melhus demonstrated that a single dose of retinyl palmitate (15 mg) significantly reduced the intestinal calcium absorption response to 1,25-dihydroxyvitamin D₃ [$1,25(\text{OH})_2\text{D}_3$], as the rise in serum calcium decreased from 2.3% to 1.4% (33). This finding

provides direct evidence that vitamin A can exert an antagonistic effect on vitamin D at the intestinal level.

Clinical data also support the idea that isotretinoin may influence vitamin D metabolism. In a prospective study by Ertugrul et al., 50 acne patients treated with oral isotretinoin (0.5–0.8 mg/kg/day) for three months showed a significant reduction in serum 25-hydroxyvitamin D [25(OH)D] and calcium levels ($p < 0.0001$ and $p < 0.05$, respectively), alongside significant increases in $1,25(\text{OH})_2\text{D}_3$, parathyroid hormone (PTH), and bone alkaline phosphatase levels. (32). These findings suggest that isotretinoin may exacerbate vitamin D deficiency and lead to secondary hyperparathyroidism. Taken together with Johansson's acute interaction findings, the decline in vitamin D levels during isotretinoin therapy may be related to retinoids suppressing calcium absorption and vitamin D bioavailability via VDR–RXR–mediated mechanisms.

In a large prospective study involving 217 adolescents, DiGiovanna et al. excluded individuals with baseline 25(OH)D levels below 10 ng/mL and found no clinically significant changes in bone mineral density during isotretinoin therapy (34). This methodological detail indicates that, in individuals with sufficient vitamin D levels, short-term isotretinoin use may have minimal skeletal impact, whereas in vitamin D deficiency, the effects may become more pronounced.

In summary, isotretinoin, as a vitamin A derivative, can interact antagonistically with vitamin D at both the experimental and clinical levels. This interaction may impair bone metabolism by reducing intestinal calcium absorption, lowering 25(OH)D levels, and triggering secondary elevations in PTH. Therefore, it is recommended to measure serum vitamin D levels before initiating isotretinoin therapy and to provide supplementation if deficiency is present.

Effects on Muscle

The effects of isotretinoin on muscle tissue mostly manifest as myalgia and elevations in serum creatine kinase (CK) levels. CK elevation is usually asymptomatic but is observed more prominently in male patients and in those performing intense physical exercise. Reported rates of CK elevation in patients receiving isotretinoin range from 5.6% to 41% (35).

One of the underlying mechanisms of muscle toxicity is that isotretinoin induces oxidative stress in muscle cells, which increasing cell membrane permeability and leading to CK leakage (35).

These biochemical changes are often subclinical; however, when combined with intense physical activity, they may increase the risk of rhabdomyolysis. For example, Marson et al. reported a case of exertional rhabdomyolysis in a young athlete on isotretinoin treatment whose CK level rose to 146,000 IU/L following an intensive pre-season training session (36). In such cases, the classic triad consists of myalgia, muscle weakness, and dark urine, though all three features may not always be present.

In larger series, this complication is considered rare. In a retrospective analysis of 442 acne patients by Cleary et al., CK levels above 5,000 IU/L were observed in only 1.58% of cases. Most of these patients were asymptomatic or experienced only mild muscle cramps. The CK elevations were usually related to physical activity and returned to normal spontaneously within two weeks; in most cases, isotretinoin therapy could be continued without interruption (35).

In conclusion, isotretinoin may increase CK levels through oxidative stress in muscle tissue and raise the risk of rhabdomyolysis when combined with intense exercise. Clinically, patients should be questioned about muscle pain or weakness, and CK levels should be monitored when indicated. Patients should be advised to avoid excessive physical exertion and dehydration, especially during the early phase of therapy. In cases with CK levels exceeding 5,000–10,000 IU/L or with symptomatic presentation, closer monitoring, activity restriction, hydration, and temporary discontinuation of therapy should be considered (37).

