

Elevated creatine kinase levels, exercise, and isotretinoin for acne



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INTRODUCTION

Approximately 44% of patients on isotretinoin develop elevated levels of creatine kinase (CK), a proxy for potential muscle tissue damage.¹ Mild elevations are typically transient and well-tolerated, whereas marked elevations can indicate rhabdomyolysis (CK level of ≥ 5 times the reference range [approximately 200 IU/L]) and can be life-threatening.² Here, we present 2 physically active patients with clinically divergent presentations of elevated serum CK levels during isotretinoin therapy.

CASE REPORT

Case 1

A 43-year-old male firefighter on intramuscular testosterone, who engages in daily weightlifting and 5-mile runs, presented for the treatment of moderate mixed acne. The patient was initially instructed to discontinue testosterone and was trialed on doxycycline 120 mg twice daily and adapalene 0.3%/clindamycin 1.4% gel daily. After 6 weeks without improvement, the patient resumed intramuscular testosterone and was started on isotretinoin 20 mg/day. At baseline (off testosterone), the patient had an elevated CK level of 739 IU/L. Isotretinoin dose was doubled every 2 months until 80 mg/day at month 4 and reached a target total dose of 147 mg/kg (Table I). Despite consistently elevated CK level throughout the therapeutic course, the patient remained asymptomatic. Of note, the patient independently reported decreased physical activity that coincided with decreased serum CK level.

Abbreviation used:

CK: creatine kinase

Case 2

A 20-year-old male long-distance runner and soccer player presented with moderate mixed acne. After 2 months on minocycline (extended release 1 mg/kg), tazarotene gel (0.1% cream), and benzoyl peroxide (9.8% foam) with minimal improvement, the patient was started on isotretinoin 20 mg/day and titrated by 10 mg/day/month to 40 mg/day. The baseline laboratory levels were within normal limits (Table II), and the patient tolerated the therapy. At months 3 and 14, the patient had marked asymptomatic isolated CK level elevations (4268 IU/L and 4896 IU/L, respectively). Both times, the patient was instructed to discontinue isotretinoin for 1 week, increase oral hydration to a minimum of 2 L/day for 2 days, and repeat serum CK level evaluation at the end of the week. Both repeat serum CK levels had returned to near baseline and reference range (212 and 207 IU/L at months 3 and 14, respectively). The patient reported completing a long-distance running event and “increasing exercise frequency/intensity” prior to these 2 episodes, respectively. After the first elevation, the patient’s dose was transiently decreased to 30 mg/day for 4 months, and he was able to complete his course without further incident.

DISCUSSION

Multiple factors that can affect CK include younger age; male sex; Black race; history of

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Table I. CK levels of patient 1*

Patient 1 clinical information	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
CK (IU/L)	739 [†]	761	968	460 [‡]	910	454 [‡]	546
OI (mg/day)	20	20	40	40	80	80	80
OI (mg/kg)	—	6.12	12.24	24.44	48.97	73.47	97.96

CK, Creatine kinase; OI, oral isotretinoin.

*Total cholesterol, triglycerides, and gamma-glutamyl transferase levels were all within normal limits and have not been shown.

[†]Evaluated off intramuscular exogenous testosterone; baseline exercise: weightlifting 2 h/day.

[‡]Decreased activity: test 3 assessed after vacation; test 5 assessed after honeymoon.

Table II. CK levels of patient 2*

Patient 2 clinical information	Baseline	Month 1	Month 2	Month 3	Month 6	Month 9	Month 14
CK (IU/L)	145 [†]	369	168	4268 [‡] 212 [§]	64	134	4896 [‡] 207 [§]
OI (mg/day)	20	30	40	30	30	40	40
OI (mg/kg)	—	8	20	36	72	116	154

CK, Creatine kinase; OI, oral isotretinoin.

*Total cholesterol, triglycerides, and gamma-glutamyl transferase levels were all within normal limits and have not been shown.

[†]Baseline exercise: soccer, long-distance running.

[‡]Increased activity: test 3 days after competition; 6 days after "increased exercise frequency/intensity."

