

## CLINICAL REPORT

# Clinical Significance of Markedly Elevated Serum Creatine Kinase Levels in Patients with Acne on Isotretinoin

MARINA LANDAU<sup>1</sup>, RONIT MESTERMAN<sup>2</sup>, JOSEPH OPHIR<sup>1</sup>, BARUKH MEVORAH<sup>3</sup>, JOSEPH ALCALAY<sup>4</sup>, AVIKAM HAREL<sup>5</sup> and YORAM NEVO<sup>2</sup>

<sup>1</sup>Dermatology Unit, Edith Wolfson Medical Center, Holon, <sup>2</sup>Pediatric Neurology Unit, <sup>3</sup>Department of Dermatology, <sup>5</sup>Pediatric Dermatology Service, Tel Aviv Sourasky Medical Center, <sup>4</sup>Maccabi Health Services, Tel Aviv, Israel

**Muscle-related complaints and high creatine kinase (CK) blood levels have been reported in 16–51% of patients with acne treated with isotretinoin. It has been suggested that this retinoid and exercise have a synergistic effect on muscle. The presence of marked hyperCKemia during the treatment raises concern about rhabdomyolysis. The objective of this report was to evaluate the incidence, course and clinical significance of severe hyperCKemia in isotretinoin therapy for acne. Out of 442 patients on isotretinoin, we reviewed 7 patients (1.58%) with CK values above 5,000 IU/l. Only two of them had myalgia. Physical activity or intramuscular injection prior to blood testing was reported in 6 patients. CK values returned to normal within 2 weeks and all subjects except 2, completed treatment. In conclusion, marked hyperCKemia with or without muscle-related complaints in isotretinoin-treated patients with acne is a benign phenomenon. Key words: retinoids; rhabdomyolysis; muscle enzymes.**

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Marina Landau, Dermatology Unit, Edith Wolfson Medical Center, Holon, Israel. E-mail: landau@post.tau.ac.il

Isotretinoin is a mainstay therapy for severe and nodulocystic acne. The estimated number of patients treated so far with this drug world-wide is 11 million (Hoffman-La Roche Registry). Despite the fact that the treatment period is usually accompanied by bothersome mucocutaneous side effects, severe systemic toxicity, except for teratogenicity, is rarely associated with this drug. Myalgia and muscle stiffness have been reported in 16–51% of patients treated with isotretinoin (1, 2), while elevated serum creatine kinase (CK) levels have been found in up to 41% (2). Furthermore, it has been suggested that exercise in patients receiving isotretinoin may trigger increased serum CK levels (3). If so, this would imply special caution during the treatment period, since acne affects the age group frequently exposed to vigorous physical activity. Since increased levels of CK may indicate muscular damage, it would seem that patients under isotretinoin with higher levels of CK may be at increased risk of developing rhabdomyolysis. Recently, a 16-year-old boy under isotretinoin for severe acne was admitted to our paediatric ward for observation because of unusually high blood CK values (14,645 IU/l). This prompted us to review CK levels in patients treated for acne at the Central Israeli Defense Force Dermatological clinic. The purpose of the present report is to evaluate the

incidence, course and clinical significance of markedly elevated serum CK levels in acne patients treated with isotretinoin.

## PATIENTS AND METHODS

Between November 1999 and November 2000, 442 patients were treated with isotretinoin for severe or cystic acne at our department. Their ages ranged between 18 and 26 years. Initial dosage of isotretinoin was 20–60 mg/day. Mucocutaneous side effects permitting, daily isotretinoin dosage was gradually increased to 0.75–1.0 mg·kg<sup>-1</sup>·day<sup>-1</sup>.

Prior to treatment, blood tests, including liver function tests, lipid profile and CK levels, were conducted in all the patients and found to be normal. During treatment, these tests were repeated monthly unless found abnormal and then repeated as needed.

We retrieved files of patients who developed abnormal CK levels at least on one occasion while on isotretinoin (normal range of CK in our laboratory is 15–167 IU/l). For our study, we selected patients with grossly elevated CK levels (above 5,000 IU/l). It is assumed that high CK levels and muscle pathology are linked. We therefore chose a particularly high level of CK value as a cut-off point for the present study. Clinical files and laboratory data of these patients were analysed.

## RESULTS

Elevated CK levels recorded at least once during the treatment period were found in 165 patients (37.3%). Values above 5,000 IU/l were found in 7 patients (1.58%), aged 19–21 years. Six of them were men. Clinical data on these patients, in addition to the hospitalized boy, are summarized in Table I. One individual suffered from Familial Mediterranean Fever (FMF) and was treated with colchicine. Two others were using beclomethasone dipropionate inhaler for allergic rhinitis. The remaining subjects were in good general health. Prior to isotretinoin, these acne patients were treated with various topical and systemic medications, including antibiotics or hormones, without success. Patient 1 had developed serum sickness-like reaction while on minocycline. Patient 4 flared 2 years after a successful 5 months' course of isotretinoin; at that time the maximal daily dose of the drug was 60 mg, and his laboratory results remained normal.