CONCLUSION

From a dermatologist's perspective, it is important to recognize that isotretinoin causes musculoskeletal side effects in approximately one in five patients, at most. Most of these may also be related to dosage. Many of these undesirable effects resolve after discontinuation of the drug or with dose reduction and NSAID therapy. If more serious SpA-like findings, arthritis, myositis, hyperostosis, and other side effects cannot be prevented, consultation may be required. Dermatologists should be aware of the criteria for inflammatory back pain.

From the perspective of physiatrists and rheumatologists, it should become standard practice to ask every patient presenting with SpA-like symptoms, particularly those with acute onset, a simple screening question such as, 'Are you currently taking isotretinoin. Although this situation is rare, identifying this relationship in even one in 50 patients makes a difference. This patient is spared from being labeled with an incorrect diagnosis and from long-term NSAID use.

Building on these perspectives, several practical preventive strategies have been proposed to minimize the incidence and severity of musculoskeletal adverse effects during isotretinoin therapy, as summarized below.

Preventive Strategies for Musculoskeletal Adverse Effects During Isotretinoin Therapy

The following recommendations are compiled from recent reviews, cohort studies, and clinical research addressing the musculoskeletal (MSK) adverse effects of isotretinoin. The objective is to enable early identification of risk factors, implement preventive strategies, and establish a standardized approach to management.

Pre-treatment Evaluation and Risk Stratification

- A detailed musculoskeletal history and physical examination should be performed, including previous or current low back pain, a history of enthesopathy or tenosynovitis, and episodes of arthritis. Although SpA-like adverse effects are not very common, they have been reported, and early detection facilitates management.
- Measurement of baseline 25(OH)D and replacement of deficiency: The vitamin A–vitamin D axis has an antagonistic interaction at the level of intestinal calcium absorption; retinyl palmitate acutely reduces the calcium response to $1,25(\text{OH})_2\text{D}_3$. Therefore, if there is a vitamin D deficiency, it is recommended to complete it initially (33).
- Baseline BMD measurement (especially in at-risk adolescents/adults or those scheduled for long-term or cumulative high doses) may be considered for bone health. Clinically significant reductions in BMD in short-term standard cycles have not been demonstrated in most studies (34).

Dosage, Duration, and Treatment Planning

- Unnecessarily prolonged treatment and high cumulative doses should be avoided. Although musculoskeletal adverse effects are heterogeneous, their incidence tends to increase with longer treatment durations and higher cumulative doses. If symptoms develop, dose reduction is the first step of management (4).

Vitamin D–Calcium Axis and Metabolic Parameters Monitoring

- Monitoring of 25(OH)D levels (and, if necessary, calcium, phosphate, and PTH) is recommended. Prospective studies suggest that isotretinoin may affect vitamin D metabolism, leading to decreased 25(OH)D levels and compensatory increases in PTH. Correcting vitamin D deficiency is an appropriate approach to preventing secondary hyperparathyroidism (32).
- Clinicians should remain vigilant for hypercalcemia. Although it is common in oncologic indications (e.g., 13-cis-retinoic acid for neuroblastoma), it is rare in dermatologic acne treatment. However, symptomatic cases should be evaluated. Management usually involves temporary interruption of therapy, hydration, and diuresis (31).

Muscular Side Effects and Exercise Safety

- In the early phase, it is important to avoid excessive exertion and dehydration; if symptoms such as muscle pain or cramps or dark-colored urine occur, creatine kinase levels should be measured. The combination of isotretinoin and intense exercise can synergistically increase creatine kinase levels and, in rare cases, trigger rhabdomyolysis (36).
- Thresholds and Management: If CK levels exceed 5,000 to 10,000 IU/L or significant symptoms are present, activity restriction, adequate hydration, and temporary discontinuation of the medication should be considered. In most cases, the condition resolves spontaneously (37).

