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Isotretinoin musculoskeletal side effects: a systematic review

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Abstract

This study aimed to investigate musculoskeletal complications secondary to isotretinoin use. A systematic review was conducted, and a total of 49 studies, including analytical studies, case reports, and case series, were included in the analysis. The studies examined musculoskeletal symptoms, diagnostic findings, and treatment approaches associated with isotretinoin use. Musculoskeletal symptoms reported in the studies included lethargy, myalgia, low back pain, arthralgia, tendinopathy, and sacroiliitis. Physical examination findings and radiological findings were used to confirm the diagnoses. Treatment approaches ranged from [non-steroidal anti-inflammatory drugs (NSAIDs)] to discontinuation of isotretinoin. Some studies have explored the impact of isotretinoin dosage, treatment duration, and vitamin levels on musculoskeletal symptoms. Isotretinoin-induced sacroiliitis and [diffuse idiopathic skeletal hyperostosis (DISH)] emerged as notable musculoskeletal complications. The findings highlight the importance of monitoring patients for potential musculoskeletal side effects and implementing appropriate interventions.

Introduction

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit, as well as one of the most widespread health issues dermatologists repeatedly face, influencing many people at some point in their lives.[1–3]

Severe acne vulgaris can have a profound impact on an individual's quality of life, causing physical discomfort, psychological distress, and social stigma.[2] Acne affects up to 50 million Americans annually, and its severity can range from mild, with comedones and pustules, to severe, with deep nodules and cysts.[4] Isotretinoin, a synthetic derivative of vitamin A, has been widely used as an effective treatment for severe acne vulgaris since its introduction in the early 1980s. [5-7]Its remarkable success in treating this dermatological condition has made it a popular choice among physicians and patients alike.[8] However, despite its efficacy, isotretinoin use is associated with a range of potential side effects, including those affecting the musculoskeletal system.[5,9–11] They can manifest as generalized or localized symptoms, ranging from mild discomfort to severe debilitating conditions. One of the most commonly reported musculoskeletal side effects of isotretinoin is musculoskeletal pain.[10] Reports of musculoskeletal adverse events associated with isotretinoin use have been described in the medical literature, although their prevalence and significance remain topics of debate.[9,10] This systematic review aims to comprehensively analyze the existing literature to better understand the nature and prevalence of isotretinoin-induced musculoskeletal adverse events.

Methodology

Study design

This study was designed following the [Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA)].

Search strategy

We conducted a literature search of the PubMed and Google Scholar databases for all relevant studies published between 1989 and 2022. We used the following keywords: “isotretinoin,” “arthritis,” “myositis,” “backache,” and “musculoskeletal side effects.” Four investigators (R.M., A.M., N.M., and A.H.) independently screened the search results for inclusion in the study. We included studies that met the following criteria: (1) articles published between 2000 and 2022, (2) a study population of males and females above 12 years old, and (3) the study population was treated for acne vulgaris with no other comorbidities. We excluded non-English studies, systematic reviews, review articles, expert opinions, studies conducted on animals, and studies that did not provide adequate information.

Data extraction

Two authors (A. H. and N.M.) independently extracted data from the included studies using a standardized data extraction form. We collected the following data: author, publication year, study design, sample size, age of the patient, sex, isotretinoin dose (of symptoms), onset of the symptoms, initial presentation, physical examination findings, laboratory/pathological/radiological findings, medical history, family history, drug and supplement intake, smoking status, and symptoms after dose reduction. Discrepancies in the data extraction were resolved by the third author (R.M.).

Data synthesis

We synthesized the data from the included studies to provide a comprehensive overview of the musculoskeletal side effects of isotretinoin use. Qualitative data synthesis was performed on the included studies.

Results

Search results

A total of 1,089 articles were initially identified through the search process. After removing 51 duplicates, 1,038 articles remained for screening. The screening phase involved a thorough assessment of the titles and abstracts of the identified articles. After this initial screening, 73 articles were selected for full-text assessment based on their potential relevance to the study objectives. During the full-text assessment, each of the 73 articles was carefully evaluated to

determine their eligibility for inclusion in the study. Following this assessment, 49 studies were deemed suitable and included in the analysis.

The included studies comprised various study designs, including analytical studies (Table 1, n=13), case reports (Table 2, n=28), and case series (Table 3, n=8, with a total of 54 cases).

The PRISMA flow diagram below shows a visual representation of the article selection process (Figure 1).

Characters and findings of the included analytical studies

Table 1 provides a summary of the findings from 13 analytical studies on [musculoskeletal (MSK)] side effects associated with isotretinoin treatment. The studies focused on the relationship between the dose, HLA-B27 status, and MSK side effects, as well as MSK side effects among athletes taking isotretinoin. The age of the patients ranges from 16.2 to 25 years. The most commonly reported symptoms included back pain, myalgia (muscle pain), arthralgia (joint pain), and sacroiliitis. Back pain was the predominant symptom, reported in 41% to 74% of cases, followed by myalgia and arthralgia. Other symptoms such as lethargy, hip pain, weakness, and Achilles enthesopathy were also mentioned in some studies. However, the frequencies of these symptoms were not consistently provided across all studies. Information regarding the specific doses of isotretinoin used varied among the studies. Reported dosages ranged from as low as 0.25 mg/kg to as high as 2 mg/kg per day. In some studies, the dosage was reported as a range or a median value, while in others, a mean or a specific daily dose was mentioned. Cumulative doses were also reported in some studies, ranging from 120 to 150 mg/kg.

