

Approach to a patient with elevated CK

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Disclosures

None



Outline

- Creatine kinase biochemistry
- Normal values
- Factors which can affect CK levels
- CK as a biomarker for muscle disease
- Approach to a patient with elevated CK
- Asymptomatic elevations in CK

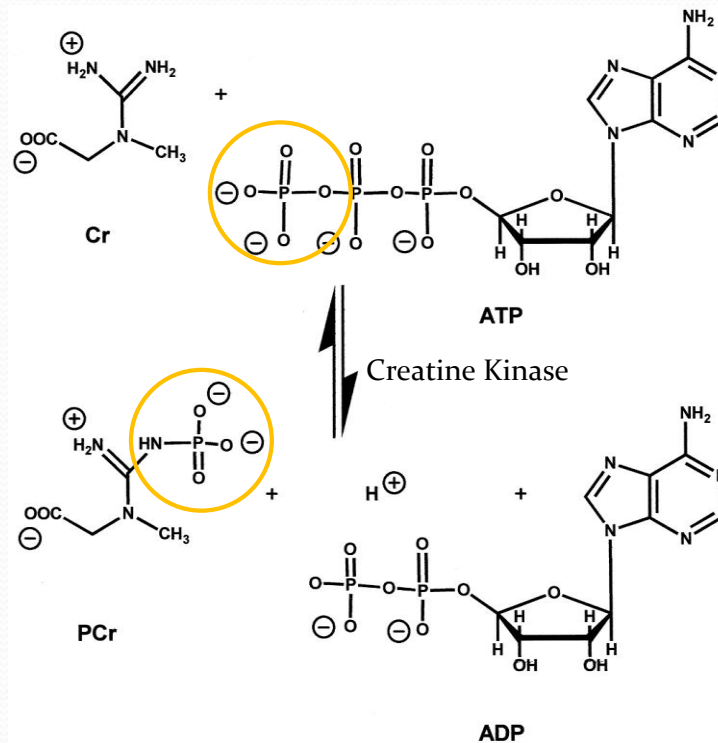
Creatine Kinase Biochemistry



Phosphocreatine System

- Used by tissues that have high demand for energy
 - Skeletal muscle
 - Cardiac muscle
 - Brain tissue
- Creatine is used as a buffer to store energy which is easily converted to ATP
 - ATP concentration in muscle is 2-5 mM
 - Creatine concentration in muscle is 20-40 mM

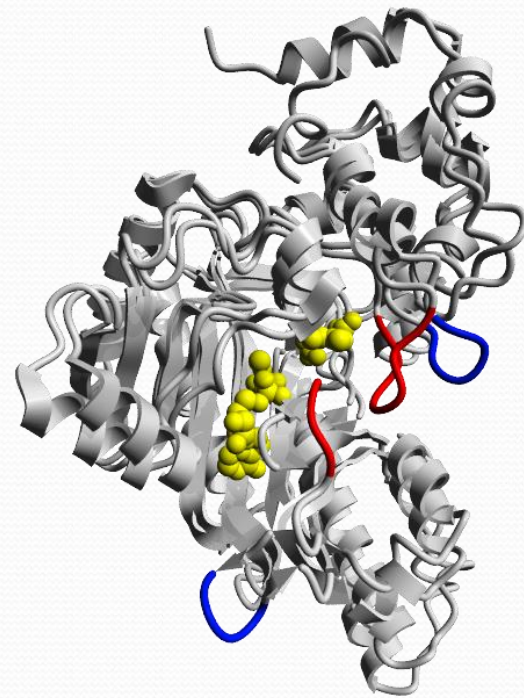
Phosphocreatine System



Persky and Brazeau. Pharmacol Rev (2001) 53: 161-176

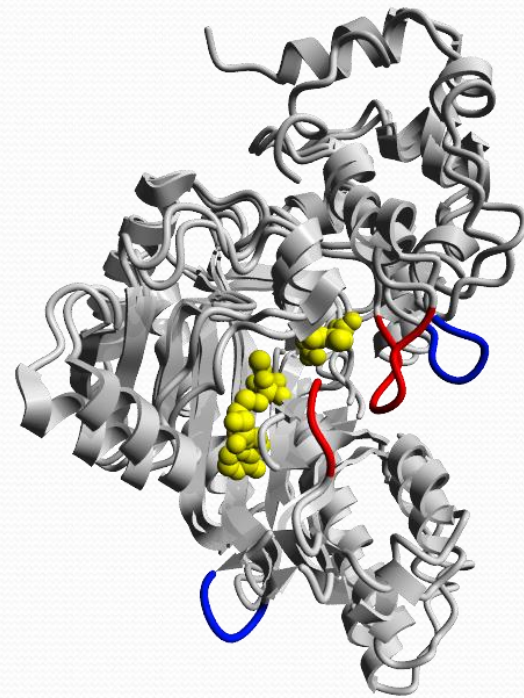
Creatine Kinase

- Catalyzes the transfer of a high energy phosphate between ATP and creatine
- Functions as a dimer
- Two subunit types
 - M type
 - B type