SpA-Like Findings and Algorithm for Sacroiliitis

- Warning symptoms include new-onset inflammatory back pain, gluteal/buttock pain, morning stiffness, and enthesitis or fusiform tenosynovitis. If these features are present, sacroiliac joint MRI should be considered. Systematic reviews and recent case series support the occurrence of isotretinoin-associated sacroiliitis (3).
- First-line management: Dose reduction or drug discontinuation and NSAIDs in symptomatic patients; clinical and MRI improvement is usually observed within weeks to months in most cases. Rheumatology evaluation is recommended in persistent or severe cases (38).
- Risk awareness: HLA-B27 has been frequently reported as negative in the literature; there is no recommendation for routine screening, but close follow-up is rational in those with previously known HLA-B27 positivity (39).

Precautions for Tendinopathy/Enthesopathy (especially Achilles)

- If Achilles pain or stiffness develops, it usually resolves with load avoidance, cold application, short-term NSAIDs, and dose reduction or pause. Associated cases have been reported (3).

Patient Education and Counseling

Before you begin: Has 25(OH)D been checked? Is there active inflammatory low back pain or enthesopathy? Is the planned cumulative dose reasonable?

- During treatment: Seek medical advice immediately if new inflammatory low back pain, Achilles tendon overload, or unexplained muscle pain or dark-colored urine occurs within the first 1–3 months. Avoid heavy exercise and dehydration.

The musculoskeletal adverse effects of isotretinoin are generally mild and reversible, but awareness and early recognition are essential to prevent misdiagnosis and unnecessary interventions. Integrating preventive strategies and fostering collaboration between dermatology and musculoskeletal specialists can optimize patient care.

Authorship Contributions: Concept – IU, MB.; Design – IU, MB.; Supervision – IU, MB.; Resource – IU, MB.; Materials – IU, MB.; Data collection &/or processing – IU, MB.; Analysis and/or interpretation – IU, MB.; Literature search – IU, MB.; Writing – IU, MB.; Critical review – IU, MB.

Conflict of Interest: None declared

Financial Disclosure: The authors received no financial support.

REFERENCES

1. Zaenglein AL, Davis SA, McClain RW, Eichenfield LF, Feldman SR. AAD guidelines update: management of acne vulgaris. *J Am Acad Dermatol*. 2024;90(1):1-12. doi:10.1016/j.jaad.2023.10.001.
2. McLane J. Analysis of common side effects of isotretinoin. *J Am Acad Dermatol*. 2001;45(5 Suppl):S188-94.
3. Almutairi RR, Almutairi AG, Alhallafi AF, et al. Isotretinoin musculoskeletal side effects: a systematic review. *Dermatol Rep*. 2024;16(4):9845. doi:10.4081/dr.2024.9845.
4. Karaosmanoğlu N, Mülkoğlu C. Analysis of musculoskeletal side effects of oral isotretinoin treatment: a cross-sectional study. *BMC Musculoskelet Disord*. 2020;21:631.
5. Kapała J, Lewandowska J, Placek W, Owczarczyk-Saczonek A. Adverse events in isotretinoin therapy: a single-arm meta-analysis. *Int J Environ Res Public Health*. 2022 May 26;19(11):6463. doi:10.3390/ijerph19116463.
6. Alkan S, Kayıran N, Yılmaz S, Can B, Erdem T, Babaoğlu S, et al. Musculoskeletal side effects of isotretinoin. *J Rheumatol*. 2015;42(11):2098-103.
7. Baykal-Selçuk L, Aksu Arıca D, Yaylı S, Özçelik S. Musculoskeletal findings during isotretinoin therapy. *Cutan Ocul Toxicol*. 2017;36(2):176-9.
8. Elnady B. New onset of axial spondyloarthritis during isotretinoin therapy. *Clin Rheumatol*. 2020;39:1829-38.
9. Zhao S, Sun W, Peng L, et al. Clinical features, treatment, and outcome of isotretinoin-associated sacroiliitis. *Arthritis Res Ther*. 2025;27:115. doi:10.1186/s13075-025-03582-z.
10. Dincer Ü, Çakar E, Kıralp MZ, Dursun H. Isotretinoin may cause sacroiliitis: three cases. *Turk J Rheumatol*. 2008;23:157-9.
11. Agak GW, Qin M. Propionibacterium acnes induces an interleukin-17 response in acne vulgaris that is regulated by vitamin A and vitamin D. *J Invest Dermatol*. 2014;134(2):366-73.
12. Eksioğlu E. Sacroiliitis and polyneuropathy during isotretinoin treatment. *Clin Exp Dermatol*. 2008;33(2):122-4. doi:10.1111/j.1365-2230.2007.02532.x.
13. Acar EM, Şaş S, Koçak FA. Isotretinoin-associated arthritis: case report. *Arch Rheumatol*. 2022;37(2):223-9.
14. Bottomley WW, Cunliffe WJ. Acute Achilles tendonitis