Characteristics and findings of the included case reports

Table 2 provides information on the characteristics of the included case reports, including age, sex, initial presentation, isotretinoin dose, onset of symptoms, diagnosis, and symptoms after dose reduction. The age range of the patients varies from 15 to 55 years, with a mean age of approximately 25.4 years. Among the reported cases, 17 were male (60.7%), and 11 were female (39.3%). The most common presentations include severe back pain (3 cases), bilateral hip pain (2 cases), wrist and MCP joint pain (2 cases), groin pain (1 case), myalgia and low back pain (1 case), acne fulminans with inflammatory lesions (1 case), and other specific symptoms in the remaining cases. The prescribed isotretinoin doses varied among the reported cases. In some cases, the initial dose was mentioned explicitly, while in others, it was not specified or the cumulative dose couldn't be confirmed. The reported daily doses ranged from 20 mg to 500 mg/kg/day, with the majority of cases receiving doses in the range of 20 mg to 40 mg per day.

In some instances, symptoms appeared shortly after treatment, while in others, they developed months or even years later. The exact onset of symptoms was not mentioned for a few cases. Based on the case reports, various diagnoses were made for the patients' symptoms. The reported diagnoses include bilateral sacroiliitis and left hip arthritis, isotretinoin-induced arthritis and sacroiliitis, rhabdomyolysis, chronic sacroiliitis, acne-associated musculoskeletal syndrome, acute hip monoarthritis, diffuse idiopathic skeletal hyperostosis (DISH), acute subacromial bursitis or calcific tendinitis, retinoid-induced sclerosis, polyneuropathy, retinoid-induced premature epiphyseal closure, non-union distal fibula avulsion fracture, skeletal hyperostosis, and acute sacroiliitis. The information regarding symptoms after dose reduction or discontinuation of isotretinoin was available for some cases. In many instances, symptoms improved or resolved completely after reducing the dose or stopping the treatment. However, in a few cases, symptoms persisted or recurred even after discontinuation.

Characteristics and findings of the included case series

Table 3 provides an overview of the case series, each row in the table represents an individual case, and various parameters are recorded for analysis. Among the 54 cases, 50% were male and 50% were female. The age range of the patients was between 15 and 44 years. Regarding the initial presentation, the most commonly reported symptom was back pain (74%), followed by hip pain (39%) and joint pain (17%). Other symptoms included neck pain, chest pain, gluteal pain, and knee pain. In some cases, the symptoms were accompanied by morning stiffness. In some cases, the initial presentation was missing. The reported doses ranged from 10 mg to 120 mg per day. However, some studies did not specify the exact dosage. In some cases, the dosage was increased during the course of treatment. The duration of treatment with isotretinoin ranged from 1 month to 7 years. The onset of symptoms after the initiation or discontinuation of isotretinoin also varied among the cases. Symptoms were reported to occur as early as 15 days after initiation and as late as 16 years after treatment. Similarly, symptoms resolved at different time points after discontinuation, ranging from a few weeks to several months. The most commonly reported diagnosis was isotretinoin-induced sacroiliitis (63%). Other reported diagnoses included costochondritis, sacroillitis, and active sacroiliitis. In some cases, the diagnosis was not specified. It is important to note that not all studies provided detailed information about the diagnosis. After dose reduction or discontinuation of isotretinoin, the majority of cases showed improvement or complete resolution of symptoms. In some cases, additional treatment with medications such as adalimumab or nonsteroidal anti-inflammatory drugs (NSAIDs) was required to achieve symptom relief. However, a small number of cases did not show complete resolution of symptoms even after treatment.

Discussion

This systematic review aimed to investigate the [musculoskeletal (MSK)] side effects associated with isotretinoin treatment. The analysis included a total of 49 studies, consisting of analytical studies, case reports, and case series. The analytical studies included in this review focused on different aspects of MSK side effects associated with isotretinoin treatment. The studies varied in sample size, ranging from 15 to 154 patients, and included both male and female participants with varying age ranges. The reported musculoskeletal symptoms included lethargy, myalgia, low back pain, arthralgia, tendinopathy, sacroiliitis, and other MSK side effects. Some studies have distinguished between inflammatory and mechanical low back pain, highlighting the nature of the pain. Isotretinoin doses administered in the studies ranged from 0.25 to 0.8 mg/kg/day, with variations in cumulative doses. The onset of symptoms occurred within a few months of treatment initiation.

The studies examined the relationship between isotretinoin use and musculoskeletal side effects, focusing on factors such as dose, HLA-B27 status, and their impact on the occurrence and severity of symptoms.