Creatine Kinase

- Tissue isoforms
 - Skeletal muscle
 - 2 M subunits (MM)
 - Brain
 - 2 B subunits (BB)
 - Cardiac muscle
 - One of each (MB)





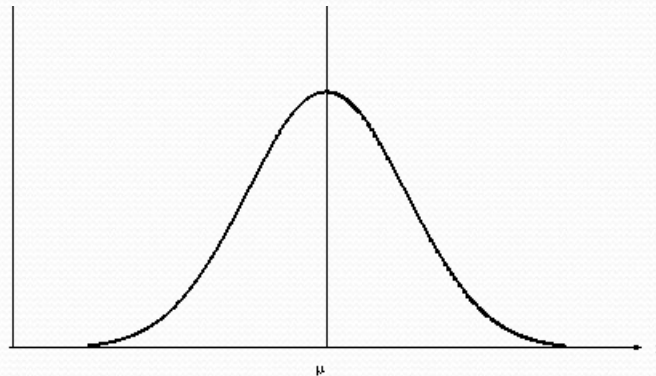
Laboratory Testing

- Total CK
 - Assay based on enzyme activity
 - One unit of activity is defined as the transfer 1 micromole of phosphate from phosphocreatine to ADP per minute
 - Laboratory reference is U/L
- CK-MB
 - Assay to quantitate amount of protein using a specific antibody to CK-MB
 - Laboratory reference is ng/mL

What is normal?

What is normal?

- Normal laboratory reference ranges are typically defined as the interval containing 95% of reference population
- The “reference population” may not accurately reflect your patient population
- Laboratory normal ranges typically assume Gaussian distribution

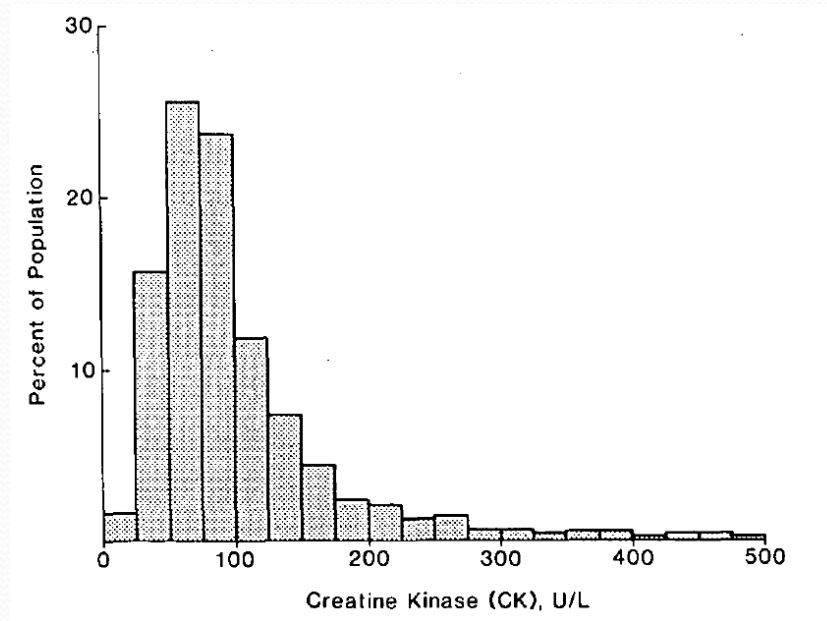


What is normal?

- Total CK
 - Swedish lab
 - Male: 24-204 U/L
 - Female: 24-173 U/L
 - UW lab
 - Male: 62-325 U/L
 - Female: 43-274 U/L
 - Mayo Clinic lab
 - Male: 52-336 U/L
 - Female: 38-176 U/L

Creatine Kinase

- Creatine kinase levels are non-Gaussian



Wong et al. Am J Clin Pathol (1983) 79:582-586

Creatine Kinase (Netherlands)