- following oral isotretinoin therapy for acne vulgaris. *Clin Exp Dermatol*. 1992;17(4):250-1. doi:10.1111/j.1365-2230.1992.tb02159.x.
15. Matsuoka LY, Wortsman J, Pepper JJ. Acute arthritis during isotretinoin treatment for acne. *Arch Intern Med*. 1984;144(9):1870-1.
16. Tasdelen OY, Yurdakul FG, Duran S, Bodur H. Isotretinoin-induced arthritis mimicking both rheumatoid arthritis and axial spondyloarthritis. *Int J Rheum Dis*. 2015;18(4):466-9.
17. Parada-Artunduaga MD, Cáceres-Bedoya JJ, Rojas-Villarraga A. Isotretinoin-induced arthritis: a rare but feasible diagnosis. *Rev Colomb Reumatol (Engl Ed)*. 2022;29(4):314-8.
18. Luthi F, Eggel Y, Theumann N. Isotretinoin-related arthritis: case report. *Joint Bone Spine*. 2012;79(3):314-6.
19. Duvalyan A, Cha A, Goodarzi F, Arkader A, Villablanca JG, Marachelian A. Premature epiphyseal growth plate arrest after isotretinoin therapy for high-risk neuroblastoma: a case series and review of the literature. *Pediatr Blood Cancer*. 2020;67(8):e28236. doi:10.1002/pbc.28236.
20. Park WK, Choi HS, Chung CY, Park MS, Sung KH. Genu varum deformity due to premature epiphyseal closure after treatment with isotretinoin for neuroblastoma: a case report. *J Orthop Surg (Hong Kong)*. 2020;28(2):2309499020924483. doi:10.1177/2309499020924483.
21. Alazawi S, Hendriks T. Analysis of the effects of isotretinoin on the premature epiphyseal closure in pediatric populations: a literature review. *J Osteopath Med*. 2021 Oct 11;122(1):45-53. doi:10.1515/jom-2021-0108.
22. Pittsley RA, Yoder FW. Retinoid hyperostosis: skeletal toxicity associated with long-term isotretinoin. *N Engl J Med*. 1983;308(17):1012-4.
23. Kilcoyne RF, Cope R, Cunningham W, et al. Minimal spinal hyperostosis with low-dose isotretinoin therapy. *Invest Radiol*. 1986;21(1):41-4.
24. Chamot AM, Benhamou CL, Kahn MF, Beranek L, Kaplan G, Prost A. Le syndrome acné pustulose hyperostose ostéite (SAPHO). *Rev Rhum Mal Osteoartic*. 1987;54(3):187-96.
25. Ibáñez Barceló M, Estremera Rodrigo A, Ros Vilamajó I, Juan Mas A. Diffuse idiopathic skeletal hyperostosis in a young woman treated with isotretinoin. *Reumatol Clin (Engl Ed)*. 2020;S1699-258X(20)30229-1.
26. Melhus H, Michaëlsson K, Kindmark A, et al. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Ann Intern Med*. 1998 Nov 15;129(10):770-8. doi:10.7326/0003-4819-129-10-199811150-00003.
27. Rejnmark L, Vestergaard P, Charles P, Hermann AP, Brot C, Eiken P, Mosekilde L. No effect of vitamin A intake on bone mineral density and fracture risk in perimenopausal women. *Osteoporos Int*. 2004 Nov;15(11):872-80. doi:10.1007/s00198-004-1618-1.