The physical examination findings reported in the studies included features such as sacroiliac joint tenderness, muscle weakness, and erythema. Radiological findings, such as sacroiliac joint X-rays or MRI, were utilized to confirm diagnoses of sacroiliitis and other related conditions. The diagnosis of musculoskeletal conditions varied across the studies, encompassing mechanical back pain, inflammatory back pain, tendinopathy, sacroiliitis, hyperCKemia (elevated CK levels), and others. Treatment approaches ranged from the use of NSAIDs to the discontinuation of isotretinoin, depending on the severity of the symptoms. Some studies have also explored potential risk factors or associations by assessing the medical history of chronic diseases, family history, and smoking status. Additionally, investigations into the impact of isotretinoin dosage, treatment duration, and vitamin levels on musculoskeletal symptoms and laboratory markers were conducted. Among the individual studies, Selçuk et al.[12] reported musculoskeletal symptoms, such as lethargy, myalgia, and low back pain, in a study involving 73 individuals aged 15–34 years. Acute sacroiliitis was observed in 8.2% of the cases, and no significant pathology was found in the laboratory findings. Karaosmanoğlu and Mülkoğlu [13] examined 94 participants with a mean age of 20.8 years who reported musculoskeletal symptoms, including arthralgia, myalgia, low back pain, and sacroiliitis. Sacroiliitis was observed in 11.7% of the cases, while radiological and laboratory findings did not reveal significant pathology. Acar et al.[14] investigated 99 individuals with a mean age of 20.5 years, reporting back pain, inflammatory back pain, and mechanical back pain as musculoskeletal symptoms. Among the reported cases, isotretinoin-induced sacroiliitis emerged as a notable musculoskeletal complication.

Several cases, such as those presented by Yılmazer et al. [26], Bilecik et al. [35], Toledo et al.[36], Cheng et al. [37], Levinson et al. [45], and Kibar et al.[49], described individuals who developed sacroiliitis after isotretinoin treatment. Encouragingly, the symptoms either resolved or improved upon discontinuation of the medication or with the use of anti-inflammatory medications. These findings underscore the importance of monitoring patients undergoing isotretinoin therapy for potential sacroiliitis symptoms and implementing appropriate interventions when necessary. Another musculoskeletal complication identified in the case reports was DISH. A case presented by Zhao and Goodson [38] exemplified a patient who experienced thoracic back pain and morning stiffness following one year of isotretinoin treatment. Although complete resolution of symptoms was not achieved, they showed improvement with the use of gabapentin. Similarly, Barceló et al. [40] reported a case of DISH in a female patient after 11 years of isotretinoin use. These cases suggest a potential association between isotretinoin and DISH, highlighting the need for further investigation and monitoring of patients on long-term isotretinoin therapy.

The case reports also revealed other musculoskeletal complications associated with isotretinoin use. Drezner and Sennett [41] described a case of acute subacromial bursitis or calcific tendinitis in a female patient presenting with shoulder pain that improved with antibiotics. Atalay et al. [42] reported a case of arthralgia and elevated serum ALP levels, leading to a diagnosis of retinoid-induced sclerosis and a gradual decline in bone mineral density. Eksioglu et al. [43] presented a case of bilateral hip pain that completely resolved after three months of isotretinoin treatment. These cases provide further insights into the diverse musculoskeletal effects associated with isotretinoin use, highlighting the importance of recognizing and managing such complications in clinical practice.

Overall, the included case reports collectively contribute to our understanding of the musculoskeletal effects of isotretinoin. While the presented cases demonstrate a range of musculoskeletal complications, it is important to note that many of the reported symptoms improved or resolved with appropriate interventions, such as discontinuing the medication or administering anti-inflammatory drugs. These findings emphasize the significance of vigilant monitoring and prompt intervention to mitigate potential musculoskeletal side effects in individuals undergoing isotretinoin treatment. Among the case series, isotretinoin-induced sacroiliitis emerged as a significant musculoskeletal complication. Several studies have reported cases in which patients developed sacroiliitis after starting isotretinoin treatment. Notably, the symptoms of sacroiliitis typically appeared after a few months of treatment, and discontinuing isotretinoin led to symptom resolution in most cases. This suggests a potential causal relationship between isotretinoin and sacroiliitis. The studies by Ozdel et al. [53], Bilge et al. [54], Aydog et al. [55], Kavadar et al. [58], and Yavuz Pehlivan et al. [59] provide compelling evidence for this association. Furthermore, the cases described in these studies demonstrate the

importance of recognizing sacroiliitis symptoms and implementing appropriate management strategies, such as discontinuing medication or using anti-inflammatory agents.

