

Serum Creatine Kinase Levels and Renal Function Measures in Exertional Muscle Damage

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ABSTRACT

CLARKSON P. M., A. K. KEARNS, P. ROUZIER, R. RUBIN, and P. D. THOMPSON. Serum Creatine Kinase Levels and Renal Function Measures in Exertional Muscle Damage. *Med. Sci. Sports Exerc.*, Vol. 38, No. 4, pp. 623–627, 2006. **Purpose:** Serum creatine kinase (CK) levels are commonly used to judge the severity of muscle damage and to determine when to hospitalize patients who present with symptoms of exertional rhabdomyolysis in order to prevent renal failure. However, no CK standard exists because of the limited information available regarding exercise-induced CK elevation and renal function. This study determined the magnitude of CK elevation and the effect on renal function produced by exercise in a large subject group. **Methods:** Blood samples were obtained from 203 volunteers who performed 50 maximal eccentric contractions of the elbow flexor muscles. The samples, taken before and 4, 7, and 10 d after exercise, were analyzed for markers of muscle damage (CK, myoglobin (Mb), lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) and for measures of renal function (creatinine, blood urea nitrogen, phosphorus, potassium, osmolality, and uric acid). **Results:** All indicators of muscle damage increased significantly after exercise ($P < 0.01$). CK levels were 6420, 2100, and 311% above baseline on days 4, 7, and 10 after the exercise, respectively ($P < 0.01$), and Mb was 1137, 170, and 28% above baseline on days 4, 7, and 10 after exercise, respectively ($P < 0.01$). Of the 203 participants, 111 had CK values at 4 d postexercise $> 2,000 \text{ U}\cdot\text{L}^{-1}$ and 51 had values $> 10,000 \text{ U}\cdot\text{L}^{-1}$, levels used to diagnose myopathy (e.g., statin myositis) and rhabdomyolysis, respectively. There were no significant increases in any measure of renal function. Despite marked CK and Mb elevations in some subjects, none experienced visible myoglobinuria or required treatment for impaired renal function. **Conclusions:** Exertional muscle damage produced by eccentric exercise in healthy individuals can cause profound CK and Mb elevations without renal impairment. **Key Words:** RHABDOMYOLYSIS, MYOGLOBINEMIA, KIDNEY, CREATININE, ECCENTRIC EXERCISE

Strenuous exercise can damage skeletal muscle, a condition known as exertional rhabdomyolysis (6,20). This damage is manifested by delayed-onset pain and soreness, weakness, and increases in the circulation of such muscle proteins as creatine kinase (CK), lactate dehydrogenase (LDH), and myoglobin (Mb) (6,18). Severe exertional rhabdomyolysis can lead to renal failure because Mb released from injured muscle cells can precipitate in renal tubules. CK levels parallel the increase in Mb and are used clinically as a surrogate marker of muscle injury to determine the possibility of renal injury and

whether to administer treatment to prevent renal failure. Recently, with the widespread use of statins (cholesterol-lowering drugs) to reduce atherosclerotic risk and the ability of these agents to produce rhabdomyolysis with renal failure, CK levels have been extensively used to evaluate myopathy in statin users.

Currently, there is no commonly accepted algorithm for determining when to hospitalize and treat individuals who present with elevated CK. CK > 10 times the upper limit of normal (ULN), or approximately $2000 \text{ U}\cdot\text{L}^{-1}$, is frequently used as the criterion measurement for statin myopathy and a reason to stop the statin therapy (26), and CK $> 10,000 \text{ U}\cdot\text{L}^{-1}$ is accepted as diagnostic of rhabdomyolysis (7). Terpilowski and Criddle (25) recently published an algorithm for rhabdomyolysis where a CK $> 20,000 \text{ U}\cdot\text{L}^{-1}$ was the threshold to begin mannitol and bicarbonate infusions.

Our laboratory over the past 20 yr has used strenuous one-arm exercise to examine muscle soreness, muscle function loss, and serum CK elevation produced by exercise-induced muscle injury (12,15,16,19–22). We and others have observed that some subjects are high responders to this

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Submitted for publication April 2005.

Accepted for publication October 2005.