Study with 1411 subjects

Table I. Distribution of serum CK in different population groups

Sex and ancestry	N	Age	BMI	Serum CK distribution			>ULN (N%)*
				2.5th percentile	Median	97.5th percentile	
All subjects †	1411	45 (7)	27 (5)	40	111	460	508 (36)
Women	831	45 (7)	28 (6)	36	95	349	304 (37)
Men	580	46 (7)	26 (4)	51	143	616	204 (35)
White subjects	503	48 (7)	26 (5)	35	88	286	64 (13)
Women	252	47 (7)	26 (5)	29	72	201	21 (8)
Men	251	48 (7)	26 (4)	47	110	322	43 (17)
South Asian subjects	270	44 (6)	27 (5)	40	104	382	62 (23)
Women	147	45 (6)	27 (5)	37	87	313	23 (16)
Men	123	44 (6)	26 (5)	47	143	641	39 (32)
Black subjects	570	44 (6)	28 (5)	51	149	627	278 (49)
Women	387	43 (6)	29 (6)	48	124	414	164 (42)
Men	183	44 (6)	26 (4)	71	213	801	114 (62)

Data for age and body mass index (BMI) are means (SD). Data are rounded to the nearest integer. CK is expressed as international units per liter.

*Number (percentage) of participants with a CK above the ULN, as recommended by the manufacturer (140 IU/L for women, 174 IU/L for men; with appropriately established reference intervals, 2.5% of the subjects are expected to have values above the ULN).

†Including participants of "other" ancestry (n = 68), with the exclusion of outliers (n = 3, 1 South Asian and 2 black participants) and those using statins (n = 30, 21 South Asian, 8 black participants, and 1 of other ancestry).

Brewster et al. Am Heart J (2007) 154:655-661

Creatine Kinase in the US

**Characteristics of NHANES subjects 2011–2014,
age ≥ 20, nonpregnant, with available creatine kinase**

N	10,096
Female	5136 (51%)
Race-ethnicity	
White	4119 (41%)
Black	2256 (22%)
Hispanic	2159 (21%)
Asian	1270 (13%)
Other race*	292 (3%)
Age, y	
20–29	1686 (17%)
30–49	3514 (35%)
50–69	3340 (33%)
≥70	1556 (15%)
Survey year	
2011–2012	4833 (48%)
2013–2014	5263 (52%)
Body mass index, kg/m ² (n=9970)	29 +/- 7
Glomerular filtration rate, [†] mL/min/1.73 m ²	89 +/- 26
Hypertension	3616 (36%)
Smoking	2038 (20%)
Diabetes	1586 (16%)
Cholesterol medication use	1979 (20%)
Thyroid disease	719 (7%)
Vigorous work	1738 (17%)
Vigorous recreation	2243 (22%)
Exercise past 3 days (n=4331)	1086 (25%)
Heavy alcohol use (n=4384) [‡]	355 (8%)
Creatine kinase, IU/L	102 (72,158)

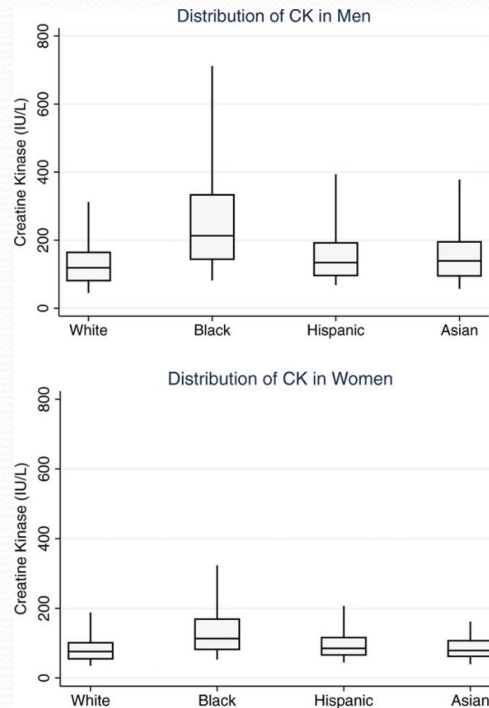
N=10,096

Average CK 102

Proportions (%), mean +/- SD, and median (IQR) calculated accounting for sampling design.
 NHANES = National Health and Nutrition Examination Survey.
 * Includes patients with multiple race categories self-selected.
 † Based on the MDRD equation.
 ‡ >14drinks/week for men or >7drinks/week for women.