The case series by Ozdel et al. [53] investigated two cases, both of which experienced hip and back pain as initial presentations. Isotretinoin-induced sacroiliitis manifested after different durations of treatment, but symptom improvement was not achieved until adalimumab was administered. This highlights the potential efficacy of adalimumab in managing isotretinoin-induced musculoskeletal symptoms. Manfredini et al. [57] focused on abnormal CK levels that exceeded the reference range in several patients. Although these cases did not present other musculoskeletal symptoms, they suggest that isotretinoin treatment may lead to elevated CK levels, those findings are also consistent to Faygia et al. [58]. Kavadar et al. [59] described cases of lumbar and hip pain, walking difficulties, and morning stiffness that resolved completely upon discontinuation of isotretinoin. These cases provide further evidence of the association between isotretinoin use and sacroiliitis. Yavuz Pehlivan et al. [60] reported cases of backache, hip joint pain, and morning stiffness. The symptoms appeared after a certain duration of isotretinoin treatment, and while specific details regarding symptom resolution were not provided, it can be inferred that the symptoms gradually improved over time. Bilge et al. [54] reported multiple cases demonstrating complete resolution of symptoms upon discontinuation of isotretinoin. These cases involved individuals who experienced symptoms such as costochondritis, sacroiliitis, and painful sacroiliac joint symptoms, underscoring the importance of promptly recognizing and managing these complications. Aydog et al. [55] presented several cases in which lumbar back pain and active sacroiliitis were observed. Discontinuation of isotretinoin led to the resolution of symptoms, further supporting the association between isotretinoin use and the development of active sacroiliitis.

In terms of MSK side effects in relation to dose, several studies have examined the cumulative dose of isotretinoin and its association with different MSK symptoms. Selçuk et al. [12] reported that low back pain symptoms developed in 2–3 months of treatment with a mean isotretinoin dose of 0.53 mg/kg/day. Karaosmanoğlu and Mülkoğlu [13] found a significant linear relationship between low back pain and a cumulative dose of isotretinoin. Acar et al. [14] observed that the mean cumulative isotretinoin dose was significantly higher in patients with moderate and severe back pain than in those with mild back pain. These findings suggest that there may be a dose-dependent relationship between isotretinoin and MSK side effects, particularly low back pain.

Regarding HLA-B27 and MSK side effects, Karaosmanoğlu and Mülkoğlu [13] reported that there was no significant difference in the total cumulative isotretinoin dose between patients with inflammatory back pain and those with mechanical back pain. This suggests that HLA-B27 status may not play a significant role in the development of MSK side effects in patients taking isotretinoin. However, it is important to note that this finding is based on a single study, and further research is needed to confirm

this relationship. Kaymak [19] found that out of 89 patients treated with isotretinoin, only 11 experienced myalgia and weakness, and 8 of them were athletes. This study suggests that strenuous physical activity prior to isotretinoin treatment may increase the risk of MSK side effects. It is important for athletes and individuals engaging in high-intensity physical activities to be aware of these potential risks and to discuss them with their healthcare providers. The cumulative dose of isotretinoin may be associated with the development and severity of MSK side effects, specifically low back pain. However, the relationship between HLA-B27 status and MSK side effects requires further investigation.

Strengths

1. This study conducted a systematic review to ensure a comprehensive evaluation of the available literature on musculoskeletal complications associated with isotretinoin use.
2. The inclusion of various study designs provided a broader perspective on the topic.
3. The study included numerous studies, enhancing the robustness and reliability of the findings.
4. The analysis explored a range of musculoskeletal symptoms, diagnostic findings, and treatment approaches, contributing to a better understanding of isotretinoin-related musculoskeletal complications.

Limitations

1. The analysis was based on existing studies, which may have variations in methodology, sample sizes, and reporting biases.
2. The included studies comprised various study designs, which may have introduced heterogeneity in the analysis.

Conclusions

The study findings indicate that musculoskeletal side effects, such as low back pain, myalgia, and arthralgia, are common among patients using isotretinoin. Isotretinoin-induced sacroiliitis and DISH were identified as significant complications. The cumulative dose of isotretinoin may be associated with the development and severity of musculoskeletal side effects, particularly low back pain. However, further research is needed to investigate the relationship between HLA-B27 status and musculoskeletal side effects. The study emphasizes the importance of monitoring patients undergoing isotretinoin therapy for potential musculoskeletal complications and of implementing appropriate interventions when necessary. Overall, this study provides valuable insights into the musculoskeletal

complications associated with isotretinoin use and highlights the need for further research and clinical monitoring in this area.

