

Review

The creatine kinase conundrum: a reappraisal of the association of isotretinoin, creatine kinase, and rhabdomyolysis

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Capsule Summary

- Since 1982 there have been multiple reports of patients who had elevated creatine kinase levels during their course of isotretinoin, mostly with concurrent exercise.
- Physicians should consider obtaining baseline creatine kinase in elite athletes and counseling patients that vigorous exercise and male gender are associated with elevated creatine kinase.

Introduction**How are isotretinoin and creatine kinase related?**

Isotretinoin is a prescribed oral therapy for severe, nodulocystic acne or recalcitrant acne unresponsive to conventional therapy.¹ Approximately 25% to 51% of patients on isotretinoin report

Abstract

Background Isotretinoin has been reported to elevate creatine kinase, which may lead to fatal rhabdomyolysis.

Objective To review the literature and propose practice guidelines for management of elevated creatine kinase during isotretinoin therapy.

Findings Patients have intrinsic and extrinsic qualities that may synergistically work with isotretinoin to elevate serum creatine kinase. Darker skin types and males on isotretinoin are more likely to have elevated creatine kinase. Isotretinoin may induce oxidative stress within muscle tissue, thereby leading to elevations in serum creatine kinase.

Conclusion Evidence supports a tenuous correlation between isotretinoin, elevated creatine kinase, and exercise. Physicians should consider obtaining baseline creatine kinase on elite athletes and counseling patients on risk factors that may elevate creatine kinase. However, the potential for elevated CK is not a contraindication for isotretinoin therapy.

fatigue and myalgias, respectively, and 44% of patients also have elevated creatine kinase (CK).^{2–7} However, there is neither consensus on the clinical significance of, nor guidelines on how to manage, elevated CK on isotretinoin.

CK is a cytosolic enzyme that facilitates energy usage.^{8,9} The three most common CK isoenzymes include: skeletal muscle CK-MM; cardiac tissue CK-MB; and brain tissue CK-BB^{8,9} (“CK” will refer to CK-MM). The normal reference range for CK, which normally falls between 58–280 IU/l, reflects a combination of these three isoforms. There are a multitude of factors that affect CK including: younger age, male sex, darker skin type, and prolonged, eccentric physical activity.^{8–11} Notably, an athlete can have a baseline average CK of 500–1,000 IU/l while long-distance runners can have a CK 20 times normal 24 h post-marathon.^{8,9,12–15} CK will rise to peak levels within 24–96 h and return to baseline within 4–10 days (half-life of approximately 1.5 days).^{9,16} Furthermore, while athletes may have elevated baseline CK, they have smaller increases in CK after exercise compared to untrained individuals.^{8,9}

When does elevated CK mean rhabdomyolysis?

When CK values approach or exceed 1,000–2,500 IU/l, there is concern for rhabdomyolysis: generalized muscle damage that spills electrolytes and myoglobin into circulation causing cardiac arrhythmias, acute kidney injury (AKI), and possibly death.^{10,16–18} While the etiology of rhabdomyolysis can vary, 60% of cases have at least two contributing factors.^{11,16} A study of 475 patients with rhabdomyolysis found the average CK to be 4206, ranging from as little as 1,500 IU/l to as high as 100,000 IU/l.¹⁸ There is some evidence that suggests higher CK correlated with worse outcomes as values greater than 15,000 IU/l are 70% more likely to adversely affect kidney function.¹⁶ Serum CK levels can quantitatively complement history and physical examination as the stereotypical triad of rhabdomyolysis (weakness, muscle pain, and myoglobinuria) appears in approximately 10% of clinical presentations while approximately 50% of presentations can be asymptomatic.¹⁶

What have others observed and how did they manage?

