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ORIGINAL ARTICLE

Should Serum Levels of Creatine kinase be Evaluated in Patients with Acne Vulgaris Treated with Systemic Isotretinoin?

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Abstract: *The laboratory tests that should be performed and their frequency during isotretinoin treatment are controversial. We wanted to investigate muscle and joint pain and laboratory tests in acne patients who received isotretinoin. Between April 2019 and February 2023, serum CK, AST, ALT, and GGT levels were retrospectively evaluated in acne patients before and three months after systemic isotretinoin treatment. This study included 410 patients. The median serum AST, ALT, and GGT levels significantly increased, whereas serum CK levels were similar in all patients three months after treatment. 23 (5.6%) patients revealed muscle or joint pain after treatment. No significant difference was detected in patients with or without pain in the median serum CK, AST, ALT, and GGT levels after treatment. Isotretinoin treatment at a dose of 10 mg/day was more common in patients with pain than in those without pain, whereas none of the patients who received isotretinoin 40 mg/day developed muscle or joint pain. We suggest that routine evaluation of serum CK levels is unnecessary in acne patients treated with isotretinoin. However, muscle and joint pain may develop even at doses as low as 10 mg/day. Furthermore, monitoring AST, ALT, and GGT levels may be beneficial in acne patients treated with isotretinoin.*

Keywords: *acne vulgaris; creatine kinase; isotretinoin; joint pain; muscle pain; treatment*

INTRODUCTION

Acne vulgaris is a common and chronic inflammatory skin disease that usually occurs during adolescence. Acne vulgaris may also affect adults or even initiate in adulthood. The etiopathogenesis of acne includes seborrhea, follicular hyperkeratinization, Cutibacterium acnes, and inflammation. Lesions mainly appear on the face and may lead to scarring and pigmentation changes. Therefore, acne has been associated with psychological complications such as depression and anxiety. Prompt and appropriate treatment is crucial both to improve lesions and to prevent the development of hyperpigmentation and scars [1].

Oral isotretinoin is a systemic retinoid used to treat patients with moderate to severe acne. Oral isotretinoin inhibits the function of sebaceous glands and shows anti-inflammatory effects [2]. Cheilitis is the most frequent dose-dependent side effect of isotretinoin, observed in approximately 90% of patients [3]. However, various side effects such as xerosis, pruritus, hair loss and photosensitivity have been reported after systemic isotretinoin treatment. In addition, musculoskeletal system disorders such as tendinitis and muscle and joint pain can also develop [2,3].

It has been suggested that about 50% of patients under isotretinoin treatment might develop increased serum creatine kinase (CK) levels, which indicate muscle damage [4]. Slight elevations in creatine kinase are usually reversible, while significant elevations may show rhabdomyolysis. Half of the patients with rhabdomyolysis are asymptomatic, and a minority of patients may develop fatigue and myalgia. Therefore, it has been proposed that it might be useful to evaluate serum CK levels before the initiation of isotretinoin treatment and regularly or when necessary during treatment [5].

In addition, patients with acne are usually monitored monthly, performing laboratory tests for potential side effects such as deterioration of the lipid profile and liver enzymes or complete blood count abnormalities such as leukopenia [6]. However, no consensus exists on the tests that should be performed in

patients treated with isotretinoin. For instance, routine evaluation of complete blood count has not been recommended by Hansen et al. [6,7]. Moreover, it is controversial whether frequent laboratory testing is necessary during systemic isotretinoin treatment. It has been reported that laboratory tests might be checked before and two months after treatment, and in case the results are within normal limits, there is no need for further evaluation [6,8].

Herein, we investigated muscle and joint pain and serum levels of CK, aspartate aminotransferase (AST), alanine amino-transferase (ALT), and gamma-glutamyl transferase (GGT) in patients with acne vulgaris treated with systemic isotretinoin.

MATERIALS AND METHODS

Gazi University Ethics Committee approval was obtained before this study (approval number: 2023-210). Between April 2019 and February 2023, medical records of patients with acne vulgaris treated with systemic isotretinoin were reviewed retrospectively. Age, sex, past medical history, chronic medication use, duration of acne, the age of onset of acne, and the severity of acne were evaluated. The severity of acne was classified as papulopustular and nodular acne. Isotretinoin dose, muscle or joint pain developed after isotretinoin treatment, localization of the pain, and time to onset of pain after treatment were also noted. In addition, serum levels of CK, AST, ALT, and GGT before and three months after the initiation of systemic isotretinoin treatment were evaluated by the biochemistry panel. The reference range was (46-171 U/L) for CK, (<34 U/L) for AST, (<49 U/L) for ALT and (<73 U/L) for GGT. Exclusion criteria were having liver and kidney diseases, using medications that may affect liver or muscle enzymes and intense exercise.

