The Elevated CK

ROBERT HAWKINS, M.D.
What is the difference between “CK” and “CPK”

- One has a “P” in it.
- One has “kinase” in it, the other has “phosphokinase” in it.
- There is no true difference.
  - A kinase is, by definition, an enzyme that phosphorylates a molecule.
  - So Creatine Phosphokinase is redundant.
- Like saying “Overbinging.”
- So just say CK.
What is the difference between “CK” and “CPK”

- The One Exception
What does CK do?

- It is an important enzyme in energy metabolism.
- Immediate source of ATP in contracting muscle.
Where is CK located? Are there different isomers?

- **CK-MM** Skeletal muscle
  - Injury
  - Inflammation
- **CK-MB** Cardiac muscle
  - Cardiac injury
  - Defibrillation
  - Cardiac surgery
- **CK-BB** Brain and Lungs
  - Brain cancer, injury, seizure, ECT
  - Pulmonary infarction
What about Ethnicity and Gender?

Do they influence serum CK values?
Which of these famous individuals is likely to have the highest CK?
<table>
<thead>
<tr>
<th>Sex and ancestry</th>
<th>N</th>
<th>Age</th>
<th>BMI</th>
<th>Serum CK distribution</th>
<th>&gt;ULN (N percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.5th percentile</td>
<td>Median</td>
</tr>
<tr>
<td>All subjects</td>
<td>1411</td>
<td>45 (7)</td>
<td>27 (5)</td>
<td>40</td>
<td>111</td>
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<tr>
<td>Women</td>
<td>831</td>
<td>45 (7)</td>
<td>28 (6)</td>
<td>36</td>
<td>95</td>
</tr>
<tr>
<td>Men</td>
<td>580</td>
<td>46 (7)</td>
<td>26 (4)</td>
<td>51</td>
<td>143</td>
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<tr>
<td>White subjects</td>
<td>503</td>
<td>48 (7)</td>
<td>26 (5)</td>
<td>35</td>
<td>88</td>
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<tr>
<td>Women</td>
<td>252</td>
<td>47 (7)</td>
<td>26 (5)</td>
<td>29</td>
<td>72</td>
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<tr>
<td>Men</td>
<td>251</td>
<td>48 (7)</td>
<td>26 (4)</td>
<td>47</td>
<td>110</td>
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<tr>
<td>South Asian</td>
<td>270</td>
<td>44 (6)</td>
<td>27 (5)</td>
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<tr>
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<td>123</td>
<td>44 (6)</td>
<td>26 (5)</td>
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<td>143</td>
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<tr>
<td>Black subjects</td>
<td>570</td>
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<td>28 (5)</td>
<td>51</td>
<td>149</td>
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<tr>
<td>Women</td>
<td>387</td>
<td>43 (6)</td>
<td>29 (6)</td>
<td>48</td>
<td>124</td>
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<tr>
<td>Men</td>
<td>183</td>
<td>44 (6)</td>
<td>26 (4)</td>
<td>71</td>
<td>213</td>
</tr>
</tbody>
</table>

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 percent 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).

What is Rhabdomyolysis?

- Any process that damages muscle
- Any process that causes an elevated serum CK
- Any process that causes an elevated serum CK with myoglobinuria
- Any process that results in acute muscle damage
- Any process that causes persistent muscle damage
A Definition of Rhabdomyolysis

A Process of:

- Acute muscle necrosis
- *Five fold* elevation of CK above upper limit of normal
- *Maybe* myoglobinuria (seen in less than 50%)
CK and Myoglobin

CK
- Serum half life = 36 hrs
- Declines after reaching peak by 40%-50% / day

Myoglobin
- Serum half life = 2-3 hrs
- Serum levels may normalize in several hours
Myoglobinuria and the UA

