

## Creatine kinase activity in sickle cell disease

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**SUMMARY** Creatine kinase activity was measured in 28 patients in the steady state of sickle cell disease and ranged from 4-45 IU/l, comparable with that found in healthy adult caucasians. Creatine kinase activity was also measured in 14 patients admitted consecutively for the treatment of vaso-occlusive sickle cell crises. Creatine kinase activity remained within the normal range in eight of these 14 patients throughout their admission; none had muscle pain or a chest syndrome. In the remaining six, three with muscle pain and three with a chest syndrome, increased activity was found on one or more days. A further 17 patients with vaso-occlusive sickle cell crises, associated with muscle pain, were studied. Creatine kinase activity was significantly raised in all 17, the mean creatine kinase activity for men was 578.8 IU/l and 210.6 IU/l for women, with the highest values (up to 1790 IU/l) found in those who had exercised before admission.

Measurement of creatine kinase activity may therefore be a useful marker of muscle perturbation due to sickling.

Serum creatine kinase activity is a sensitive index of the membrane permeability of tissues containing creatine kinase. The enzyme is present in the brain, skeletal, and cardiac muscles, and so increased serum creatine kinase activity usually reflects either hypoxic or metabolic damage of these tissues. Severe muscle necrosis produces greatly increased creatine kinase activity and rhabdomyolysis, resulting in free plasma myoglobin with consequent metabolic changes, myoglobinuria, and often, renal failure.

Devereux *et al* reported one case of rhabdomyolysis and renal failure in a young man with sickle cell disease and a salmonella septicaemia.<sup>1</sup> Apart from this, there have been no other studies of creatine kinase activity in any aspect of sickle cell disease. In some sickle cell crises muscular pain is the prominent symptom and is often associated with swelling and tenderness of the muscle itself; creatine kinase activity may therefore be predicted to be increased.

The aim of this study was to assess creatine kinase activity in sickle cell disease, both in the steady state and in acute vaso-occlusive crises, especially those involving painful muscles.

### Material and methods

Serum creatine kinase activity was measured using a kinetic ultraviolet NADPH-linked assay with N-acetyl-cysteine as the activator. The recommended Scandinavian optimal procedure was followed.<sup>2</sup> Reagents were purchased from Merck Sharpe and Dome, in kit form, for use on the ERIS analyser, which operates at a single assay temperature of 37°C. The results presented are expressed in IU/l at 25°C in accordance with local practice. (This permits continued use of reference ranges applicable to previous instrumentation and reaction conditions. The correction factor is based on correlation studies between two instruments and is expressed by the equation:  $y = 0.59x - 19$ , where  $x$  represents output from the ERIS and  $y$  the converted result in IU/l at 25°C). The coefficient of variation (CV) for the method was 5%. Confidence limits of 95% may be expressed in terms of CV as  $\pm 10\%$ . The method is linear to 1000 IU/l. Samples with greater activity were appropriately diluted. The reference range at 25°C in a healthy caucasian population is 10-70 IU/l for women and 10-80 IU/l for men.<sup>2</sup>

None of the patients studied was clinically hypothyroid, acromegalic, hypokalaemic, hypocalcaemic, alcoholic, or had a personal or family history of muscular dystrophies, any of which may be associated

Table 1 Details of all patients studied

State	Sex	Number studied	Age		Genotypes			
			Mean	(Range)	SS	SC	Sbeta+	SD
Steady state	M	14	26.5	(16-34)	10	1	3	
	F	14	24	(16-32)	11	3	—	
Crises with muscular pain	M	14	20.6	(14-26)	10	2	2	
	F	3	15	(15-16)	3			
Sequential vaso-occlusive crises studied	M	9	24.8	(18-27)	8	1		
	F	5	20.6	(17-28)	3	1		1

with increased creatine kinase activity. All patient details are shown in table 1.

#### STEADY STATE

Creatine kinase activity was measured in 14 men and 14 women in the steady state attending the Central Middlesex haemoglobinopathy clinic. They had not received any intramuscular injections or blood transfusions in the preceding three months and were leading normal lives.

#### ASSESSMENT OF VASO-OCCLUSIVE CRISES

##### With muscle pain:

Creatine kinase activity was measured in any patient admitted with a vaso-occlusive sickle cell crisis between March 1984 and May 1987, who had pain in any of the large muscle groups (shoulders, thighs, or buttocks). These patients were treated in the standard way<sup>3</sup> with intramuscular pethidine "on demand" up to 100 mg hourly.