The incidence of elevated serum CK while on isotretinoin therapy varies across populations from 5.6 to 41% (Table 1), while one study found upwards of 44% of patients had at least one elevated CK on isotretinoin.^{2,19,20}

Studies suggest that males are 2.6 times more likely to develop elevated CK compared to females, with 70–87.5% of affected individuals being male.^{9,13,19,21–24} Furthermore, males had a ten-fold greater frequency of repeated elevations.²

There is also a correlation between physical activity and elevated CK on isotretinoin. Not only do 63% of CK elevations on isotretinoin involve concurrent physical activity, but also these are usually “supra-baseline” activities conducted within 6 days of serum evaluation.^{24,25} While there is some evidence that isotretinoin may elevate serum CK independently of physical activity, CK evaluations are typically more exaggerated in the setting of concurrent exercise and isotretinoin therapy.²² Indeed, in a predisposed individual, there may be possible synergy between exercise and isotretinoin. Chen *et al*²⁴ noted that CK normalized in four out of 12 patients when either isotretinoin or exercise was discontinued independently. Furthermore, they reported a patient who had normal CK (i) while exercising on isotretinoin and (ii) while sedentary on isotretinoin but who had markedly elevated CK levels while exercising on isotretinoin therapy.

Myalgia has so far proven to be a poor clinical indicator of elevated CK on isotretinoin. Symptomatic reports ranged from less than 10–51% on isotretinoin while only 10–20% of individuals with elevated CK reported myalgia.^{19,20,23,25,26} In some cases, there were no reports or correlations of myalgia with CK.^{21,25} Kaymak had more nuanced results: only one of 11 patients with myalgia was found to have elevated CK; furthermore only one of five patients with an elevated CK reported symptoms.¹⁹ Landau found similar disparities: only two of the five patients with CK greater than 5,000 IU/l had myalgia; the

patient with the highest and third-lowest CK (14,645 and 5,870 IU/l, respectively).²²

No large studies have looked specifically at isotretinoin and rhabdomyolysis, but there have been many case reports (Table 2). Since 1984 there have been three individual cases of asymptomatic elevations in serum CK associated with isotretinoin therapy. While two cases had notable additional factors (e.g. intense daily exercise training and attempted suicide) that potentially contributed to the CK elevations, there were no notable instigating factors in the third case.^{27–29} Of note, in that final case, the patient’s CK of 11,053 IU/l began to normalize (CK 434 IU/l) within 6 days of discontinuation of isotretinoin.²⁹

Between 1983 and 2016, there were seven reported cases of symptomatic elevations in CK on isotretinoin, five of which resulted in rhabdomyolysis.^{30–36} Six of these cases had a notable additional factor (five precipitated by weight lifting; one had an autosomal recessive myopathy).^{31–33,35–37} These individuals had a max serum CK 801–66,000 IU/l and developed fatigue, generalized muscle pain, and weakness while two additionally had myoglobinuria.^{31,32,35,36} In a majority of these cases, discontinuation of isotretinoin and/or physical activity in addition to adequate oral hydration improved both clinical and laboratory findings.^{31,32,36}

Hartung *et al*³⁵ described a fatal case of rhabdomyolysis in a 20-year-old male on isotretinoin for severe recalcitrant acne. The patient had been on isotretinoin 40 mg QD for 2 months before developing severe myalgia and arthralgia associated with moderate exercise. Despite discontinuing isotretinoin, over the next 3 weeks, the patient developed signs of hypervitaminosis A (xerosis, cheilitis, anorexia, fatigue, and myalgia) requiring hospitalization when his CK was found to be 82,100 IU/l. Three days after admission, the patient died from ventricular fibrillation secondary to generalized rhabdomyolysis. Autopsy revealed severe rhabdomyolysis of skeletal and cardiac muscle and signs of myoglobin in his renal tubules leading to acute kidney injury without signs of other underlying diseases or medications on postmortem toxicology screen.

How do we think isotretinoin elevates CK levels?

While the body of evidence connecting CK and isotretinoin continues to grow, the causal underpinnings between them all are still in its infancy. Acne is thought to induce a systemic baseline inflammatory state by increasing levels of oxidative damage and expending reserves of antioxidants.³⁸ Treatment with isotretinoin exacerbated oxidative stress, possibly via interactions with intranuclear receptors and DNA, and potentially adversely affect skeletal, liver, and epidermal tissue. Interestingly, they also found increased levels of total body antioxidants suggesting oxidative damage by isotretinoin may also subdue acne-induced inflammatory state. Of note, significant increases ($P = 0.0001$) in CK between acne patients on isotretinoin (145 ± 15 IU/l) compared to baseline laboratory evaluation (83 ± 4.7 IU/l) and control (86 ± 7.4 IU/l) were also found.