0195-9131/06/3804-0623/0

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DOI: 10.1249/01.mss.0000210192.49210.fc

standard exercise with postexercise blood CK values as high as 40,000 U·L⁻¹ (22), but without renal failure. However, in these studies, renal function was never examined.

The present report provides blood CK values as well as other indicators of muscle damage (Mb, LDH, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and measures of renal function (potassium, osmolality, blood urea nitrogen (BUN), creatinine, phosphorus, and uric acid) in a large group of subjects who performed strenuous one-arm exercise. Factors such as heat stress, dehydration, drugs, alcohol abuse, and crush trauma are known to produce high CK levels, rhabdomyolysis, and renal failure (9,24). However, no study to our knowledge has examined the natural history of exertional muscle damage and renal function with profoundly elevated CK values in such a large population of healthy subjects. Based on our past studies, we hypothesized that exertional rhabdomyolysis with marked CK and Mb elevation in healthy individuals is not sufficient to induce renal compromise.

METHODS

Written informed consent, as approved by the human subjects review committee at the University of Massachusetts, Amherst, MA, was obtained from subjects 18–40 yr of age to participate in a clinical trial of an experimental, topical nonsteroidal antiinflammatory (NSAID) agent. The purpose of this clinical trial was to assess the effects of one NSAID application given at approximately 12–14 h after exercise on exertional muscle soreness. However, for safety reasons (because exercise is known to result in high circulating levels of CK), the sponsor required monitoring of renal function starting at 4 d postexercise. There was no effect of the NSAID on measures of renal function, so the grouped data are presented. Volunteers were recruited from the campus and surrounding community and received compensation for their participation. Subjects were excluded if they had performed resistance exercise training within 6 months or had an occupation that required heavy lifting, abnormal baseline blood values, known muscle disease, diabetes mellitus, or hyperthyroidism. Subjects refrained from analgesic use, muscle treatments, physical activity,

and alcohol during the study. Subjects underwent a physical examination by a physician and were further screened for any medications that might affect muscle damage or renal function. Two hundred three subjects had blood samples taken and assessed for renal function (creatinine, BUN, potassium, osmolality, phosphorus, uric acid) and markers of muscle damage (CK, Mb, ALT, AST, and LDH). Subjects with baseline blood values indicating a serious underlying problem that would affect their participation in the study were excluded from the study.

Subjects performed two sets, separated by a 5-min rest, of 25 maximal eccentric (muscle lengthening) contractions of the elbow flexor muscles on a modified preacher curl bench. Each contraction was 3 s long and followed by a 12-s rest. Subjects maximally contracted their elbow flexor muscles to resist the downward motion of a lever moved by the test administrator. All subjects were instructed to drink water during the exercise visit and verbal and written reminders to maintain hydration throughout the study were given to the subjects at each visit. Subjects returned to the lab 4, 7, and 10 d postexercise for repeat blood measurements. We chose 4 d postexercise as the first time point because this is the time when peak CK response occurs (12). Those individuals with CK values $\geq 15,000$ U·L⁻¹ were contacted by phone and instructed to maintain hydration and to monitor their urine color. They were instructed to call the 24-h study phone to report whether the urine changed from clear or yellow to a brownish color. All patients were followed until their laboratory values had returned to near normal.

Data were analyzed with repeated-measures ANOVA to detect significant differences over time. Pearson product-moment correlations were calculated among the variables.

RESULTS

The average peak CK levels were 6420, 2100, and 311%, and average Mb was 1137, 170, and 28% above baseline on days 4, 7, and 10 after the exercise, respectively ($P < 0.01$). Of these participants, 111 had CK values at 4 d postexercise > 2000 U·L⁻¹, and 51 had values $> 10,000$ U·L⁻¹, levels used to diagnose myositis and rhabdomyolysis, respectively (26).