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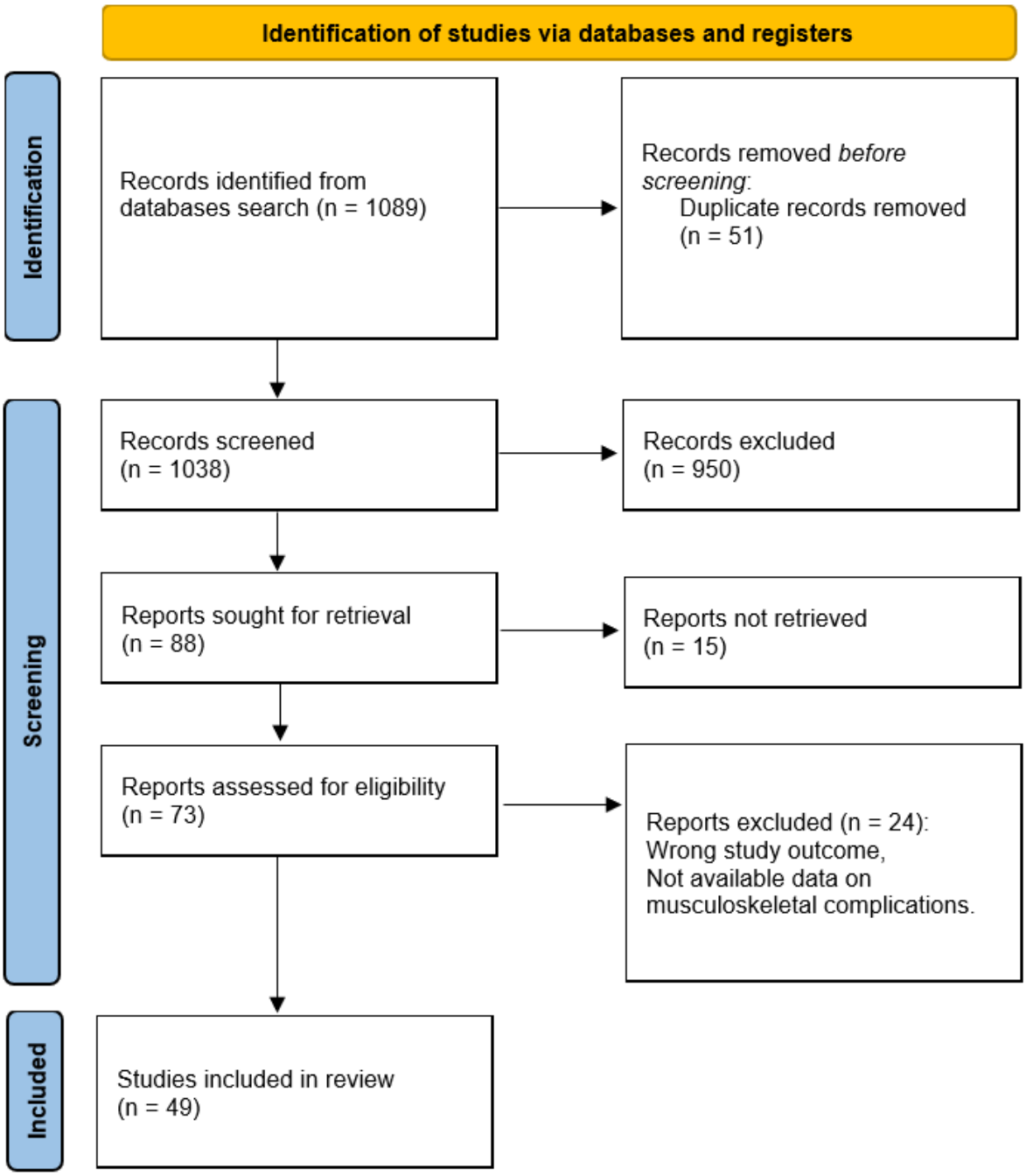

Figure 1. PRISMA flow diagram summarizing the search and screening process.

Table 1. Characters of included analytical reports (n=13).

Study	Sample Size	Age Range	Musculoskeletal Symptoms	Isotretinoin Dose	Radiological Findings	Lab Findings
Selçuk et al., 2016 [12]	73	15-34 years	Lethargy, myalgia, low back pain	Range: 0.4-0.8 mg/kg/day	Acute sacroiliitis in 8.2%	No significant pathology
Karaosmanoğlu & Mülkoğlu, 2020 [13]	94	20.8 ± 4.0 years	Arthralgia, myalgia, low back pain, sacroiliitis	Median cumulative doses varied	Sacroiliitis in 11.7%	No significant pathology
Acar et al., 2021 [14]	99	Mean: 20.5 years	Back pain, inflammatory back pain, mechanical back pain	Mean: 0.6 mg/kg	Sacroiliitis in 4%	CK elevation in some cases
Alkan et al., 2015 [15]	42	16.2-25 years	Unilateral Achilles enthesopathy, sacroiliitis, IBD	30 mg/day	-	No significant pathology
Ertugrul et al., 2011 [16]	50	Mean: 22.0 years	-	0.5-0.8 mg/kg/day	-	Changes in vitamin D levels
Taheri et al., 2020 [17]	113	22.32 ± 3.85 years	Lethargy, myalgia, low back pain, sacroiliitis	0.55 ± 0.19 mg/kg	Sacroiliitis in some cases	No significant pathology
Ghiasi et al., 2013 [18]	40	15-40 years	Myalgia	0.25 mg/kg	-	No significant pathology