Statistical analysis was performed using SPSS version 25.0. Quantitative variables were stated as mean ± standard deviation or median (interquartile range). Categorical variables were stated as counts and percentages. The normality of the distribution of the data was evaluated by Kolmogorov-Smirnov test. Wilcoxon signed ranks test, chi-square test, and Mann-Whitney U test were used to determine the differences between the groups. P value less than 0.05 was considered statistically significant.

RESULTS

This study included 410 patients, 324 (79%) females and 86 (21%) males. The median age of the patients was 21 (6) years (range: 14-34 years). The past medical history was unremarkable in 391 (95.4%) patients. The characteristics of the patients are stated in Table 1. None of the patients reported regular use of a medication or excessive alcohol consumption. The patients were treated with oral isotretinoin at a dose of 10 to 40 mg daily. Among females, 220 (67.9%) had papulopustular, 104 (32.1%) had nodular acne, whereas among males, 44 (51.2%) had papulopustular and 42 (48.8%) had nodular acne (p=0.005). The median acne duration was 5 (5) years, (range: 1-20 years) in patients with papulopustular acne and 5 (4) years, (range: 1-20 years) in nodular acne (p=0.174). The median age of onset of disease was 15 (4) years, in patients with both papulopustular and nodular acne (p=0.693).

Table 1: Characteristics of patients with acne vulgaris

	Patients with acne vulgaris (n = 410)
Sex, n (%)	Females: 324 (79) Males: 86 (21)
Age Median (IQR), years Range, years	 21 (6) 14-34
Medical history, n (%)	Unremarkable, 391 (95.4) Seborrheic dermatitis, 3 (0.7) Asthma, 3 (0.7) Depression, 2 (0.5) Hashimoto's thyroiditis, 2 (0.5) Insulin resistance, 2 (0.5) Thalassaemia carrier, 2 (0.5) Allergic rhinitis, 1 (0.2) Urticaria, 1 (0.2) Familial Mediterranean fever, 1 (0.2) ITP, 1 (0.2) Mitral valve insufficiency, 1 (0.2)
Acne duration Median (IQR), years Range, years	 5 (5) 1-20
Age of onset of acne Median (IQR), years Range, years	 15 (4) 10-22
Severity of acne, n (%)	Papulopustular, 264 (64.4) Nodular, 146 (35.6)

IQR: Interquartile range. ITP: Idiopathic thrombocytopenic purpura. This study included 324 females and 86 males with acne between the ages of 14 and 34 years

The median serum levels of AST (p<0.001), ALT (p=0.024), and GGT (p<0.001) statistically significantly increased in all patients three months after systemic isotretinoin treatment. However, no statistically significant difference was ob-served in serum CK levels in all patients three months after systemic isotretinoin treatment (p=0.991) (Table 2). On the other hand, high serum GGT levels were significantly more frequent after isotretinoin treatment than those before treatment (p=0.012) (Table 3).

23 (5.6%) patients revealed muscle or joint pain during systemic isotretinoin treatment, while 387 (94.4%) patients did not have any musculoskeletal complaints. Low back pain was the most common and detected in 16 (3.9%) patients. In

addition, widespread pain was observed in 5 (1.2%) patients and leg pain in 2 (0.5%) patients (Table 4).

Table 2: Laboratory test results of patients with acne vulgaris before and three months after isotretinoin treatment

	Before treatment	After treatment	P value
CK, median (IQR) U/L Range: U/L	74 (43) 30-756	75 (40) 32-717	0.991
AST, median (IQR) U/L Range: U/L	18 (5) 9-215	21 (6) 8-853	<0.001
ALT, median (IQR) U/L Range: U/L	13 (9) 3-95	14 (9) 4-250	0.024
GGT, median (IQR) U/L Range: U/L	13 (6) 5-60	16 (7) 6-110	<0.001

ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. CK: Creatine kinase. GGT: Gamma-glutamyl transferase. IQR: Interquartile range. A statistically significant increase was observed in serum levels of AST, ALT, and GGT, whereas no significant difference was observed in serum CK levels three months after systemic isotretinoin treatment.