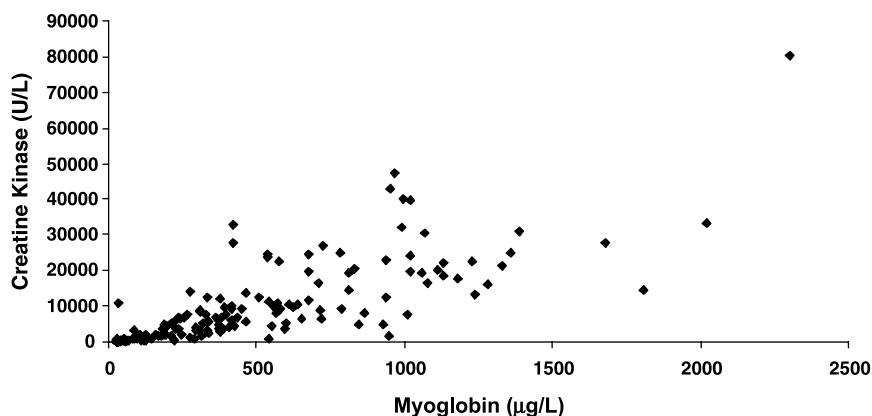


FIGURE 1—Relationship of creatine kinase and myoglobin. Values for each subject at 4 d following eccentric exercise of the elbow flexors ($r = 0.80$) ($N = 203$).

TABLE 1. Serum indicators of muscle damage.

No. of Days Post	CK (U·L ⁻¹)	Mb (μg·L ⁻¹)	LDH (U·L ⁻¹)	AST (U·L ⁻¹)	ALT (U·L ⁻¹)
Normal values	24–195	0–50	118–273	1–37	0–40
Baseline					
Mean	118	32	164	21	21
Range	33–481	27–645	105–287	10–43	5–87
SD	66	43	28	5	12
4					
Mean	7713	394	378	113	44
Range	55–80,550	27–2300	86–1608	15–911	6–289
SD	10,946	420	292	131	39
7					
Mean	2603	86	198	75	45
Range	49–21,675	27–552	98–513	14–363	5–189
SD	3126	86	59	61	30
10					
Mean	486	41	165	34	35
Range	45–7034	27–292	16–286	13–274	6–127
SD	693	28	32	23	20

Data are presented as mean, range, and SD (*N* = 203).

CK, creatine kinase; Mb, myoglobin; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

From Figure 1, it is clear that there is a large variability in the CK and Mb response to eccentric exercise, where some subjects are high responders to the exercise with dramatic increases in CK and Mb. The muscles enzymes LDH, ALT, and AST also increased significantly ($P < 0.01$) (Table 1). Despite the fact that muscle injury releases creatine, which may increase serum creatinine, there was no impairment in renal function (Table 2). Only one subject had a creatinine above ULN (1.9 mg·dL⁻¹) at day 7, and no subject had a clinically important increase in BUN defined as > 30 mg·dL⁻¹. In fact, the only significant change in measures of renal function was a significant decrease in BUN ($P < 0.05$). At 4 d postexercise, there was a high

correlation ($r = 0.80$) between CK and Mb (Fig. 1). CK was also highly correlated with LDH ($r = 0.95$), AST ($r = 0.96$), and ALT ($r = 0.91$). There were low correlations between CK and creatinine ($r = 0.23$) (Fig. 2A), CK, and BUN ($r = 0.11$) (Fig. 2B), and CK and uric acid ($r = 0.020$) (data not shown). Similar results were obtained for the relationship of Mb with creatinine ($r = 0.17$), BUN ($r = 0.07$), and uric acid ($r = 0.10$). Correlations among measures of renal function at 4 d postexercise were low except for correlations of $r = 0.41$ for creatinine with BUN and $r = 0.63$ for creatinine with uric acid.

DISCUSSION

CK levels are used clinically both to diagnose myositis and rhabdomyolysis and to predict acute renal failure and the need for treatment in cases of rhabdomyolysis. In a retrospective study, de Meijer et al. (8) found that 17 of 26 patients admitted to the hospital for rhabdomyolysis due to vascular obstruction, crush injury, sepsis, heatstroke/hyperthermia, or hyponatremia developed renal failure. Patients who experience renal failure had an average peak CK of $55,366 \pm 33,240$ U·L⁻¹ compared with $28,643 \pm 16,492$ U·L⁻¹ for those who did not develop renal failure. Approximately half of the patients who developed renal failure had peak CK levels under 60,000 U·L⁻¹. Importantly, rhabdomyolysis was not attributed to exertion in any subject in the de Meijer et al. study (8), and many of the patients had other conditions that could contribute to renal failure.

