

Elevated Serum Creatine Kinase Levels in Acne Vulgaris Patients Treated with Isotretinoin: A Retrospective Single-Center Study

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Abstract

Background: Oral isotretinoin is a highly effective and widely used therapeutic agent for acne; however, it requires close follow-up due to its potential to produce various side effects. Slightly increased levels of serum creatine kinase (CK) that are either associated or not associated with musculoskeletal symptoms have been commonly reported and are typically considered innocuous. **Objectives:** The aims of the study are to investigate the frequency of our acne vulgaris patients with elevated serum CK levels during isotretinoin treatment, to analyze their course, and to determine the potential risk factors. **Materials and Methods:** Data of the patients in an outpatient clinic who were treated with isotretinoin due to acne vulgaris were retrospectively analyzed. **Results:** A total of 154 patients with at least 3 months of follow-up were included in the study. Elevated serum CK levels were found in 31 patients, and two patients had elevated levels over 1000 IU/l. While male sex was found to be a significant risk factor of CK elevation ($P < 0.001$), the mean age during the therapy was not found to be significantly different between the two groups. Of the patients with elevated serum CK levels, 16.2% were symptomatic and 29% had a recent history of physical exercise. **Conclusions:** Although mild elevation of serum CK has a benign course and is not uncommon among acne vulgaris patients who are treated with isotretinoin, remarkable elevations and symptomatic cases are relatively rare. Even CK elevations of more than 1000 IU/l may occur without symptomatic rhabdomyolysis if they are triggered by strenuous physical exercise or other causes during isotretinoin treatment. Further investigation of whether an agreed upon and not currently recommended upper limit for CK level that is tolerable can ensure safer follow-up during isotretinoin treatment is needed.

Keywords: Acne vulgaris, creatine kinase, muscle, rhabdomyolysis, side effect

INTRODUCTION

Isotretinoin (13-cis-retinoic acid) is a synthetic vitamin A analogue that has seen wide global use for almost 40 years for the treatment of moderate-severe acne and acne that is resistant to topical or systemic treatments.^[1] It is generally considered an efficacious and safe treatment with minor side effects and, very rarely, severe ones.^[2,3] One of isotretinoin's minor side effects includes the elevation of creatine kinase (CK) with or without musculoskeletal symptoms.^[3] CK is a specific marker of muscle damage, and its mild elevations during isotretinoin treatment are not uncommon nonetheless, significant CK elevations of more than five-fold

the upper limit of normal (an indicator of rhabdomyolysis) have occasionally been reported.^[4,5] The clinical importance of CK elevation has been a matter of debate due to its inconsistent relationship with physical exercise history and musculoskeletal symptoms. As such, the risk factors associated with it remain controversial.^[5] The current study aims to investigate the frequency of CK elevations among patients who were treated with oral isotretinoin due to acne vulgaris, analyse their course and determine the potential risk factors.

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MATERIALS AND METHODS

This retrospective cross-sectional study was conducted on patients who had been diagnosed with acne vulgaris and treated with isotretinoin in a secondary hospital between July 2019 and December 2020. Laboratory tests were requested at the beginning of treatment and after the first, third and fifth months for all patients. If necessary, tests were also occasionally requested in other months (i.e. in cases of CK elevation, other laboratory abnormalities in previous visits or when patients had recent histories of physical exercise). The test orders during treatment were as follows: complete blood count, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), CK, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, total cholesterol, very low-density lipoproteins, low-density lipoproteins, high-density lipoproteins, and triglycerides. The doses of isotretinoin were 30–70 mg/day (0.5–1 mg/kg/day) depending on the patient's weight and the course of the disease. The study included patients who were treated with isotretinoin for three to six months. Data including the patients' ages, sex, daily doses of isotretinoin and laboratory results were recorded and analysed. Other data from the patients with elevated serum CK levels (normal, <190 IU/l), such as musculoskeletal symptoms at the time of CK elevation and potentially associated risk factors, including recently performed physical exercises, injections, infections, fever or the presence of other drugs that had already been recorded into the system, were analysed retrospectively. The data were stored and analysed for statistical analysis with SPSS-22 software (SPSS Inc., Chicago, IL, USA). Continuous data were presented as means \pm standard deviation, median, and range. The student's *t*-test was used to compare the mean of normal variables and the Chi-square test was used to compare categorical variables. Values of $P < 0.05$ were considered statistically significant.