Maximal serum CK values recorded for each patient ranged between 5,320 and 14,645 IU/l. In all but one, the significant increases in CK levels were recorded during the first 6 weeks of treatment, or during the first weeks of maximal isotretinoin dosage. Two patients complained of mild muscle cramps. The others were completely asymptomatic and rejected any muscular discomfort when specifically questioned about it.

Information on strenuous physical activity prior to the abnormal blood tests was obtained in five patients, while

Table I. Summary of cases with markedly increased creatine kinase (CK) blood levels

Patient (No./Sex/Age)	General health	Physical activity	Maximal CK level (IU)	Treatment duration (weeks), dosage $\text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ at maximal CK	Muscular symptomatology
1. M/19	Normal	Jogging, weights	10,520	6w/0.8	None
2. M/21	Allergic rhinitis	None <sup>a</sup>	5,320	4w/0.5	None
3. M/21	Allergic rhinitis	Jogging, weights	12,100	12w/0.6	None
4. M/21	Normal	None	7,420	6w/1.0 <sup>b</sup>	None
5. F/19	Normal	Jogging	5,870	3w/1.0 <sup>c</sup>	Cramps
6. M/20	FMF	None	5,370	5 w/0.9	None
7. M/21	Normal	Jogging, weights	7,600	6w/0.6	None
8. M/16	Normal	Jogging	14,645	4w/0.55	Cramps

<sup>a</sup>Intramuscular steroid injection for allergic rhinitis.

<sup>b</sup>After 3 weeks of  $0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , the dosage was increased to  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  3 weeks prior to maximum CK elevation.

<sup>c</sup>After 12 weeks of  $0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , the dosage was increased to  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  3 weeks prior to maximum CK elevation. FMF = Familial Mediterranean Fever.

another reported on intramuscular steroid injection for relief of an allergic rhinitis attack.

Isotretinoin was discontinued in two subjects, and they were reluctant to resume therapy. In another three the drug was stopped until normalization of blood tests, after which isotretinoin was reintroduced. In two patients the medication was not stopped but its dosage reduced in spite of high CK levels. In another subject, daily dosage was not changed. All patients were instructed to avoid vigorous physical activity during the rest of the treatment course. In all of them, CK returned to normal within a maximum 2 weeks of the high levels being detected, and all except two completed the full isotretinoin course (accumulative dosage 90–116  $\text{mg} \cdot \text{kg}^{-1}$ ). Fig. 1 shows CK levels in patient 1 as an example of the characteristic findings in our patients.

## DISCUSSION

In the current series, we present 8 patients who developed serum CK levels above 5,000 IU/l while on isotretinoin for severe or cystic acne. In our experience, such CK values are not a rare finding, comprising 1.58% of patients (we do not include the inpatients in this statistics). This could be attributed to the fact that our patient population is different from that in a civilian general dermatology clinic, since soldiers are exposed to a higher baseline level of physical activity. In addition, 5 patients were having off-service strenuous physical activity while under treatment before giving blood for testing, while patient 3 received an intramuscular steroid injection prior to blood sampling (Table I). Only two of these patients had muscle symptoms. Fast normalization of CK values was observed on discontinuation of strenuous activity and/or the drug, as published in the literature (3–8).