George et al. Medicine (2016) 95:33

Creatine Kinase in the US



George et al. Medicine (2016) 95:33

Creatine Kinase in the US

	N	Male CK		
		90th percentile	95th percentile	97.5th percentile
White	532	237 (201,273)	312 (268,356)	382 (295,469)
Black	391	544 (443,645)	712 (530,894)	1001 (718,1284)
Hispanic	304	274 (234,314)	394 (258,530)	572 (338,806)
Asian	214	267 (188,346)	378 (185,571)	520 (222,818)
	N	Female CK		
		90th percentile	95th percentile	97.5th percentile
White	655	142 (130,154)	188 (122,254)	295 (216,374)
Black	485	254 (205,303)	323 (218,428)	487 (310,664)
Hispanic	359	145 (124,166)	207 (176,238)	279 (88,470)
Asian	216	135 (120,150)	162 (139,185)	194 (163,225)

CK = creatine kinase, NHANES = National Health and Nutrition Examination Survey.

What factors affect the CK level?

Exercise

Effect of 3 days of 45 min aerobic exercise sessions on 15 medical students

Table 2. Serum CK, muscle pain, and recovery pulse after aerobic exercise.

Subject	Days after exercise						Mean resting serum CK§	Muscle pain (day)‡	Mean recovery pulse (beats/min)	CK ratio (peak/resting)
	1	2	4	5	6	7				
1†	204	363	—	—	149	—	110	1,2	122	3.30
2†	232	147	87	31	—	—	23	1,2,3	94	10.09
3	472	—	—	—	—	—	68	-2	140	6.94
4	256	152	103	—	—	—	44	-3,-2	123	5.82
5	392	234	—	184	117	67	71	-1,1	147	5.52
6	546	428	—	—	171	—	124	1	145	4.40
7	103	58	—	59	—	53	64	1	111	1.61
8	282	173	162	—	—	—	80	Nil	143	3.53
9	3473	3465	911	408	—	99	102	-1,-2,1,2,3	128	34.05
10	264	121	90	127	—	—	50	1 + 3	110	5.28
11	90	50	44	—	—	—	37	1	107	2.43
12	164	110	—	—	—	—	106	1	116	1.55
13	—	1458	—	140	—	48	42	-3,-1,2	130	34.71
14	178	121	—	—	89	—	110	-1,-2	—	1.62
15*	892 (379)	689 (235)	532	325	174	126	77†	-2,-1,1,2,3	120	11.58 (4.92)
Mean							73.87			8.85
SD							31.12			10.77

*This subject was the aerobics instructor who was carrying out three classes per week. The values shown are the values obtained when she first began classes. Values in parentheses are the values obtained while giving this test program.

†Subjects 1 and 2 carried out regular exercise at least 3 times per week. Subject 1 jogged for 40 minutes 2-3 times per week and played netball twice per week. Subject 2 cycled 5 km to the hospital and attended gymnastics twice per week. She was also taking propranolol for hypertension.

‡Days -3,-2,-1 were the 3 aerobic exercise days, days 1-7 were days following the aerobic exercise.

§Resting serum CK values were obtained from the mean of a minimum of three serum CK values obtained at weekly intervals, using the collection protocol described in Materials and Methods.

Nicholson et al. Muscle Nerve (1986) 9:820-824

Exercise

Study of 499 recruits undergoing basic military training

Table 3. Comparison between race and serum CK (IU/L).

	Number	Baseline CK, mean/median (<i>P</i> -value)	Day 7 CK, mean/median (<i>P</i> -value)
African-American	27	664.4/371.5	2762.1/1548.0
Asian	8	351.0/247.5 (0.220)	1563.0/529.0 (0.141)
Caucasian	379	186.8/152.0 (< 0.001)	1184.1/556.0 (< 0.001)
Hispanic	57	260.4/153.0 (< 0.001)	1070.0/536.0 (< 0.001)
Native American	9	233.6/183.0 (0.015)	1006.5/961.5 (0.054)
Pacific Islander	15	171.3/118.0 (< 0.001)	695.0/387.5 (< 0.001)

P-values (two-tailed) are with respect to the log of serum CK, with all comparisons made vs. African-Americans. Bold = statistically significant at *P* < 0.05.

Exercise

Study of 499 recruits undergoing basic military training

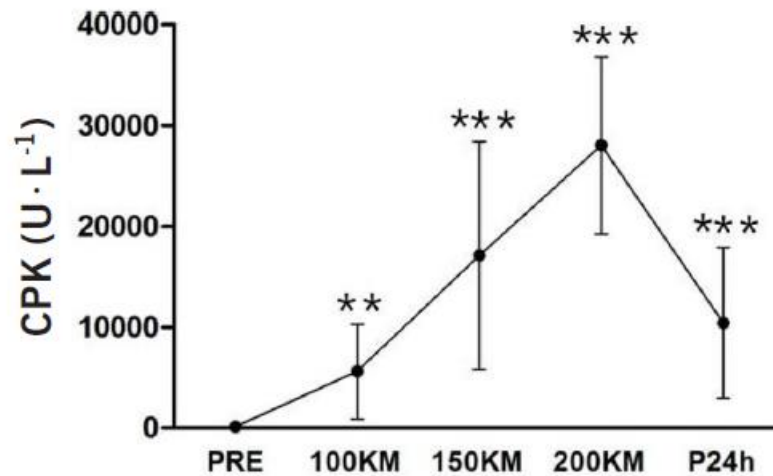
Table 1. Mean serum CK values at baseline, and at days 3, 7, and 14 after starting BMT.