Kaymak, 2008 [19]	89	18-24 years	Myalgia, weakness	0.6-0.8 mg/kg/day	Elevated CPK levels in some cases	HyperCPKemia
Sayar, 2021 [20]	154	14-36 years	Elevated serum CK levels, myalgia	Various doses	-	-
Yıldızgören et al., 2015 [21]	15	20.1 ± 4.9 years	Myalgia	-	-	-
Elnady et al., 2020 [22]	513	26.5 ± 7.8 years	IBP without HLA-B27	0.5-1 mg/kg daily, cumulative dose 120-150 mg/kg	Sacroiliitis in 52 patients	Elevated CRP in sacroiliitis patients
DiGiovanna et al., 2004 [23]	217	15.1 ± 6 years	Back pain (41%), arthralgia (31%)	Mean daily dose 66 mg (1 mg/kg/day)	BMD changes in various locations	Creatine kinase elevation in 2 patients
Mülkoğlu & Karaosmanoğlu, 2021 [24]	30	Median age 19	Mild to moderate back pain	1-2 mg/kg/day, cumulative dose 120-150 mg/kg	-	No significant difference in CPK levels

Table 2. Characters of included case reports (n=28).

Study	Age/Sex	Initial Presentation	Isotretinoin Dose	Onset of Symptoms	Diagnosis	Symptoms After Dose Reduction

Kulaklı et al., 2018 [25]	30/M	Sever left hip and leg pain for two days	20 mg daily	Two months after treatment	Bilateral sacroiliitis and left hip arthritis	Symptoms improved
Tasdelen et al., 2015 [26]	23/M	Wrist and five metacarpophalangeal (MCP) joints pain	Initial: 20 mg/day	Six months after treatment	Isotretinoin-induced arthritis and sacroiliitis	Symptoms resolved completely
Tres et al., 2018 [27]	16/M	Severe back pain with inability to walk	-	20 days after treatment	Sacroiliitis	Symptoms improved with NSAIDs
Dasgta et al., 2020 [28]	16/F	Bilateral hip pain after a strenuous workout	1mg/kg/day initially	Six months after treatment	Rhabdomyolysis	Symptoms improved completely
Mülkoğlu & Nacir, 2020 [29]	26/F	Right hip and low back pain with morning stiffness	40 mg daily	Since the 4th month of treatment	Chronic sacroiliitis	Symptoms resolved completely
McCarthy, 2014 [30]	26/M	Back pain and stiff hips	-	Shortly after treatment	-	-
Haskin et al., 2008 [31]	15/M	Sever chest and back pain and inability to walk	-	3 weeks after treatment	Acne-associated musculoskeletal syndrome	-
Mahou et al., 2006 [32]	19/F	Groin pain	30 mg/day	7 weeks after treatment	Acute Hip Monoarthritis	Symptoms improved with naproxen
Barbareschi et al., 2010 [33]	17/M	Acne fulminans with inflammatory, ulcerative, hemorrhagic lesions	30 mg/day	After few days of treatment	Isotretinoin-induced sacroiliitis	Symptoms resolved without sequelae
Yılmazer et al., 2013 [34]	20/F	Myalgia, bilateral hip, pelvic, and low back pain	1m: 30 mg/day, 2m: 40 mg/day	3 months after treatment	Isotretinoin-induced sacroiliitis	Symptoms resolved after 6 weeks
Bilecik et al., 2014 [35]	18/M	Back and sacroiliac pain	-	10 weeks later	Isotretinoin-induced sacroiliitis	Symptoms resolved completely
Toledo et al., 2021 [36]	17/M	Back pain	40 mg daily	4 months after treatment	Isotretinoin-induced sacroiliitis	Symptoms improved after stopping

Cheng et al., 2020 [37]	15/M	Hip pain, intermittent low-grade fever, myalgia	20 mg/day	1 month after treatment	Isotretinoin-induced sacroiliitis	Completely recovered after discontinuing
Zhao & Goodson, 2015 [38]	35/M	Thoracic back pain, morning stiffness	500 mg/kg/day oral dose	1 year	Diffuse idiopathic skeletal hyperostosis (DISH)	Symptoms improve with gabapentin
Maria et al., 2019 [39]	16/M	Right knee ACL lesion reoccurrence	-	2 years	Graft integration success after stopping isotretinoin	-
Barceló et al., 2021 [40]	36/F	Cervical pain	Can't confirm cumulative dose	11 years	Diffuse idiopathic skeletal hyperostosis	-
Drezner & Sennett, 2004 [41]	55/F	Shoulder pain	1 mg/kg/day	6 months	Acute subacromial bursitis or calcific tendinitis	Symptoms improved with antibiotics
Atalay et al., 2004 [42]	38/M	Arthralgia and elevated serum ALP	80 mg/day for 17 months, then 40 mg/day	22nd month of treatment	Retinoid-induced sclerosis	Gradual decline in bone mineral density
Eksioglu et al., 2008 [43]	20/M	Bilateral hip pain	30 mg/day for 2 months, then 40 mg/day	3 months	Sacroiliitis and polyneuropathy	Symptoms completely resolved
Luthi et al., 2011 [44]	16/M	Knee pain	0.5 mg/kg	6 months	Retinoid-induced premature epiphyseal closure	Symptoms regressed over 2 months
Levinson et al., 2011 [45]	17/M	Unable to walk	20 mg daily, increased to 40 mg daily	1 month	Isotretinoin-induced sacroiliitis	Symptoms resolved with naproxen
Constantinou & Brown, 2012 [46]	16/M	12-week ongoing ache over right lateral malleolus	-	6-12 months	Non-union distal fibula avulsion fracture	Symptoms reduced after 4 weeks