Table 1 Case series of creatine kinase (CK) elevations during isotretinoin therapy

Study	# Patients (CK/total)	Sex (M/F)	Age	Isotretinoin dosage (mg/kg)	Max CK range (IU/l)	Week of CK elevation	# physically active	MSK symptoms	# CK >5× reference or CK >1,000 IU/l (Reference IU/l)
Webster <i>et al</i> ^f	109/246	30/22 56/1 ^a	NR	NR	NR	NR	NR	NR	NR ^b
Kaymak <i>et al</i> ¹⁹	5/89	4/1	19–21	0.6–0.8	292–594	4–16	2	1	0 (24–195)
Heudes <i>et al</i> ²⁰	25/60	NR	14–37	0.5	NR ^c	NR	NR ^d	NR ^e	5 (NR)
Lipinski <i>et al</i> ²¹	7/98	6/1	17–27	1.0–1.2	318–3,520	1–22	1	None	2 (0–224)
Landau <i>et al</i> ²²	165 (7 ^f)/442	6/1	19–21	0.55–1.0	5320–14,645	3–12	6 ^g	2	7 (15–157)
McBurney <i>et al</i> ²³	10/31	7/3	15–26	NR	198–4,210	NR	2	1	2 (NR)
Chen <i>et al</i> ²⁴	19/NR	15/4	NR	NR	145–20,800	NR	12	NR	7 (NR)
Tillman <i>et al</i> ²⁵	26/NR	21/5	16–34	NR	225–613	0–16	NR	NR	0 (10–171)
Bettoli <i>et al</i> ²⁶	10/63	NR	13–26	0.29–0.69	114–4,158	3–12	3	1	2 (10–80)

CK, creatine kinase; M, male; F, female; MSK, musculoskeletal; NR, not reported.

^a22/52 patients with one-time CK elevations were female; 1/57 patients with multiple CK elevations were female.

^bCK elevation <2× reference range $n = 35$; 2–3×, $n = 38$; 3–4×, $n = 18$; >4× $n = 18$. No specific values given.

^caverage CK of 2× “reference range”; maximum CK 7.6× “reference range”.

^dReported 70% of total participants were physically active.

^eReported 69% of symptoms were associated with physical activity.

^fPatients in study CK > 5,000 IU/l*.

^gOne additional patient received an intramuscular injection.

Table 2 Case reports of serum creatine kinase (CK) elevations during isotretinoin therapy

Report	Age	Sex	Max CK (IU/l)	Isotretinoin dosage (mg/kg)	Week of max elevation	Secondary factor	MSK symptoms	CK >5× reference
Del Campo <i>et al</i> ²⁷	16	M	3,000	30 mg BID ^a	5	Physical activity	No	Yes
Sanchez <i>et al</i> ²⁸	16	M	7,000	40 mg QD ^a	8	Suicide attempt	No	Yes
Trauner <i>et al</i> ²⁹	49	M	11,053	0.5	5	None	No	Yes
Tripp <i>et al</i> ³⁰	24	M	422	NR	10 ^b	Muscular hyperactivity ^c	Yes	no
Gomez-Bernal <i>et al</i> ³¹	16	M	801	0.3	44	Weight lifting	Yes	Yes
Guttman-Yassky <i>et al</i> ³²	23	M	35,503	0.5	4	Weight lifting	Yes	Yes
Mashiah <i>et al</i> ³³	16	F	3,180	40 mg QD ^a	NR	Dysferlinopathy	Yes	Yes
Sameem <i>et al</i> ³⁴	25	M	317	0.5	4	“long-distance” travel	Yes	No
Hartung <i>et al</i> ³⁵	20	M	82,100	40 mg QD ^a	8	Weight lifting, travel	Yes	Yes
McBurney <i>et al</i> ³⁶	20	F	6,230	1.5	16	Weight lifting	Yes	Yes
Phillips <i>et al</i> ³⁷	33	F	66,000	1.0	3	210 pull ups	Yes	Yes

CK, creatine kinase; MSK, musculoskeletal; M, male; F, female; NR, not reported.

^aDosage was not reported as “mg/kg”.

^bPersistently elevated CK from baseline.

^cPossible underlying myotonic dystrophy.