- Serum level $>1.5$ mg/dl spills to urine
- Visible (Coke colored urine) $>100-300$ mg/dl
- Dipstick detects $>0.5-1.0$ mg/dl
- Myoglobin and Hemoglobin detected as “blood”
- Absence of RBCs suggests myoglobin in urine
- Proteinuria seen in $\frac{1}{2}$.
  - Myoglobin & other proteins from myocytes
The Elevated CK in the Hospital
# Rhabdomyolysis in the Hospital*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age (yr) mean</td>
<td>47</td>
</tr>
<tr>
<td>Male</td>
<td>68%</td>
</tr>
<tr>
<td>Creatine Kinase IU/L (mean)</td>
<td>168,052</td>
</tr>
<tr>
<td>Creatine Kinase IU/L (range)</td>
<td>2,975 – 250,000</td>
</tr>
<tr>
<td>Urine myoglobin positive</td>
<td>19%</td>
</tr>
<tr>
<td>Multiple causes</td>
<td>60%</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>46%</td>
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</tbody>
</table>

## Rhabdomyolysis in the Hospital*

<table>
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<tr>
<td>HIV/AIDS</td>
<td>02</td>
<td>67</td>
<td>11,314</td>
<td>33</td>
<td>01</td>
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<tr>
<td>Metabolic Causes</td>
<td>02</td>
<td>56</td>
<td>13,989</td>
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<td>01</td>
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<tr>
<td>ICU Myopathy</td>
<td>01</td>
<td>75</td>
<td>11,225</td>
<td>25</td>
<td>100</td>
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<tr>
<td>Exercise</td>
<td>01</td>
<td>56</td>
<td>13,989</td>
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Statins in lipid Therapy

- HMG-CoA reductase inhibitors
Statin Myopathy: A Spectrum Disorder

- Myalgia / Myopathy 2%-11%
- Severe myonecrosis 0.5%
- Rhabdomyolysis 0.1%
Statin Myopathy Clinical Findings

Myalgia

↑ or Nl CK

Weakness
Statin Myopathy Risk Factors

- Higher doses
- Lipophilic vs hydrophilic
  - Lipophilic ↑ risk
    - Simvastatin
    - Lovastatin
  - Hydrophilic ↓ risk
    - Fluvastatin
    - Pravastatin
    - Rosuvastatin
- CYP3A4 metabolism
- Genetic
  - SLCO1B1 homozygotes
- Ethnic
  - Chinese / simvastatin niacin
- Age > 80 yrs
- Frailty
- Female
- Small body frame
- Liver / renal disease
- Concomitant drug therapy
  - Gemfibrozil, niacin, colchicine
Statins and the CYP3A4 System

Metabolized by CYP3A4
- Simvastatin
- Lovastatin
- Atorvastatin

Metabolized by Other
- Fluvastatin
- Pravastatin
- Rosuvastatin
- Pitavastatin
Statins and the CYP3A4 System
Statin Myopathy
Time Course

- **Onset**
  - Mean time to onset: 6 months
  - Range: 0.25 – 48 months

- **Resolution**
  - Mean time to resolution: 2.3 months
  - Range: 0.25 – 14 months
Does Statin Myopathy Always Resolve?

- Statin-associated immune mediated necrotizing myopathy
  - Antibody to HMG CoA reductase
  - Macrophage infiltrate engulfing necrotic muscle fibers
  - Responds to immunosuppressive Rx
Management of Suspected Statin Myopathy

- Stop the drug
- Look for co-conspirator drugs
- Evaluate for and treat AKI
- Consider restarting with statins not metabolized by CYP3A4
  - Fluvastatin
  - Pravastatin
  - Rosuvastatin
Other Prescribed Drugs

- Colchicine
- Anti-malarials
  - Chloroquine
  - Hydroxychloroquine
- Emetine
- Imatinib mesylate (Gleevec)
- Zidovudine
- Amiodarone
  - neuromyopathy
- Vincristine
  - Polyneuropathy
  - Rare myopathy
Colchicine Myopathy

- Acute overdose
- Chronic therapeutic doses
- Proximal muscle weakness
- ↑ CK 10-to 20 fold
- Bx Vacuolar changes
Colchicine Myopathy

