

SERUM CREATINE KINASE: A MARKER FOR MUSCLE DAMAGE IN SICKLE CELL PAINFUL CRISIS

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Serum creatine kinase (CK) was first used as a diagnostic aid in progressive muscular dystrophy in 1959 by Ebashi et al.¹ It has since become an important clinical marker for muscle damage.²

The painful crisis is a major manifestation of sickle cell disease, accounting for over 80% of hospital admissions for this hemoglobinopathy.³ Classically, the pain occurs in the extremities, back, abdomen and chest.⁴ The pain in the extremities has been attributed to ischemic necrosis of bone marrow in the juxta-articular areas of the long bones.⁵

Skeletal muscle has not been implicated in the pathology of this disease or the painful crisis associated with it. In recent years, however, anecdotal but firm evidence of skeletal muscle damage in the painful crisis has evolved.^{6,7} CK levels have now been used as a marker of muscle damage in a small number of patients in sickle cell crisis, but some of them had strenuous exercise before the onset of pain, and this may have vitiated some of the results.⁸

Sickle cell disease is very common in the Eastern Province of Saudi Arabia, with the frequency of the trait ranging from 20% to 27% in some areas.⁹ This study was initiated to use CK routinely in a larger series of patients with painful crises to verify the presence of muscle damage and its frequency, and to relate it to other clinical and biological parameters.

Materials and Methods

All patients were seen in the emergency room (ER) at Qatif Central Hospital in the Eastern Province of Saudi Arabia, and had a clinical diagnosis of sickle cell crisis. Of the 207 patients, seven were excluded because they had a history of recent intramuscular injection. One patient with epileptic convulsions occurring before the sickle cell crisis was also not considered for the study. Thus, a total of 199 patients took part in the study. The other common causes of raised CK, for example, strenuous exercise, muscular

dystrophy and hypothyroidism, were excluded by history and physical examination.

Blood samples were collected in the ER by Vacutainer® (Beckton Dickinson, New Jersey, USA) tubes without any anticoagulant for the biochemical assessment, and with EDTA anticoagulant for the hematological workup. The sampling was done within 4-6 hours of the sickle cell crisis before intravenous infusions and intramuscular injections were given. The serum was separated immediately after centrifugation, stored at 4°C and analyzed within 12 hours of collection. All patients had electrophoretic confirmation of sickle cell disease.

The total CK activity was measured at 37°C on the Astra system analyzer (Beckman Instruments, Brea, California, USA), using Beckman reagents. This instrument uses the reoptimized procedure of Oliver modified by Rosalki.¹⁰ The reference range is 22-269 U/L, and the coefficient of variation in our laboratory was 3.4%, at a mean of 250 U/L. The Qatif hospital laboratory participates in an external quality control (QC) program (MEEQAS) and the internal QC is overseen by a clinical chemist (MMA).

Student's *t*-test was used to compare the means of the age of patients, and CK values of patients with normal and raised values. Differences in sex, admission rate and probability of receiving narcotic analgesia were determined by chi-square tests.

Results

Of the 199 patients studied, 31 had an elevated CK value, while 168 had levels within the reference range. The difference in the two groups was statistically significant ($P<0.001$).

Table 1 shows the age and sex distribution in the two groups. There was a male preponderance in the group with abnormal CK values ($P<0.001$, $\chi^2=10.84$, $DF=1$). No statistical difference was found in the age distribution ($P<0.05$).

The data for admissions and usage of narcotic analgesia are shown in Table 2. The nine patients without admission data and the eight patients without data on analgesia were excluded from the analysis. The patients with elevated CK had a higher probability of admission ($P<0.05$, $\chi^2=7.81$, $DF=1$).

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TABLE 1. Age and sex distribution of patients with normal and raised CK.

CK status	Number	Sex/No.	Age (range)	Mean±SD
Normal	168	M/76 F/92	4-50	19.9±9.9
Raised	31	M/24 F/7	8-45	20±9.1
Total	199	M/100 F/99	-	

TABLE 2. Admission status and narcotic analgesia in patients with normal and raised CK.