Isotretinoin is thought to affect the cell cycle, proper differentiation, and apoptosis within epidermal keratinocytes and sebocytes by modulating levels of transcription factor FoxO3a, and thereby upregulate the expression of tumor necrosis factor-related apoptosis inducing ligand (TRAIL).³⁹ Upregulation of TRAIL within muscle tissue may explain the myalgia and elevated CK while on isotretinoin.³⁹

Oikarinen *et al*⁴⁰ assayed markers specific for skeletal muscle in patients with various dermatologic disorders including those with acne who did and did not receive isotretinoin. Although not statistically significant, their findings did point to

higher mean levels of serum skeletal muscle markers in participants who received isotretinoin.

Further investigations into symptomatic myopathy suggest that isotretinoin may alter both muscle tissue at a structural level as well as impulse conduction at the neuromuscular junction.^{41,42} Studies determined that although motor and sensory nerve conduction was preserved, electromyography revealed altered “myopathic” patterns.^{34,41,42} Muscle biopsies taken from two individuals revealed variation and reduction in muscle fiber size without inflammation. Further evaluation on electron microscopy also found changes within muscle tissue at the cellular level.^{41,42}

Table 3 Additional causes of elevated creatine kinase⁴⁴

Endocrinopathies	Metabolic derangements	Trauma	Medications	Inflammation	Chronic disease
Hyper/hypoparathyroidism	Hyponatremia	Exercise	Statins	Malignancy	Heart failure
Acromegaly	Hypokalemia	Intramuscular injections	Angiotensin II receptor blockers	Celiac disease	Chronic kidney disease
Cushing syndrome	Hypophosphatemia	Seizures	Antiretrovirals	Viral infection	Inherited/genetic myopathies ^a
Hyperparathyroidism			Beta-blockers Quinolones Fibrates Colchicine		

^aIncludes: mitochondrial disorders, muscle dystrophies, glycogen storage disorders, inflammatory myopathies, etc.

Discussion

Although some studies suggest muscle damage and elevated CK by isotretinoin might be caused by oxidative damage or apoptosis, there is not conclusive evidence for its mechanism of action, the relation to myalgias, and how to best apply this information to patient care.^{38,39}

By definition, rhabdomyolysis is evidenced by an elevated CK. However, not all elevated CKs clinically manifest as rhabdomyolysis, especially considering intrinsic (e.g. darker skin types, male sex) or extrinsic (e.g. regular athletic activity) traits that predispose individuals to having benign “supra-normal” CK levels. It is likely that clinically relevant elevations in creatine kinase require several key factors: a predisposition as well as a “second-hit”. A majority of the case reports noted that elevated creatine kinase levels occurred in the setting of concurrent exercise/activity or had an additional instigator (i.e. ischemia, inherited myopathy).^{27,28,31–36,43} Theoretically, the litany of elevated CK etiologies may also serve as second-hit factors, though such events have yet to be reported (Table 3).⁴⁴ However, two-factors aside, there appears to be a component of genetic predisposition, as not all who exercise develop “hyper-CK-emia”, whereas some may demonstrate synergy, as reported by Chen and Rofsky.²⁴

There are currently no accepted guidelines for CK evaluation and management for patients on isotretinoin and, at least in the current literature, no evidence to suggest myalgias may serve as a reasonable clinical sentinel. Further research is needed to determine not only the population that would benefit from regular CK evaluation and timing of CK evaluations but also how to manage patients who develop an elevated CK/rhabdomyolysis while on isotretinoin.

Of very important note is that, while perhaps statistically significant, the clinical significance of hyper-CK-emia is still in question, especially given the mere handful of clinically relevant reports over the 30 plus years isotretinoin has been United States Food and Drug Administration approved. Currently, there

is not enough evidence to say that exercise (or any of the other myriad of causes of elevated CK) is an absolute or even relative contraindication to isotretinoin therapy. In the meantime, patients with additional factors (i.e. elite male athletes) may benefit from additional counseling and perhaps some form of baseline and intermittent CK evaluation.

Conclusion

Given the varied outcomes in the literature, further studies are required to elucidate the correlation between isotretinoin, CK, myalgia, and exercise. Although any patient with a potential “second-hit” factor may also be susceptible, studies suggest that young, darker-skinned, male athletes are most at risk of having elevated CK on isotretinoin. Although no guidelines yet exist regarding regular monitoring, the potential for elevated CK is not a contraindication to isotretinoin therapy; however, patients may benefit from additional history taking and counseling about the more common risk factors for elevated creatine kinase including strenuous exercise, darker skin type, and male sex.

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