	Baseline CK	Day 3 CK	Day 7 CK	Day 14 CK
Mean (IU/L)	223	734	1,226	667
Range	34–3130	76–10,243	56–35,056	80–5518
Median (IU/L)	157	478	567	486
Abnormal	24.50%	88.50%	84.20%	87.10%
>5× normal	1.20%	12.40%	26.50%	13.30%
>10× normal	0.00%	3.90%	11.30%	2.80%
>50× normal	0.00%	0.00%	0.90%	0.00%

Kenny et al. Muscle Nerve (2012) 45:356-362

Exercise

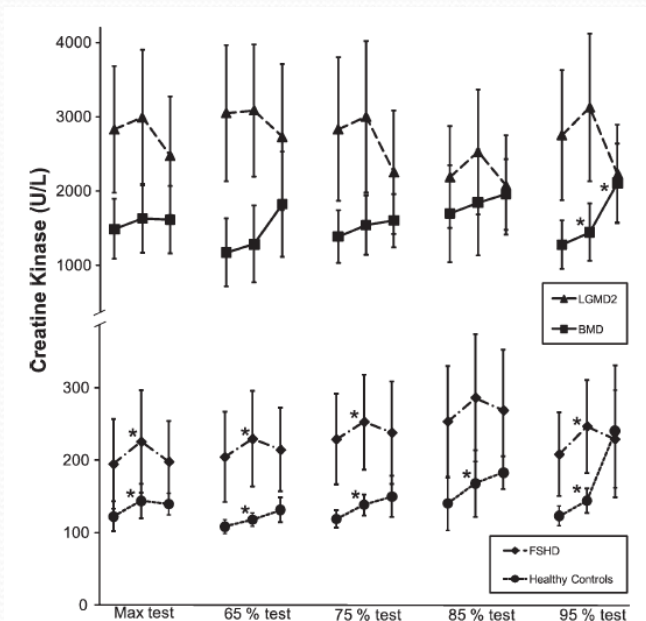
- CK was measured in 32 ultra-distance runners at stages of a 200 km race and 24 hours afterwards



Son et al. Biol Sport (2015) 32:357-361

Exercise in muscular dystrophy

Limb girdle, Becker's, and Fascioscapulohumeral muscular dystrophies



CK was measured before exercise, immediately afterwards, and 24 hours afterwards

Anderson et al. Muscle Nerve (2013) 48:897-901



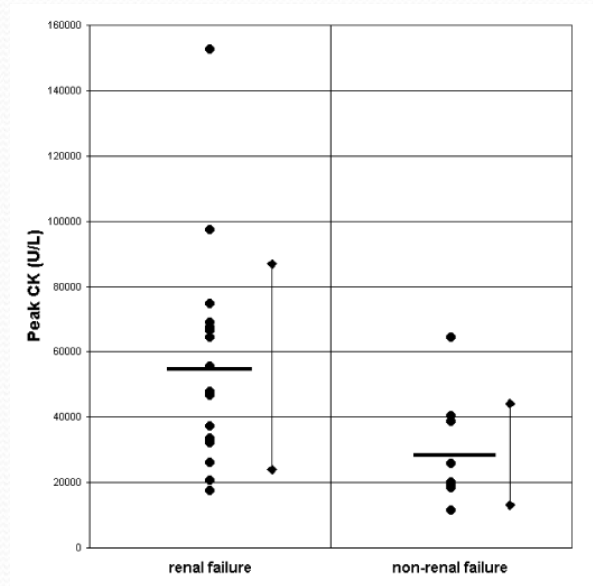
Rhabdomyolysis

- Muscle necrosis and release of intracellular contents
- Characterized by muscle pain, weakness, and dark urine, muscle tenderness/swelling
- Clinical concern is risk of renal failure
- Hallmark is elevated CK but no consensus definition based on level of elevation
 - Studies advocate for different thresholds ranging from 5x to 50x the ULN
- Risk of acute kidney injury is low when CK < 15,000 U/L on admission
 - Can occur at CK of 5000 U/L
 - Sepsis
 - Dehydration
 - Acidosis