Hartung et al., 2012 [47]	20/M	Severe myalgia and arthralgia after exercise	40 mg/day	8 weeks after isotretinoin	Rhabdomyolysis	Severe symptoms and vitamin A intoxication
Graf & Whittle, 2014 [48]	29/M	Mild painless reduction in cervical and thoracic spine range of motion	2 mg/kg	6 months after isotretinoin	Skeletal hyperostosis	-
S Kibar et al., 2016 [49]	31/F	Left buttock and lower back pain	20 mg-gradually increased to 40 mg	Onset of isotretinoin therapy	Acute sacroiliitis	Recurrence of pain after treatment
Alexander P. Rozin et al., 2010 [50]	28/M	Bilateral hip, pelvic, and low back and buttock pain with severe disability	30 mg/day	20 days	Sacroiliitis	Symptoms improved after discontinuation
Yilmaz Tasdelen et al., 2015 [51]	23/M	Wrist and MCP joint pain lasting for 2 weeks	40 mg/day	Not clear	Isotretinoin-induced arthritis	Symptoms resolved
GÖKBEL et al., 2020 [52]	26/F	Inflammatory pain in lower back and right hip region	30 mg daily	After 8 weeks	Active sacroiliitis	No active sacroiliitis

Table 3. Characters of included case series (n=8; cases=54).

Study	Age/Sex	Initial Presentation	Isotretinoin Dose	Onset of Symptoms	Diagnosis	Symptoms after dose reduction
Ozdel et al., 2020 [53]	16/M	Hip and back pain	1 mg/kg per day	60 days after initiation	Isotretinoin-induced sacroiliitis	No improvement after discontinuation, responded to Adalimumab
	17/F	Left hip and lower back pain	0.5 mg/kg/day	Sixth month of treatment	Isotretinoin-induced sacroiliitis	No improvement after discontinuation, responded to Adalimumab
Bilge et al., 2014 [54]	31/F	-	-	3 months	-	Symptoms resolved completely upon stopping isotretinoin
	16/M	-	-	11 months	-	Symptoms resolved completely upon stopping isotretinoin

	22/M	-	-	24 months	Costochondritis, sacroillitis	Symptoms resolved completely upon stopping isotretinoin
	19/F	-	-	3 months	-	Symptoms resolved completely upon stopping isotretinoin
	22/F	-	-	9 months	Painful sacroilliac joint	Symptoms resolved completely upon stopping isotretinoin
Aydog et al., 2019 [55]	21/F	Lumbar back pain	50 mg daily	Two months after initiation	Active sacroiliitis	Resolved upon isotretinoin discontinuation
	29/M	Lumbar back pain with no morning stiffness	40 mg daily	Two months after stopping	Active sacroiliitis	Symptoms resolved with NSAID and MRI showed regression
	36/F	Lumbar and dorsal back pain	50 mg daily	One month after initiation	Active sacroiliitis	Symptoms completely resolved 6 months after stopping isotretinoin
	28/F	Hip and gluteal pain	25 mg daily	Two months after treatment	Active sacroiliitis	Symptoms resolved one year after stopping isotretinoin
	21/F	Lumbar back pain	25 mg daily	Two months after treatment	Active sacroiliitis	Symptoms resolved six months after stopping isotretinoin
	16/M	Lumbar back pain	Various dosages	7th month of treatment	Active sacroiliitis	Symptoms resolved few weeks after stopping isotretinoin
	44/F	Neck and lower back pain	-	7 years after treatment	Active sacroiliitis	Symptoms lessened but did not resolve with NSAID
	28/F	Back, chest and hip pain	50 mg daily	5 years after treatment	-	Symptoms resolved few months after NSAID
	36/F	Back, chest and neck pain	50 mg daily	16 years after treatment	Active sacroiliitis	Symptoms resolved one year after NSAID
Dinçer et al., 2008 [56]	18/M	Lumbar back and hip pain	25 mg daily	3 months after treatment	Sacroiliitis	Improved with NSAIDs