[§]Re-evaluation after 1 week off isotretinoin and increased oral hydration.

endocrinopathies or genetic myopathies; concurrent medications; and prolonged, eccentric physical activity.^{3,4} Athletes can have average CK levels of 500 to 1000 IU/L, whereas marathon runners can have CK levels of approximately 20 times the reference range 24 hours after a marathon.⁵ Furthermore, individuals with no previous physical conditioning can reach materially higher CK levels than age-/sex-matched athletes after similar levels of physical exertion.⁶

Clinically, it is concerning that despite similar dosing, the 2 cases presented here had such disparate isotretinoin experiences. The classic triad of rhabdomyolysis (fatigue, myalgia, and myoglobinuria) occurs in less than 10% of the cases, whereas 50% of the cases may be asymptomatic.⁴ Neither patient 1 nor patient 2 reported new or worsening physical symptoms, despite matching the laboratory definition of "rhabdomyolysis."

Patient 1's perpetually elevated CK levels may reflect his continual, strenuous activity, given the baseline elevation off exogenous testosterone.⁶ Furthermore, the 2 times patient 1's CK level approached the reference range, he had independently noted decreased physical activity. Patient 1 also had additional, independent, classic risk factors for elevated serum CK levels—testosterone and intramuscular injections.⁷ These findings suggest that patient 1's "normal" CK levels may already be outside the normal reference range and highlights

the importance of baseline evaluation in a patient with multiple pre-existing risk factors and that not all elevated serum CK levels are clinically significant.

Conversely, the majority of patient 2's CK levels were similar to his baseline/reference range. Patient 2 reported significantly more strenuous activity coinciding with the evaluations that approached a (potentially) clinically significant level of 5000 IU/L. Patient 2's case highlights a nuance behind CK assessment timing. Even if a patient has a normal CK level at baseline and at the maximum therapeutic dose, there is still potential to develop aberrant results during therapy if additional novel risk factors are introduced. For these scenarios, there may be benefit for an additional CK evaluation timed around the supranormal physical activity. Although this finding may favor exercise-induced CK level elevations, we were unable to evaluate patient 2's CK level with exercise alone to rule out interactions with isotretinoin.

There also appears to be a yet poorly understood synergism between isotretinoin and exercise. Chen and Rofsky⁸ documented CK level elevations in 4 patients in whom the levels normalized with the discontinuation of either only isotretinoin or only exercise. The investigators also reported 1 patient who had normal CK levels while exercising alone or while on isotretinoin alone; however, the patient showed marked elevated serum CK levels while

exercising when they were on isotretinoin therapy.⁸ This may suggest not only a synergy but also an inherent predisposition to developing elevated serum CK levels in certain individuals.

The gamma-glutamyl transferase levels were within the reference range during all evaluations for these individuals (and in all patients in our practice). This supports the findings by Webster et al¹ that elevations in aspartate aminotransferase/alanine aminotransferase levels most likely originate from muscle damage (not liver pathology), suggesting that CK may be a more accurate marker for muscle damage, and gamma-glutamyl transferase may differentiate liver pathology from muscle tissue damage with isotretinoin.¹

Further studies are needed to better determine potential interactions between risk factors (both innate and modifiable) for elevated serum CK and isotretinoin levels. Additional prospective studies can improve clinical management by determining ideal timing for CK (re-)evaluation. Studies suggest that traditional isotretinoin laboratory monitoring at 2 months/maximum therapeutic dose may be sufficient.⁹ However, as noted in our patients, CK elevations may occur sporadically and recur with supranormal activity levels. Although there are currently no official guidelines, dermatologists may also consider additional CK evaluation at approximately 96 hours (approximately 4 CK half-lives) after supranormal activity.⁶

Until further studies determine the correlation between isotretinoin and CK, dermatologists should continue to inquire about physical activity and additional potential predisposing historic risk factors for elevated serum CK levels (eg, medical conditions such as genetic myopathies or poorly-controlled endocrinopathies, anabolic steroid/testosterone use, intramuscular injections, and medications such as antiepileptics).¹⁰ Although formal guidelines do not yet exist, baseline CK prior to isotretinoin therapy coupled with targeted regular and/or

as-needed CK re-evaluations may benefit patients with more common additional potential risk factors (eg, young men engaged in regular, rigorous physical activity) for elevated serum CK and rhabdomyolysis.

Conflicts of interest

Dr Baldwin has served as advisor, investigator, and on the speakers' bureaus for Almiral, Cassiopea, Foamix, Galderma, Ortho Dermatologics, Sol Gel, and Sun Pharma. Dr Marson does not have any relevant conflicts of interest or disclosures.

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