RESULTS

A total of 154 acne vulgaris patients, consisting of 59 males (38.3%) and 95 females (61.7%), were treated with oral isotretinoin during the study period. Their mean age at the initial visit was 21.2 ± 5.3 years (range, 14–36 years; median, 19 years) with no statistically significant difference between the men (20.9 ± 4.9 years) and the women (21.4 ± 5.5 years). The general characteristics of the patients are summarized in Table 1. Elevated serum CK levels were observed among 31 (20.1%) patients in either one visit or more during the follow-up period. Serum CK elevations were occurred more frequently among men ($n = 27$; 87.1%) compared in women ($n = 4$; 12.9%), and the difference was statistically significant (Chi-square, odds ratio: 19.23; confidence interval: 5.88–6.25; $P < 0.001$). However, the mean age was not significantly different between patients with (20.9 ± 3.9 years) and without (21.2 ± 5.6 years) elevated CK levels. CK elevation was most frequently seen after the 1st month of the therapy ($n = 14$), followed by the 2nd ($n = 6$) and 3rd months ($n = 6$) [Table 1]. The most common daily dose of isotretinoin was 40 mg/day ($n = 16$), followed

Table 1: Demographic and clinical characteristics of the patients in the current study

Characteristics	<i>n</i> (%)
Number of patients	154
Male	59 (38.3)
Female	95 (61.7)
Mean age at the initial visit (years)	21.2 \pm 5.3
Male	20.9 \pm 4.9
Female	21.4 \pm 5.5
CK elevations	31 (20.1)
Male	27
Female	4
Physical exercise history	9 (29)
Musculoskeletal symptoms	5 (16.1)
Male	4
Female	1
Therapy duration prior to CK elevation (months)*	
1	14 (45.2)
2	6 (19.3)
3	6 (19.3)
4	2 (6.5)
5	3 (9.7)
Mean daily dosage of isotretinoin during CK elevation (mg/day)*	
30	3 (9.7)
40	16 (51.6)
50	6 (19.3)
60	4 (12.9)
70	2 (6.5)

*The first elevation of CK in the patients with recurrent elevations. CK: Creatinine kinase

by 50 mg/day ($n = 6$) at the time of the elevation [Table 1]. Only five patients (16.1%) with elevated serum CK levels, including 1 female patient, complained of myalgia [Table 2]. The classical combination of symptoms of rhabdomyolysis including muscle pain, weakness, and pigmenturia was not seen in any of the patients. While none of the female patients had a recent history of physical exercise, nine male patients (29%) reported recent physical exercise [Table 2]. One of the male patients was a professional football player, and another was an active-duty soldier. One female patient who had a respiratory tract infection presented with a high fever before her visit.

Remarkably elevated serum CK levels over 1000 IU/l were observed in two male patients (2400 IU/l; 1614 IU/l). Their kidney functions were normal, with BUN and creatinine levels within normal limits, and they did not present with symptoms. One of the patients had recently received multiple intramuscular injections due to longstanding neck pain, and the other patient had performed strenuous, non-sports-related physical activity. The treatment was discontinued in three patients including two with CK elevations over 1000 IU/l and one with elevated levels of CK, ALT, AST, and GGT that were accompanied by myalgia. The latter patient had no other accompanying symptoms, and his other laboratory tests (i.e., lactate dehydrogenase, BUN and creatinine) were

Table 2: Distribution of the patients with creatine kinase elevation, patients with musculoskeletal symptoms and patients with a recent history of physical exercise according to the range of serum creatine kinase

Range of CK level* (IU/l)	Patients with CK elevation (n)	Patients with musculoskeletal symptoms** (n)	Patients with a recent history of physical activity** (n)
190-300	13	0	1
300-500	11	3	2
500-1000	5	2	5
>1000	2	0	1
>5000	0	-	-

*According to the highest level of CK in patients with recurrent elevations. **Among patients with CK elevations. CK: Creatinine kinase

within normal limits. After one month, isotretinoin was started again at a lower dose; however, control tests revealed similar results during this second attempt. In the two patients with remarkable CK elevations, the CK levels returned to normal in one month's time. Nonetheless, the patients were unwilling to continue treatment. In the other patients, isotretinoin was not discontinued, and its doses remained unchanged. However, patients performing exercises were asked to stop or reduce these activities. Although serum CK levels did return to normal limits in seven patients during treatment, they showed a stable course. In addition, these patients' serum CK levels never crossed the three-fold upper limit of normal. Recurrent elevated levels of CK were only seen among men.