Sinert et al. (23) reported 35 cases of exertional rhabdomyolysis with admission CK levels between 700 and 167,000 U·L⁻¹. Exertional rhabdomyolysis was defined as a history of strenuous exercise, CK levels > 500 U·L⁻¹,

TABLE 2. Serum indicators of renal function.

No. of Days Post	Potassium (mmol·L ⁻¹)	Osmolality (mOsm·kg ⁻¹)	BUN (mg·dL ⁻¹)	Creatinine (mg·dL ⁻¹)	Phosphorus (mg·dL ⁻¹)	Uric Acid (mg·dL ⁻¹)
Normal values	3.5–5.1	281–305	9–16	0.5–1.4	2.7–4.5	3.4–7.0
Baseline						
Mean	4.4	292	14	0.9	4.2	5.2
Range	3.3–5.8	220–315	7–25	0.5–1.3	2.7–6.3	2.5–10.6
SD	0.4	8	4	0.2	0.6	1.5
No. above ULN	13	6	45	0	62	26
4						
Mean	4.6	293	13	0.9	4.3	5.3
Range	3.5–6.2	278–313	6–24	0.5–1.3	2.8–7.2	2.7–9.4
SD	0.5	6	4	0.2	0.8	1.5
No. above ULN	27	9	37	0	67	25
7						
Mean	4.6	296	13	0.9	4.3	5.2
Range	3.4–5.8	282–320	6–30	0.5–1.9	2.2–7.2	2.2–9.7
SD	0.4	7	4	0.2	0.7	1.5
No. above ULN	24	28	32	1	68	22
10						
Mean	4.6	295	13	0.9	4.1	5.5
Range	3.7–6.2	282–331	6–22	0.5–1.4	2.4–6.5	2.3–9.8
SD	0.5	8	3	0.2	0.7	1.5
No. above ULN	26	19	30	0	45	30

Data are presented as mean, range, SD, and number of subjects above the upper limit of normal (ULN) (*N* = 203).