Bosch et al. NEJM (2009) 361:62-72

Rhabdomyolysis

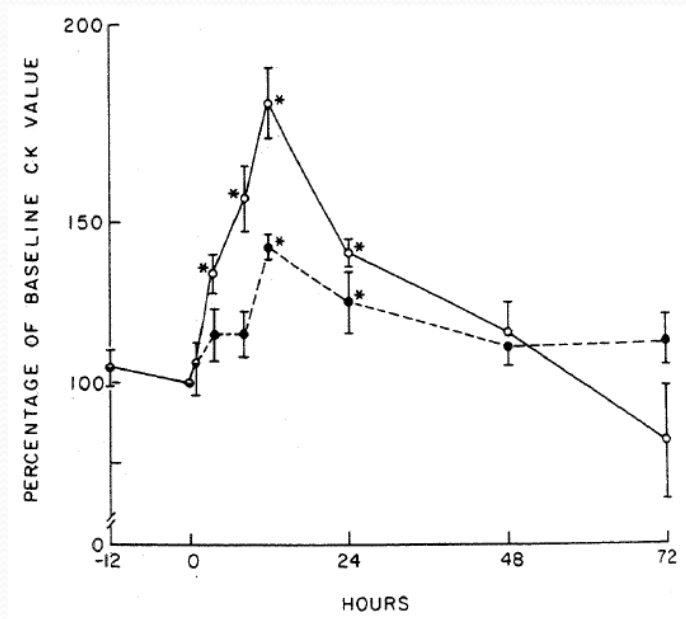
- Case series of 26 patients with rhabdomyolysis



de Meijer et al. Intensive Care Med (2003) 29:1121-1125

Effect of electromyography

- Needle EMG can affect CK level



Levin et al. Muscle Nerve (1987) 10:242-245



Cardiac considerations

- Creatine kinase and CK-MB were widely used as biomarkers for myocardial infarction prior to the availability of troponin
- CK-MB is relatively high in cardiac tissue
- CK-MB is also increased in skeletal muscle with regeneration of muscle fibers
 - CK-MB can be increased in patients with chronic muscle disease or in athletes

Non-neuromuscular Causes of Elevated CK

- Strenuous exercise
- Trauma/Procedures (EMG, injection, surgery)
- Toxins (alcohol, heroin, cocaine)
- Endocrine (hypothyroid, hyperthyroid, hyperparathyroid)
- Electrolyte derangements (hyponatremia, hypokalemia, hypophosphatemia)
- Renal failure
- Viral illness
- Chronic cardiac disease
- Malignancy
- Obstructive sleep apnea
- Neuroacanthocytosis syndromes
- Macro-CK
- Malignant hyperthermia syndromes

Kyriakides et al. Eur J Neurol (2010) 17:767-773



Medication Causes of Elevated CK

- Medications
 - Statins
 - Fibrates
 - Colchicine
 - Antipsychotics
 - Zidovudine
 - Certain beta blockers (pindolol, carteolol)
 - Isoretinoin



Effect of denervation on CK

- Creatine kinase can be mildly elevated in conditions causing acute denervation of the muscle
 - Motor neuron disease
 - Motor neuropathies
 - Radiculopathy
 - Plexopathy

Motor neuron disease

- CK levels in patients with ALS (36) and SBMA (33)

	ALS	SBMA
Mean \pm SD*	304 \pm 392	939 \pm 590
Range	38–2123	215–2795
Number of patients with elevated CK level†	9 of 36	28 of 33
Number of patients with CK >1000 U/L	2	12

* $P < 0.001$; † $P = 0.005$.

Biomarker for muscle disease



Biomarkers

- Objective measures used as a markers of a disease process
- Ideally, only abnormal in the pathological state
- In practice, most biomarkers have variable sensitivity and specificity



Creatine Kinase as a Biomarker

- Pros
 - High in muscle and relatively low in other tissues
 - Mostly localized to muscle (95%) and brain
 - Measurable in serum
 - Enzyme activity is easily measured
- Cons
 - Non-neuromuscular causes of elevation
 - Can be elevated in the absence of disease
 - Not elevated in all myopathies



Patient with elevated CK

- How do you decide when to pursue further workup?
 - Asymptomatic patient vs patient with weakness
 - What is the likelihood of finding a specific diagnosis?
 - Should we pursue invasive testing (muscle biopsy)?
 - How likely are we to find a treatable cause?