DISCUSSION

Despite the considerable number of studies and case reports, the correlation between CK elevations during isotretinoin treatment and exercise and musculoskeletal symptoms has yet to be clearly demonstrated.^[6-12] Although CK elevations were not rare in a series of acne vulgaris patients in whom serum CK levels were periodically measured, significant elevations or symptomatic cases appear to be uncommon.^[6,7] Among our patients, the frequency of serum CK elevations (20.1%) was generally consistent with the literature, which has indicated CK elevation rates of 5%–44%.^[6-11] Only 6.4% of our patients exhibited a serum CK level over 1000 IU/l, and none of them presented with a level above 5000 IU/l. In a large study of 442 acne vulgaris patients, CK levels over 5000 IU/l were detected in 1.58% of the patients (the normal range in this study was 15–167 IU/l).^[6] A striking finding in the present series was that 87.1% of the patients with CK elevations were men, a rate which has ranged from 70%–87.5% in previous studies.^[6-11] Male gender was the only significant risk factor for CK elevation in the current study. In addition, due to the narrow age range of the disease itself and the preference for isotretinoin treatment, it was unsurprising that the mean age did not significantly differ between patients with and without CK elevations. Due to the retrospective design of the study, other variables could not be compared between the two groups.

According to previous reports and the results of the current study, isotretinoin-associated elevation of serum CK levels

without accompanying myalgia or other musculoskeletal symptoms is not surprising.^[6,8] Although we could not compare the symptoms between patients with and without CK elevations, only 16.1% of the patients with elevated CK levels had musculoskeletal symptoms. This rate has previously been reported to range from 0%–20%.^[6-11] Moreover, in the present series, there were no musculoskeletal symptoms in either of the two patients with significantly elevated CK levels over 1000 IU/l. While studies have suggested that isotretinoin and physical exercise have a synergistic effect on muscle, less than one-third of the patients with CK elevations from the current study were performing physical exercise.^[5] The limits of exercise intensity and duration that result in the elevation of serum CK levels remain unknown.^[6] Although physical exercises combined with isotretinoin treatment may increase serum CK levels, elevated CK levels in patients who do not exercise indicate the potential presence of other factors and suggest that exercise may not be the predominant cause of CK elevation during isotretinoin treatment.

Concerns about elevated CK levels during isotretinoin treatment have primarily focused on an acute and occasionally fatal complication called rhabdomyolysis, a complex medical condition characterized by the release of the components of skeletal muscle to the plasma following its destruction.^[4] There have been several case reports of severe rhabdomyolysis during isotretinoin treatment,^[13-18] one of which resulted in a death.^[17] Elevated serum CK, particularly with levels greater than the five-fold the upper limit of normal, is accepted as a major indicator for the diagnosis of rhabdomyolysis.^[4] Nevertheless, normal levels of serum CK can vary considerably depending on several factors, including gender and physical activity.^[4,19] Although nearly half of rhabdomyolysis cases are expected to lack classical symptoms, they may still lead to rapid severe damage to the body, most commonly, acute renal failure.^[4,19] Therefore, as soon as the diagnosis of rhabdomyolysis is suspected, a prompt approach that is primarily based on rehydration is essential.^[4] Because the clinical significance of slightly elevated serum CK levels during isotretinoin treatment as marker of rhabdomyolysis remains controversial, regular monitoring of CK has previously been recommended only for male athletes and patients who have abnormal levels of CK at the beginning of treatment.^[20,21]

This study was limited by its retrospective design and the absence of testing for the detection of myoglobin in the sera and urine of patients with CK elevation. Although the presence of myoglobin in urine is considered pathognomonic for the diagnosis of rhabdomyolysis, it is neither necessarily needed for the diagnosis nor always visible.^[22]

CONCLUSIONS

Although mild elevation of serum CK has typically a benign course and is not uncommon among acne vulgaris patients who are treated with isotretinoin, remarkable elevations (more than five-fold upper limit of normal) and symptomatic cases in this group are relatively rare. Although not all remarkably elevated serum CK levels reflect a symptomatic rhabdomyolysis in the presence of strenuous physical exercise, injections or other triggers during isotretinoin treatment, they should still be considered alarming. Thus, close follow-up, temporary discontinuation of treatment and/or exercise and vigilant monitoring of the signs and symptoms of rhabdomyolysis seem to be essential. Further investigation of whether an agreed upon and not currently recommended upper limit for CK level that is tolerable can ensure safer follow-up during isotretinoin treatment is needed.

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Conflicts of interest

There are no conflicts of interest.

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