Table 3: The frequency of high enzyme levels in patients with acne vulgaris before and three months after isotretinoin treatment

	Before treatment n (%)	After treatment n (%)	P value
CK	Normal: 379 (92.4) High: 31 (7.6)	Normal: 377 (92) High: 33 (8)	0.739
AST	Normal: 403 (98.3) High: 7 (1.7)	Normal: 398 (97.1) High: 12 (2.9)	0.251
ALT	Normal: 398 (97.1) High: 12 (2.9)	Normal: 395 (96.3) High: 15 (3.7)	0.532
GGT	Normal: 404 (98.5) High: 6 (1.5)	Normal: 393 (95.9) High: 17 (4.1)	0.012

ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. CK: Creatine kinase. GGT: Gamma-glutamyl transferase. High serum GGT levels were significantly more frequent after isotretinoin treatment

Table 4: Patients with acne vulgaris who revealed muscle or joint pain after systemic isotretinoin treatment

	Patients n (%)
Muscle or joint pain	Yes: 23 (5.6) No: 387 (94.4)
Localization of the pain	Low back: 16 (3.9) Widespread: 5 (1.2) Leg: 2 (0.5)
Time to onset of pain after treatment	Within the first month: 5 (1.2) Within the second month: 9 (2.2) Within the third month: 9 (2.2)
Isotretinoin dose	10 mg/day: 6 (26.1) 20 mg/day: 10 (43.5) 30 mg/day: 7 (30.4)

Muscle or joint pain was detected in 23 (5.6%) patients with acne vulgaris after systemic isotretinoin treatment. Among them, low back pain was the most common

When patients were evaluated according to whether muscle and joint pain developed or not, no difference was observed in age (p=0.640), gender (p=0.436), duration of acne (p=0.919), the age of onset of acne (p=0.898) and the severity of acne (p=0.660). Nevertheless, among patients who developed muscle or joint pain, 6 (26.1%) received oral isotretinoin 10 mg/day, 10 (43.5%) received 20 mg/day, and 7 (30.4%) received 30 mg/day, whereas, among patients without pain, 13 (3.4%) received oral isotretinoin 10 mg/day, 177 (45.7%) received 20 mg/day, 174 (45%) received 30 mg/day and 23 (5.9%) received 40 mg/day (p=0.001). Furthermore, no statistically significant difference was detected in patients with or without pain in the median serum levels of CK, AST, ALT and GGT before and after systemic isotretinoin treatment (Table 5).

DISCUSSION

Musculoskeletal symptoms have been reported in about 25% to 87% of patients under isotretinoin treatment [9,10]. Various adverse effects have been described in patients with acne following systemic isotretinoin treatment such as myalgia, arthralgia, gout, spondyloarthritis, low back pain, muscle weakness, muscle stiffness, and myopathy [9,11,12]. Among them, temporary arthralgia or myalgia is the most common [13]. Musculoskeletal symptoms have been described even with low-dose regimens [9]. Drozd et al. revealed that low back pain was the most frequent musculoskeletal complaint in patients with skin diseases who received isotretinoin and that symptoms initiated within the first month of the treatment in 32.9% of patients, whereas between the second and the sixth

month in 64.7% of patients. A dose reduction or temporary discontinuation of isotretinoin was recommended in patients with muscle pain or high CK levels [10].

On the contrary, De Francesco et al. stated that arthritis did not have a dose-dependent effect that it was unnecessary to discontinue the drug or reduce the dose, and that isotretinoin treatment could be continued at the same amount without complications [13]. Furthermore, Feily reported patients with acne aged 18 to 29 years who developed musculoskeletal symptoms such as back and leg pain within two months after the initiation of oral isotretinoin treatment and responded to folic acid and vitamin B12 supply [14].

Table 5: Characteristics and laboratory test results of patients with and without muscle or joint pain after systemic isotretinoin treatment

	Patients with pain	Patients without pain	P value
Sex, n (%)	Female: 20 (87) Male: 3 (13)	Female: 304 (78.6) Male: 83 (21.4)	0.436
Age, median (IQR) years Range, years	21 (4) 16-31	21 (6) 14-34	0.640
Acne duration, median (IQR) years Range, years	5 (2) 1-14	5 (5) 1-20	0.919
Age of onset of acne, median (IQR) years Range, years	15 (3) 10-22	15 (4) 10-22	0.898
Acne severity, n (%)	Papulopustular: 16 (69.6) Nodular: 7 (30.4)	Papulopustular: 248 (64.1) Nodular: 139 (35.9)	0.660
Patients received different isotretinoin doses, n (%)	10 mg/day: 6 (26.1) 20 mg/day: 10 (43.5) 30 mg/day: 7 (30.4)	10 mg/day: 13 (3.4) 20 mg/day: 177 (45.7) 30 mg/day: 174 (45) 40 mg/day: 23 (5.9)	0.001
Before treatment CK, median (IQR) U/L	70 (29)	75 (45)	0.494
n (%)	Normal: 22 (95.7) High: 1 (4.3)	Normal: 357 (92.2) High: 30 (7.8)	0.549
AST, median (IQR) U/L	17 (3)	18 (5)	0.389
n (%)	Normal: 22 (95.7) High: 1 (4.3)	Normal: 381 (98.4) High: 6 (1.6)	0.334
ALT, median (IQR) U/L	14 (7)	13 (9)	0.620
n (%)	Normal: 23 (100) High: 0	Normal: 375 (96.9) High: 12 (3.1)	0.392
GGT, median (IQR) U/L	13 (5)	13 (6)	0.299
n (%)	Normal: 23 (100) High: 0	Normal: 381 (98.4) High: 6 (1.6)	0.548
After treatment CK, median (IQR) U/L	69 (39)	75 (41)	0.147
n (%)	Normal: 22 (95.7) High: 1 (4.3)	Normal: 355 (91.7) High: 32 (8.3)	0.502
AST, median (IQR) U/L	21 (8)	21 (5)	0.649
n (%)	Normal: 23 (100) High: 0	Normal: 375 (96.9) High: 12 (3.1)	0.392
ALT, median (IQR) U/L	15 (14)	14 (9)	0.832
n (%)	Normal: 21 (91.3) High: 2 (8.7)	Normal: 374 (96.6) High: 13 (3.4)	0.203
GGT, median (IQR) U/L	16 (9)	16 (7)	0.285
n (%)	Normal: 23 (100) High: 0	Normal: 370 (95.6) High: 17 (4.4)	0.613