CK status	Admission			Narcotic analgesia		
	Yes	No	No data	Given	Not given	No data
Normal	45	117	6	39	123	6
Raised	13	15	3	14	15	2
Total	58	132	9	53	138	8

Discussion

The serum CK level in healthy individuals depends on age, race, lean body mass and physical activity.^{11,12} No references were available for the local population. We therefore used the range stated in the CK methodology. Thirty-one (15.5%) of the 199 patients had levels higher than this range, denoting a likely possibility of muscle damage.

Some common causes of an elevated CK in the serum are strenuous exercise,¹³ intramuscular injection,¹⁴ myocardial infarction,¹⁵ muscular dystrophy,¹⁶ polymyositis,¹⁷ hypothyroidism¹⁸ and cerebral infarction.¹⁹ These causes were excluded by history and clinical examination. Seven patients were rejected from the study because of an episode of a recent intramuscular injection by the referring physician. One patient with epilepsy was also excluded due to an episode of convulsions prior to the onset of the painful crisis. Therefore, the most likely cause of the skeletal muscle damage in our patients with increased CK was ischemia secondary to vaso-occlusion in the affected muscles.

CK is not generally used in the workup of patients with sickle cell crisis, as shown by some of the literature.^{20,21} A Medline search revealed only one study relating sickle cell crisis and skeletal muscle injury evidenced by raised CK. In that study by Hunt et al.,⁸ a disproportionate number of patients with increased CK had a history of strenuous exercise before the onset of the painful crisis. None of the patients in our sample had exercised prior to the crisis. Thus, we could determine more accurately the frequency of significant muscle damage in sickle cell painful crisis.

The patients with an elevated CK had a higher hospital admission rate ($P<0.05$) and a greater likelihood of receiving narcotic analgesia ($P<0.01$). Thus, an elevated CK due to the antecedent skeletal muscle damage may imply a more severe crisis. The male preponderance

(77.4%, $P<0.001$) among our patients with increased CK may be related to the increased muscle bulk in men.

After muscle damage, CK levels rise significantly in about 2 to 3 hours and peak within 24 hours.^{2,8} In this study, only the first blood samples taken at admission were used for CK estimation. The majority of our patients (60%) were given intramuscular injections in the ER after the blood sampling. Also, most (66%) of our patients were discharged within 24 hours after examination and treatment. Both these factors made serial sampling difficult. Thus, it is possible that some patients with significant skeletal muscle damage may have been missed if the rise in CK occurred after the blood collection. In Hunt's study,⁸ the samples at day one had a 25% false-negative rate.

Severe muscle injury in sickle cell crisis can result from non-traumatic rhabdomyolysis with subsequent renal failure.^{6,7} None of our patients had any evidence of these complications. Nonetheless, though uncommon, severe rhabdomyolysis is serious and potentially fatal. Sickle cell patients presenting in painful crisis with myoglobinuria and muscle pain should have their CK levels and urine output monitored to identify this complication early. Then, appropriate therapeutic measures will prevent progression to acute renal failure.²²

The frequency of negative bone scans in sickle cell painful crisis is between 25% and 40%.^{23,24} Our findings suggest that many patients in our series had skeletal muscles as a major site of ischemia, with or without bone involvement. The combination of serum CK and marrow scanning may, therefore, help to categorize the relative contributions of bone and muscle ischemia to the pain of sickle cell vaso-occlusive crisis.

This study has many limitations. No reference ranges were available for the local population. Using ranges of an American population would inherently have false-positive and/or false-negative results. We did not subclassify the groups into sickle cell anemia, sickle β^0 thalassemia and sickle β^+ thalassemia, but classified the entire group as one. We also did not separate the adults and children. However, our results answer our initial question, i.e., is the skeletal muscle involved in sickle cell painful crisis?

In conclusion, this study shows that in 15.5% of patients with sickle cell painful crisis there was significant muscle damage, as shown by abnormal CK levels. Such patients are predominantly male, need more narcotic analgesia and have a greater chance of being admitted to the hospital.

Additional studies in the future could categorize the details of muscle involvement and add further to our understanding of the pathogenesis of sickle cell painful crisis.

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