	25/F	Severe lumbar pain and morning stiffness	Unknown	1 year after treatment	Sacroiliitis	Improved with NSAIDs
	24/M	Lumbar back pain with morning stiffness	15 mg daily	During and after treatment	Sacroiliitis	Improved with NSAIDs
Manfredini et al., 2020 [57]	16/F	Abnormal CK level	20 mg/daily	2 Months of treatment	-	CK Exceeding 850 IU/L: No
	22/F	Abnormal CK level	10 mg/daily	1 Month of treatment	-	CK Exceeding 850 IU/L: No
	15/M	Abnormal CK level	15 mg/daily	1 Month of treatment	-	CK Exceeding 850 IU/L: No
	17/M	Abnormal CK level	20 mg/daily	3 Months of treatment	-	CK Exceeding 850 IU/L: No
	24/F	Abnormal CK level	20 mg/daily	2 Months of treatment	-	CK Exceeding 850 IU/L: No
	22/M	Abnormal CK level	20 mg/daily	2 Months of treatment	-	CK Exceeding 850 IU/L: No
	27/M	Abnormal CK level	20 mg/daily	3 Months of treatment	-	CK Exceeding 850 IU/L: Yes but Renal function tests and urine analysis were normal and were asymptomatic
	18/M	Abnormal CK level	20 mg/daily	3 Months of treatment	-	CK Exceeding 850 IU/L: No
	18/M	Abnormal CK level	15 mg/daily	2 Months of treatment	-	CK Exceeding 850 IU/L: No
	19/M	Abnormal CK level	20 mg/daily	2 Months of treatment	-	CK Exceeding 850 IU/L: No

	20/M	Abnormal CK level	10 mg/daily	1 Month of treatment	-	CK Exceeding 850 IU/L: No
	25/M	Abnormal CK level	20 mg/daily	2 Months of treatment	-	CK Exceeding 850 IU/L: Yes but Renal function tests and urine analysis were normal
	16/F	Abnormal CK level	10 mg/daily	2 Months of treatment	-	CK Exceeding 850 IU/L: No
	17/M	Abnormal CK level	20 mg/daily	3 Months of treatment	-	CK Exceeding 850 IU/L: Yes Renal function tests and urine analysis were normal and were asymptomatic
	18/M	Abnormal CK level	10 mg/daily	2 Months of treatment	-	CK Exceeding 850 IU/L: yes Renal function tests and urine analysis were normal and were asymptomatic
	18/M	Abnormal CK level	10 mg/daily	1 Month of treatment	-	CK Exceeding 850 IU/L: No
	23/M	Abnormal CK level	30 mg/daily	4 Months of treatment	-	CK Exceeding 850 IU/L: No
	15/M	Abnormal CK level	20 mg/daily	3 Months of treatment	Not specified	CK Exceeding 850 IU/L: No
Kavadar et al., 2015 [59]	36/F	Lumber and hips pain, difficulty to walk, morning stiffness	Increased to 120 mg daily (last week)	5 months	Isotretinoin-induced sacroiliitis	Symptoms resolved completely after 6 weeks
	21/M	Lumber and hips pain, difficulty to walk, morning stiffness	Started: 30 mg/day, increased to 60 mg/day for 10 days	9 weeks	Isotretinoin-induced sacroiliitis	Symptoms resolved completely after 6 weeks
	32/F	Severe backache, hip	-	15th day	Not specified	Gradually resolved

YAVUZ PEHLIVAN et al., 2015 60		joint pain, and morning stiffness lasting 1–2 h				
	22/M	Backache and hip joint pain that led to disrupted sleep	15 mg/day	20th day	Not specified	-
	19/M	Backache, hip joint pain, and morning stiffness	-	4 months	Not specified	-
	35/F	Severe backache and gluteal pain in the morning and at night	-	-	Not specified	-
Kocak et al., 2017 [61]	22/F	-	20–40 mg daily	4 months	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within one month
	16/M	-	20 mg daily	1 month	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within one month
	25/F	Knee pain	20–40 mg daily	3 months	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within one month
	32/F	Back pain	20–40 mg daily	3 months	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within one month
	24/F	-	20–40 mg daily	2 months	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within one month
	19/F	-	20–40 mg daily	1 month	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within one month

	17/M	Back pain	20–40 mg daily	4 months	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within one month
	21/F	-	20–40 mg daily	2 months	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within one month
	37/F	-	20–40 mg daily	2 months	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within one month
	36/F	-	20–40 mg daily	5 months	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within four months
	18/M	-	20 mg daily	1 month	Isotretinoin-induced sacroiliitis	Symptoms completely resolved within one month

Table 4. Adverse events by number of patients.

Symptoms	Number of patients
Sacroiliitis	113
Inflammatory Back pain	106
Mechanical back pain	212
Arthralgia	56
Arthritis	3
Lethargy	98
Myalgia	149

Achilles tendinopathy	8
CK elevation Creatinine Kinase	46
Diffuse idiopathic skeletal hyperostosis (DISH)	2
ACL lesion Anterior Cruciate ligament	1
septic subacromial bursitis	1
abscesses on the scalp	1
fluctuant nodules	1
sensorimotor demyelinating polyneuropathy	1
knee pain	1
Hip osteoarthritis (OA)	2
mild non-inflammatory pain affecting the cervical and thoracic spine.	1
Chest pain	1
Rhabdomyolysis	1

CK: Creatinine Kinase, ACL: lesion Anterior Cruciate ligament.