##### Consecutive admissions:

Blood samples were collected daily between 9 and 10 am for creatine kinase activity from 12 patients consecutively admitted with 14 sickle cell crises presenting over two months, regardless of the site of their pain. These patients received no intramuscular injections but received continuous subcutaneous analgesia.

#### Results

The mean creatine kinase activity in 28 patients in the steady state was 19.7 (SD 10.8), range 4-45 IU/l for both men and women. The normal range for a caucasian population is 10-80 IU/l.

The figure shows the results of creatine kinase activity in 17 patients with vaso-occlusive crises and muscle pain. All the patients originally complained of pain in one or more of their large muscle groups and had tenderness of the affected muscles. The mean creatine kinase activity found was 578.8 IU/l in men and 210.6 IU/l in women. Six patients attained a creatine kinase activity greater than that usually associated with injection—that is, greater than five to

eight times the upper limit of normal<sup>4</sup>—and details of these are shown in table 2. Notably, they were all men and included those who had exercised before admission.

Table 3 shows the details of the 14 crises in 10 patients with consecutive sickle cell crises. During crises in which patients had no muscle pain, creatine kinase activity remained within the normal range. Creatine kinase activity was increased in four crises; the highest value was over 2400 IU/l in a young man (case 4) who developed a chest syndrome after presenting with muscle pain in the shoulders and arms. He

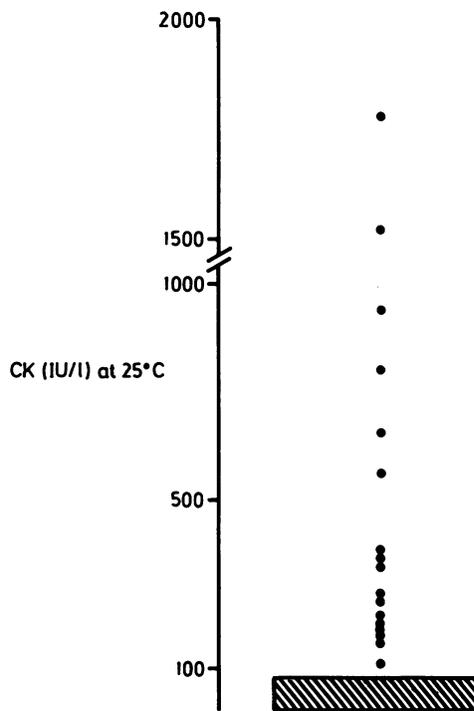


Figure Creatine kinase activity in 17 patients with vaso-occlusive crises and muscle pain.

Table 2 Patients in whom creatine kinase activity was greater than 500 IU/l

Patient	Haemoglobinopathy type	Physical activity in the day before admission	Main site of pain	Creatine kinase activity on day of stay	Length of admission (days)
23M	SC	Weight-lifting	Chest wall	935 on day 3	5
25M	SC	Played badminton 12 h before	*Thighs and buttocks	795 on day 1	4
23M	SB +	Weight-lifting	Buttocks, thighs, and calves	1790 on day 3	9
26M	SS	Nil	*Chest and back	566 on day 2	8
22M	SS	Nil	Thighs	655 on day 5	8
18M	SS	Nil	*Thighs	1510 on day 1	12

\*Swelling of muscle groups involved.

required exchange transfusion on day 3. The other two patients who had a chest syndrome with chest wall and back pain and required exchange transfusion showed a marginal increase in creatine kinase activity on the day of admission. A temporary rise in creatine kinase activity was seen in cases 1 and 2 whose main site of pain was in the thighs, and in case 3 who had pain in the thighs and abdomen. In those patients with a rise in creatine kinase activity above normal the zenith was reached on days 1 or 2.

### Discussion

This study has shown that in the steady state of sickle cell disease creatine kinase activity is within normal limits, but in some sickle cell crises, especially where muscle bulk is affected, creatine kinase activity is increased above the concentrations associated with intramuscular injections.<sup>4</sup>

Creatine kinase activity is a sensitive indicator of recent muscle membrane perturbation, rising within

two to three hours after insult. Creatine kinase comprises three separate isoenzymes in the body, but MM isoenzyme (from skeletal muscles) accounts for nearly all normal serum activity, together with a trace of MB (from cardiac muscles). We had no reason to believe that there was cardiac or cerebral disease in any of the crises studied, so we assumed that any rise in creatine kinase activity in the patients with sickle cell disease reflected increased activities of the skeletal muscle isoenzyme MM.