28. Valentini JP, Elias AN, Weinstein GD. Hypercalcemia associated with oral isotretinoin in the treatment of severe acne. *JAMA*. 1983 Oct 14;250(14):1899-900.
29. Belden TL, Ragucci DP. Hypercalcemia induced by 13-cis-retinoic acid in a patient with neuroblastoma. *Pharmacotherapy*. 2002 May;22(5):645-8. doi:10.1592/phco.22.5.645.33207.
30. Cross SF, Dalla Pozza L, Munns CF. Hypercalcemia and osteoblastic lesions induced by 13-cis-retinoic acid mimicking relapsed neuroblastoma. *Pediatr Blood Cancer*. 2009 Oct;53(4):666-8. doi:10.1002/pbc.22052.
31. Hoernberg M, Schwenzfeier R, Berthold F, Simon T, Hero B. Hypercalcemia is a frequent side effect of 13-cis-retinoic acid treatment in patients with high-risk neuroblastoma. *Pediatr Blood Cancer*. 2022;69(2):e29374. doi:10.1002/pbc.29374.
32. Ertugrul DT, Karadag AS, Tural E, Akin KO. Therapeutic hotline. Does isotretinoin have effect on vitamin D physiology and bone metabolism in acne patients? *Dermatol Ther*. 2011 Mar-Apr;24(2):291-5. doi:10.1111/j.1529-8019.2011.01406.x.
33. Johansson S, Melhus H. Vitamin A antagonizes calcium response to vitamin D in man. *J Bone Miner Res*. 2001 Oct;16(10):1899-905. doi:10.1359/jbmr.2001.16.10.1899.
34. DiGiovanna JJ, Langman CB, Tschen EH, et al. Effect of a single course of isotretinoin therapy on bone mineral density in adolescent patients with severe, recalcitrant, nodular acne. *J Am Acad Dermatol*. 2004 Nov;51(5):709-17. doi:10.1016/j.jaad.2004.04.032.
35. Cleary MA, Sadowski KA, Lee SY, Miller GL, Nichols AW. Exertional rhabdomyolysis in an adolescent athlete during preseason conditioning: a perfect storm. *J Strength Cond Res*. 2011 Dec;25(12):3506-13. doi:10.1519/JSC.0b013e318216302f.
36. Marson JW, Baldwin HE. The creatine kinase conundrum: a reappraisal of the association of isotretinoin, creatine kinase, and rhabdomyolysis. *Int J Dermatol*. 2020 Mar;59(3):279-83. doi:10.1111/ijd.14758.
37. Landau M, Mesterman R, Ophir J, et al. Clinical significance of markedly elevated serum creatine kinase levels in patients with acne on isotretinoin. *Acta Derm Venereol*. 2001 Oct-Nov;81(5):350-2. doi:10.1080/000155501317140070.
38. Sargin B, Manzo C. Oral isotretinoin and sacroiliitis: causal link or coincidence? Discussion points emerging from a case-based review. *Rheumatology*. 2022;60(5):357-360. doi:10.5114/reum.2022.120761.
39. Karadağ ŞG, Sönmez HE, Tanatar A, Çakan M, Aktay Ayaz N. Isotretinoin-induced sacroiliitis: Case series of four patients and a systematic review of the literature. *Pediatr Dermatol*. 2020 Jan;37(1):171-175. doi:10.1111/pde.14035.



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