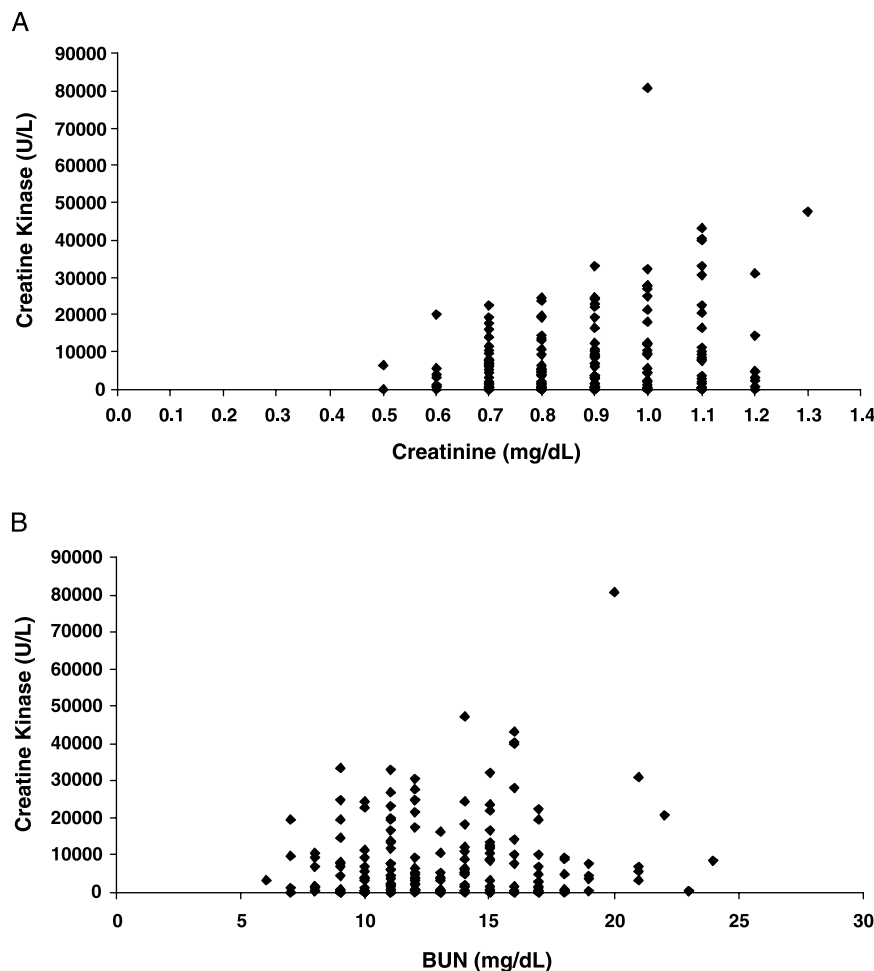


FIGURE 2—Relationship of creatine kinase (CK) and renal function at 4 d following eccentric exercise of the elbow flexors. A. CK and creatinine values for each subject ($r = 0.23$). B. CK and BUN values for each subject ($r = 0.11$) ($N = 203$).

and urine dipstick positive for blood without hematuria. No patient in that study reported pigmenturia or presented with hyperkalemia, acidosis, hypocalcemia, hyperphosphatemia, elevated creatinine ($>2.0 \text{ mg}\cdot\text{dL}^{-1}$), or elevated BUN ($>25 \text{ mg}\cdot\text{dL}^{-1}$). Patients were hospitalized for an average of 6.7 d, and all but one were treated with forced bicarbonate diuresis. Two received mannitol infusions for unclear criteria. No patient developed renal failure, despite some with marked CK elevations. Although the authors suggested that treatment was probably not responsible for the favorable outcome, there was no way to determine this because all patients but one were treated.

In the present study, 51 subjects (25%) had CK values $>10,000 \text{ U}\cdot\text{L}^{-1}$, a level used to diagnose rhabdomyolysis, and of these, 26 subjects (13%) had values $>20,000$, a level associated with renal failure in other studies (23), but no subject in the present study developed renal compromise. The exercise that subjects performed in this study has been used in our laboratory for approximately 20 yr before the present study. We have found it to be safe and reliable in our setting, with no subject requiring treatment to prevent renal failure. The results of this study support the hypothesis that marked CK and Mb elevations in response to exercise in healthy individuals are not sufficient to

induce renal compromise. Additional situational or genetic factors such as underlying disease, dehydration, supplement or drug use, environmental heat stress, or sickle cell trait may be required for exertional rhabdomyolysis to result in acute renal failure (3,9,11,13,17,27,28).

Sinert et al. (23) suggested that both dehydration and aciduria, which decreases Mb's solubility, increases the risk of renal injury. Early studies of animal models showed that an acidic urine was necessary to induce renal failure when Mb was infused (4). In two sickle cell trait patients presenting with hematuria, oral bicarbonate was administered and distilled water infused, resolving the hematuria (10). Administration of hemoglobin solutions to humans who were given oral hydration and sodium bicarbonate showed a decrease in renal function that resolved by 48 h (14). Ours is the first study to show that encouraging and likely maintaining adequate hydration without oral bicarbonate is sufficient to prevent renal dysfunction in the face of profoundly elevated blood levels of CK and Mb. Moreover, there was no heat stress involved in the present study. Exercise in the heat results in a redistribution of blood flow to the skin and away from the kidneys, which could compromise renal function, especially when combined with dehydration (30).

Our data show a high degree of variability in the blood indicators of muscle damage, a finding consistent with our earlier work (6,16,22). Genotype analysis was done in a subsample of the subjects from this study, and we found genetic polymorphisms in myosin light chain kinase (MLCK) were associated with increases in CK and Mb (5). Subjects possessing rare alleles of MLCK showed an exaggerated increase in CK and Mb response to exercise stress, and it may be these subjects who are at higher risk of rhabdomyolysis and acute renal failure in situations of heat stress and dehydration. Variability in response to heat stress has also been documented (1). The reason why some individuals develop heatstroke and renal failure in response to exertional heat stress is not fully known, but may also be explained by polymorphisms in genes that encode proteins involved in the acute phase response to heat (2,29). Thus, there may be genetic underpinnings to the susceptibility to both muscle damage and heat stress, which, combined with environmental and situational factors, may dictate the propensity for renal failure in certain individuals.

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This study was funded by Medinova, Inc.