Approach to the weak patient with elevated CK



Signs of possible myopathy

- Proximal weakness
- Atrophy or hypertrophy
- Exercise intolerance
- Family history
- Pigmenturia
- Myotonia

Signs of other neuromuscular disease

- Fatiguable weakness
- Sensory symptoms
- Fasciculations
- Reflex abnormalities



Role of EMG

- Rule out non-myopathic causes of elevated CK
 - Motor neuron disease
 - Motor neuropathy
 - Radiculopathy
 - NMJ disorders
- Determine if there is myotonia (myotonic dystrophy)
- Determine if there are myopathic changes
 - If absent, does not rule out myopathy



Role of muscle biopsy

- Gold standard for the diagnosis of myopathies
 - Histological stains (H&E, Gomori trichrome, Oil Red O, PAS, SDH, NADH, cytochrome oxidase, myophosphorylase, acid phosphatase)
 - Immunohistochemical stains
 - Mitochondrial enzyme activity
 - Glycolytic enzyme activity
 - Electron microscopy
- Biopsy an affected muscle not tested by EMG needle
- Choosing site of biopsy can be assisted with MRI imaging

Yield of muscle biopsy

- Series of 698 muscle biopsies at a neuromuscular referral center
 - Inflammatory myopathy found in 23% of all biopsies
 - Diagnostic biopsy most associated with the group with CK elevated, proximal weakness, and myopathic EMG (specific diagnosis in >50%)

Table 2. Estimated probability of both myopathy outcomes given different level of weakness and EMG.

EMG and strength status	Probability* of myopathy, %	Probability* of specific myopathy (%)
- Weakness, - EMG	34.3–50.2	7.3–14.6
+ Weakness, - EMG	39.4–64.2	18.8–27.3
- Weakness, + EMG	47.6–60.6	25.5–30.7
+ Weakness, + EMG	74.6->90	49.9–76.9

**The probability for both myopathy and specific myopathy increased in each scenario in direct proportion to the CK level.*

Approach to the patient without weakness with elevated CK

EFNS guidelines on the diagnostic approach to pauci- or asymptomatic hyperCKemia

T. Kyriakides^a, C. Angelini^b, J. Schaefer^c, S. Sacconi^d, G. Siciliano^e, J. J. Vilchez^f and D. Hilton-Jones^g

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- HyperCKemia defined as CK > 1.5x upper limit of normal

	1.5x ULN
Non-black male	504
Non-black female	325
Black male	1201
Black female	621



Asymptomatic hyperCKemia

- Asymptomatic
- Pauci-symptomatic
 - No objective weakness on exam
 - No atrophy, hypertrophy, or myotonia
 - Vague neuromuscular symptoms
 - Myalgia
 - Fatigue
 - Exercise intolerance
 - Cramps/stiffness



EFNS guidelines

- Consider and rule out non-neuromuscular causes if appropriate
 - Review medications
 - Substance abuse history (consider tox screen)
 - Check metabolic panel, phosphate
 - Check thyroid function, parathyroid function
 - Consider checking troponin



EFNS guidelines

- Determine family history of neuromuscular disease, hyperCKemia, or malignant hypertension
- Confirm hyperCKemia
 - At least two CK measurements
 - Avoid strenuous exercise for 7 days prior with samples at least 1 month apart
- If hyperCKemia confirmed, check EMG/NCS



EFNS guidelines

- Muscle biopsy recommended if:
 - Myopathic EMG
 - CK >3x normal
 - Patient < 25 years old
 - Exercise induced pain or exercise intolerance
 - Women with CK < 3x normal
 - Can first test blood lymphocytes for Becker/Duchenne mutation



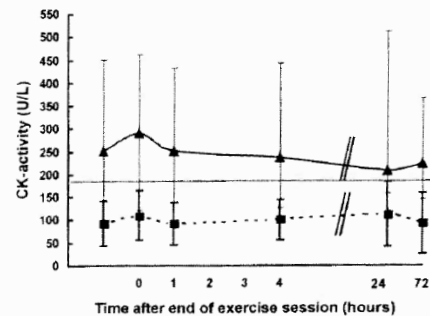
Asymptomatic hyperCKemia

- Multiple case series of muscle biopsy patients with asymptomatic hyperCKemia
- 460 patients from 8 separate studies
 - 134 (29%) were normal
 - 25 (5%) were neuropathic
 - 190 (41%) were nonspecific myopathic
 - 121 (26%) resulted in specific diagnosis
 - 42% metabolic myopathy
 - 21% subclinical muscular dystrophies