Muscle damage due to isotretinoin treatment is generally mild and presents with well-tolerated pain or tenderness of muscles and increased serum CK levels [15,16]. However, isotretinoin can lead to severe muscle damage such as rhabdomyolysis which may result in renal insufficiency and even mortality [5,16]. Evaluation of CK has been recommended in patients treated with oral isotretinoin, especially in those who exercise regularly [5,15]. Furthermore, during follow-up, muscle and joint pain should be questioned [16]. Besides CK, laboratory tests performed to evaluate possible side effects in patients treated with systemic isotretinoin include serum levels of AST, ALT, lipid panel, and complete blood count [17]. The American Academy of Dermatology guidelines of care for the management of acne vulgaris recommend monitoring liver function tests and serum lipids until treatment response is achieved [18]. Zane et al. stated that among patients who used isotretinoin, 11% developed increased serum levels of AST or ALT which was usually mild and reversible, and that they principally evaluated ALT levels since ALT was more specifically indicated liver damage than AST [19]. On the other hand, Webster et al. stated that although AST and ALT were used to detect liver damage, they were not specific to the liver, they were also found in muscles, whereas GGT was a liver-specific and CK was a muscle-specific enzyme. In addition, Webster et al. suggested that monitoring serum GGT level was more beneficial than AST and ALT to detect liver damage in patients treated with isotretinoin for acne and that the increase in AST originated from the muscle rather than the liver [17].

Within this study, the median serum levels of CK, AST, ALT, and GGT were increased three months after oral isotretinoin treatment, however, a statistically significant increase was detected in serum AST ($p<0.001$), ALT ($p=0.024$) and GGT ($p<0.001$) levels. The number of patients with high serum CK, AST, ALT, and GGT levels increased after treatment. Nevertheless, a statistically significant increase was observed only in the number of patients with high GGT levels ($p=0.012$).

Muscle or joint pain occurred in 23 (5.6%) patients, among them, low back pain was the most common. There was no significant difference in age, gender, acne severity, acne duration, age of onset of acne, and serum CK, AST, ALT, and GGT levels between patients who developed and did not develop pain after isotretinoin treatment. On the other hand, isotretinoin treatment dose differed significantly in patients with and without pain ($p=0.001$). Treatment with isotretinoin at a dose of 10 mg/day was more common in patients with muscle or joint pain than in those without pain, whereas none of the patients who received isotretinoin 40 mg/day developed muscle or joint pain.

CONCLUSIONS

In conclusion, since no significant change was detected in serum CK levels with isotretinoin treatment, as well as no association was observed between serum CK levels and muscle or joint pain, we suggest that routine evaluation of serum CK levels is not necessary in patients with acne vulgar-is treated with isotretinoin. Although muscle or joint pain was observed in 5.6% of patients with acne vulgaris used isotretinoin, it should be kept in mind that muscle and joint pain may develop regardless of the isotretinoin dose, even at doses as low as 10 mg daily. Our results revealed a significant increase in serum AST, ALT, and GGT levels due to isotretinoin which indicated that monitoring serum AST, ALT, and GGT levels might be beneficial in patients with acne vulgaris treated with systemic isotretinoin.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. This research received no external funding.

Authors' contribution

Conceptualization, F.T., L.F., E.A.; methodology, F.T., L.F.; software, F.T.; validation, F.T., L.F., E.A.; formal analysis, F.T.; investigation, F.T., L.F.; resources, F.T., L.F., E.A.; data curation, F.T., L.F., E.A.; writing-original draft preparation, F.T.; writing-review and editing, E.A.; visualization, F.T.; supervision, E.A.; project administration, F.T., L.F., E.A. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and local ethics committee approval for this study was obtained from Gazi University (approval number: 2023-210).

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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