The amount of creatine kinase activity depends on age, sex, and race.<sup>5</sup> Activities in adolescents are higher than in adults, while the reference range for women at all ages is lower than for men, presumably due to their smaller muscle mass. Previous studies of American negro populations have shown higher mean creatine kinase activities compared with those of caucasians.<sup>5</sup> Gledhill *et al* suggested that these differences could be explained by different levels of exercise or a genetic difference in response to exercise or both.<sup>6</sup> The low activities seen in our patients of Afro-Caribbean origin in the steady state of sickle cell disease compared with the normal range of the caucasian population are thus surprising. Possibly, they may reflect a lower level of physical activity or decreased muscle bulk—for most patients with sickle cell disease have an asthenic build. A constant low level of muscle membrane perturbation due to subclinical sickling was not confirmed by any increase in creatine kinase activity. There are several non-pathological reasons for increased creatine kinase activity. Creatine kinase activities up to five to eight times the upper limit of normal may occur after intramuscular injections in normal subjects<sup>4</sup>; factors such as volume, osmolarity, and type of substance injected will affect the rise in creatine kinase activity. Aware of these factors, we measured creatine kinase activity in patients with vaso-occlusive crises receiving only subcutaneous not intramuscular injections and showed large increases in creatine kinase activity during crises in which muscles were affected.

After severe exercise healthy people can attain high creatine kinase activity over 1000 IU/l after 45 minutes of exercise,<sup>7</sup> reaching a peak up to 24 hours after exercise; creatine kinase activity may remain increased

Table 3 Serial creatine kinase activity in 14 consecutive crises

Case number age/sex/haemo- globinopathy	Creatine kinase activity (IU/l) Days of admission								
	1	2	3	4	5	6	7	8	9
<b>Patients with muscle pain:</b>									
1 27M SC	218	531	280	141					
2 27M SS	399	388	36						
3 26M SS	53	295			170				28
<b>Patients with chest syndromes:</b>									
2 27M SS	503	2435	1460	59*					
4 26M SS	139	83*	12	6	9				
5 18M SS	146	7*	55						
<b>Patients without muscle pain:</b>									
6 27M SS	28	22	49						
7 27M SS	39	13	2	14					
8 18M SS	—	34	26						
9 28F SS	33	13*	<10	<10	<10				
10 18F SS		<10	<10						
10 18F SS	83	33	2	15	<10	<10	<10		
11 17F SC	14	<10	<10						
12 23F SD	<10	17	<10	<10	<10				

\*The patient was exchange transfused for a chest and/or abdominal crisis.

for up to 72 hours. Increased creatine kinase activities in our patients during sickle cell crises showed a similar pattern. Heavy exercise, especially weight-lifting (which has been shown to cause rhabdomyolysis in normal subjects<sup>8</sup>), preceded admission of three of our patients with vaso-occlusive crises involving muscular bulk. This is consistent with Diggs's hypothesis that strenuous exercise may be a precipitating factor for some vaso-occlusive crises.<sup>9</sup> This would not be entirely unexpected; in vitro studies<sup>10,11</sup> have shown that intramuscular pH and oxygen partial pressure during exercise are low enough to cause sickle haemoglobin polymerisation, even in sickle cell trait. This may result in irreversibly sickled cells occluding arterioles in the muscles with consequent ischaemia and pain. There have been reports of rhabdomyolysis, renal failure, and disseminated intravascular coagulation causing deaths in people with sickle cell trait after strenuous exercise.<sup>12</sup>

Interestingly, all the patients with increased creatine kinase activity were men and a disproportionate number of patients with sickle cell disease or  $\beta$  thalassaemia had crises affecting muscle bulk after exercise. Perhaps this is due to their lower grade of anaemia which allows them to exercise.

In conclusion, creatine kinase activity is a sensitive indicator of muscular compromise in sickle cell crises. There is a suggestion that exercise is a precipitating factor in vaso-occlusive crises which affect muscles. Creatine kinase activity should be measured in patients in sickle cell crisis with painful or swollen muscles as the muscle damage may be sufficiently severe to cause rhabdomyolysis and subsequent renal damage. Further studies of creatine kinase activity, including the effect of isoenzymes are needed to assess

the importance of increased creatine kinase activity in vaso-occlusive crises and also to look at other indicators of rhabdomyolysis.

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