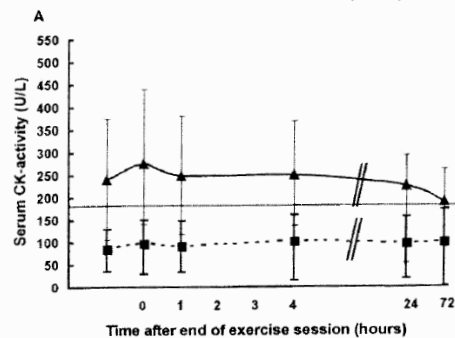
Prognosis of asymptomatic hyperCKemia

- D'adda et al reported a 6 year follow up study of 55 patients with asymptomatic hyperCKemia
 - Most remained asymptomatic
 - 1 became symptomatic
 - 45 (78%) still had elevated CK but at a lower level
 - 12 (22%) had normalized CK
 - 1 patient was diagnosed with limb girdle muscular dystrophy
 - 1 patient was diagnosed as a dystrophinopathy carrier

Exercise in asymptomatic hyperCKemia



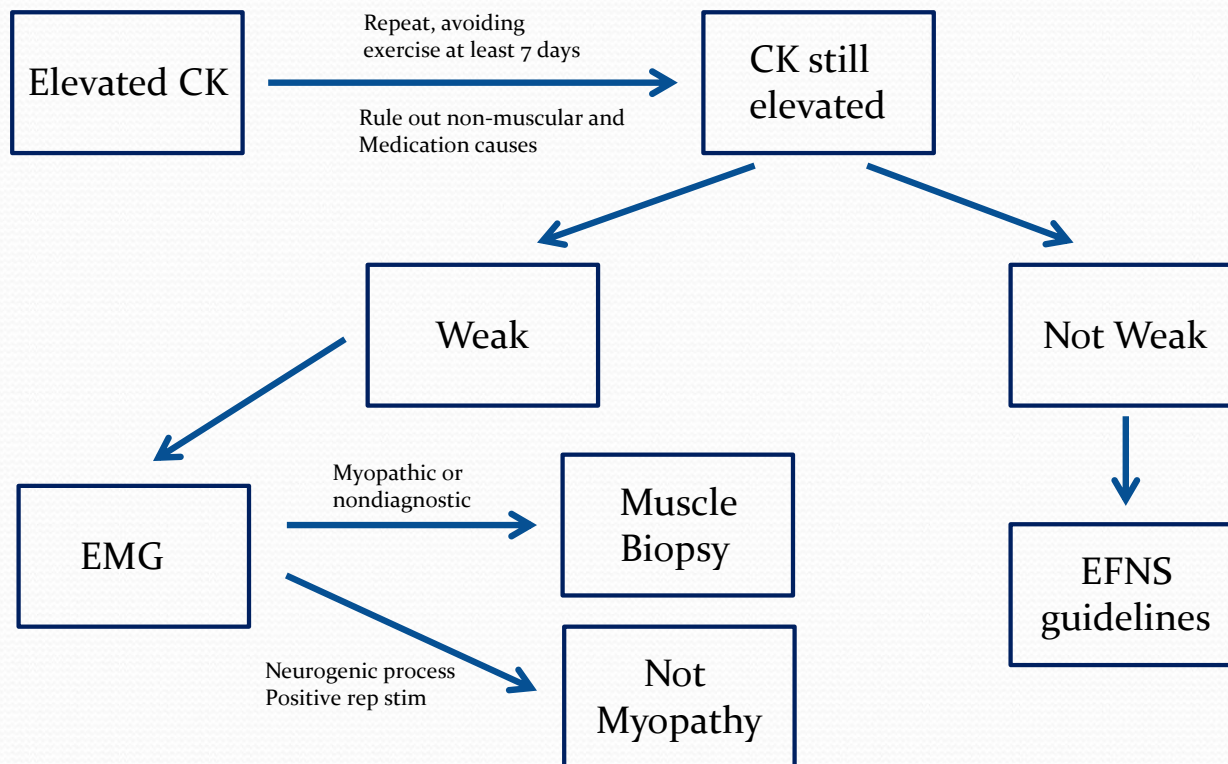
11 patients with asymptomatic hyperCKemia after maximal and submaximal exercise



Reijneveld et al. Muscle Nerve (2002) 26:832-837

Summary

Practical approach





Summary

- Creatine kinase is a biomarker with good muscle specificity
- “Normal” values can vary depending on race and sex
- Several factors can elevate CK level in the absence of underlying neuromuscular disease
- Elevated levels in an asymptomatic patient often carry a benign prognosis
- Depending on context, chances of obtaining a diagnostic muscle biopsy can range widely from 7 to 70%.



Thank you!