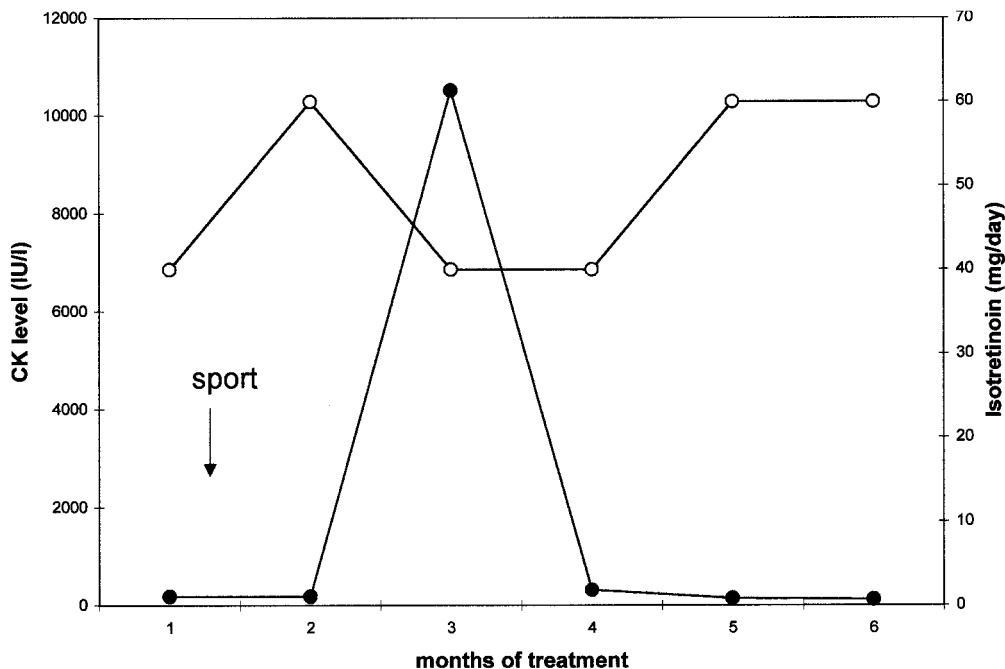


Fig. 1. Normal creatine kinase (CK) level was found in patient 1 after one month of treatment with isotretinoin  $40 \text{ mg} \cdot \text{day}^{-1}$ . During second month of treatment, while on isotretinoin  $60 \text{ mg} \cdot \text{day}^{-1}$ , the patient performed strenuous physical activity and CK levels increased to 10,520 IU/l. At this point, isotretinoin dosage was decreased to  $40 \text{ mg} \cdot \text{day}^{-1}$ , and the patient was advised to avoid extreme muscular effort. CK level was normalized and did not change with subsequent increase in isotretinoin dosage. (● = plasma CK level (IU/l); ○ = daily isotretinoin dose (mg)).

After the introduction of isotretinoin into wide clinical use in the early 1980s, reports started to appear regarding hyperCKemia in patients on this drug. The incidence of this phenomenon may reach 41% (2). In the majority of cases the abnormal CK levels were increased 2–4 times the normal values (2, 4, 7, 9–14). Usually they were found incidentally on routine blood tests because most patients were free of muscle symptoms (6–8, 10, 11, 13, 14). Since the 1980s, almost no publications have appeared dealing with hyperCKemia and/or muscle abnormalities in isotretinoin-treated patients. This could be explained by a tendency to reduce the frequency and extensiveness of laboratory follow-up in isotretinoin therapy for acne.

Notably, elevated CK levels may reflect muscle membrane injury, which causes myoglobin release into the blood stream with its load on the kidney. In these severe circumstances, kidney function can fail. This is the most serious consequence of rhabdomyolysis, while the muscular tissue itself is capable of complete regeneration.

It is not clear whether CK elevation in isotretinoin therapy is associated with myoglobinuria. The latter was reported in only one patient in whom non-specified intramuscular injections were given 4 days after isotretinoin had been discontinued (9). Since CK levels did not exceed 14,645 IU, and fast normalization of hyperCKemia was observed in all our patients, we did not test for myoglobinuria. Without causing myoglobinuria, it seems that injury induced by intramuscular injection may cause unusually prolonged hyperCKemia in isotretinoin-treated subjects (Patient 2, Table I), compared to its effect in a different patient population (15).

In a review of the literature we could find only 5 patients who had developed CK levels above 5,000 IU (3, 8, 9). In all cases but one, hyperCKemia was associated with recent strenuous physical activity. In four of them, CK levels were normalized following either withdrawal of the drug or discontinuation of both treatment and exercise. In one subject who continued to exercise, mild CK elevation persisted after isotretinoin had been stopped. In one of these five patients, CK elevation was accompanied by severe muscular cramps and debilitating weakness (3). These symptoms disappeared and CK levels returned to normal within one week of discontinuation of the drug. In the other three cases we could not find any reference to clinical signs or symptoms (9), while in the fifth case hyperCKemia was completely asymptomatic (8).

On the other hand, there are publications on acne patients under isotretinoin complaining of severe and debilitating muscular symptoms in whom CK levels were normal (4, 5). In such patients, myopathy or a disorder of myoneural junction was suggested by muscle biopsy. In spite of this, the clinical course in these patients was benign, with spontaneous and full recovery 1–2 months after interruption of therapy.

Queries regarding the clinical significance of hyperCKemia in isotretinoin-treated acne patients were already made as early as 1985 (9). No satisfactory answers have been given so far. It is evident that isotretinoin therapy may be associated with elevated CK levels, whether or not accompanied by muscular pain or weakness. Furthermore, elevated CK levels do not

necessarily go hand in hand with clinical symptoms of myopathy. These observations are true not only for exercising patients, but also for those who are inactive.

CK values may return to normal when vigorous physical activity is stopped, even if isotretinoin is continued at the same or lower dosage. Conversely, a similar effect may be observed by stopping the drug while continuing exercising, although rarely increased CK levels may persist. It would seem, therefore, that isotretinoin and vigorous exercise may have a synergistic effect with increased likelihood of significant hyperCKemia.

Based on our experience and review of the literature, we conclude that hyperCKemia, with or without muscle-related complaints in isotretinoin-treated acne patients, is a benign phenomenon. We therefore feel that the yield of routine blood testing for CK levels is questionable. However, drug dosage may be reduced or temporarily stopped in patients who develop muscular pain, weakness or hyperCKemia until disappearance of these findings. Exercising patients who develop muscular symptoms should be advised to avoid strenuous physical activity. So far, no scientifically based reason exists for avoiding renewal of the drug in such patients. Prospective studies are needed to clarify the mechanism of the isotretinoin effect on muscle, including its synergism with physical activity.

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