

SUPPLEMENTARY MATERIALS

Isotretinoin musculoskeletal side effects: a systematic review

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Supplementary 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

Supplementary 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
Yilmazer 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

Supplementary 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 sacroiliac 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
Yavuz pehlivan et al., 2015 ⁶⁰	32/F	Severe backache, hip joint pain, and morning stiffness lasting 1–2 h	-	15th day	Not specified	Gradually resolved
	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