- Acute overdose
- Chronic therapeutic doses
- Proximal muscle weakness
- ↑ CK 10-to 20 fold
- Bx Vacuolar changes
Antimalarial Myotoxicity
Chloroquine Hydroxychloroquine

- Neuropathy
- Myopathy
- Cardiomyopathy
- Incidence unknown
  - Very low
- Clinical presentation
  - Proximal muscle weakness
  - Mild elevation of CK
  - Heart Failure
- Pathology
Hydroxychloroquine-induced cardiomyopathy showing cardiomyocytes with Luxol stain

The histopathology, using Luxol fast blue stain with 400x magnification, highlights the vacuolated myocardial cells which contain blue intracytoplasmic granules (arrow), characteristic of abundant lysosomes.

Courtesy of Aleksandr Perepletchikov, MD.
# The “Malignant” Syndromes

## Neuroleptic Malignant Syndrome

- **Neuroleptic medications**
  - Haloperidol, fluphenazine
  - Less common
    - Chlorpromazine
    - Risperidone
    - Others
- **Clinical findings**
  - MS changes
  - Muscle rigidity
  - Fever
  - Autonomic dysfunction

## Malignant Hyperthermia

- **Depolarizing muscle relaxants**
  - Succinylcholine
  - Halothane
- **Genetic susceptibility**
- **Clinical findings**
  - Muscle rigidity
  - Fever
  - Cardiac arrhythmias
Emetine Myopathy
Emetine Myopathy
Emetine Myopathy

Karen Carpenter
Emetine Myopathy

- Emetine still available
  - Local pharmacies
  - 1 ounce limit without a prescription
- Online
"THE NURSE SAID TO LIST THE DRUGS I'M TAKING... I WROTE THE LEGAL IN THE LEFT COLUMN... ILLEGAL ON THE RIGHT."
Illicit Drugs

No Doc, I swear I’m not on anything!
The KMC Urine Drug Screen

Myotoxins
- Amphetamine
- Cocaine
- Opiates

Non-Myotoxins
- Barbiturates
- Benzodiazepines
- THC
## Serum/Urine Drug Screen

<table>
<thead>
<tr>
<th></th>
<th>Serum Half Life</th>
<th>Urine Metabolites Half Life</th>
<th>Urine Metabolites Detected (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>3-24</td>
<td>11</td>
<td>Up to 7</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1.5</td>
<td>4-8</td>
<td>2-4</td>
</tr>
<tr>
<td>Opiates</td>
<td>1.5-27</td>
<td>Variable</td>
<td>Variable</td>
</tr>
</tbody>
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Cocaine Rhabdomyolysis

- Ranges from asymptomatic CK-emia to massive rhabdomyolysis
- Usually present with other issues
  - Chest pain
  - Delirium
  - Fever
  - Cardiovascular collapse
- Muscle injury due to:
  - Severe arterial vasoconstriction – ischemia
  - Inhibition of reuptake of catecholamines at alpha adrenergic receptors
    - ↑ intracellular Ca
Alcoholic Myopathy
Alcohol Effects on Striated Muscle

- Neuropathy more common
- Cardiomyopathy common
- Chronic alcoholic myopathy
- Acute hypokalemic myopathy
- Acute necrotizing myopathy
Alcoholic Acute Necrotizing Myopathy

- Intense binge drinking, several days
- Clinical
  - Myalgia
  - Cramping
  - Swelling
  - Weakness
  - ↑ CK
- Wide spread muscle fiber necrosis
- Multifactoral
Alcoholic Acute Necrotizing Myopathy

- Found down
- Unconscious for hours
- Muscle compression
- Compartment syndromes
- Other drugs of abuse
Acute Kidney Injury in Rhabdomyolysis

- Occurs in 15% - 33% or more
- Myoglobin & hemoglobin are the culprits
  - Mechanical injury to tubules
  - Toxic effect of free iron on tubules
  - Hypovolemia
- AKI correlates with severity of rhabdomyolysis
  - Rare if CK < 20K
AKI Correlates with Severity of Rhabdomyolysis

**FIGURE 1.** Correlation between peak serum creatine kinase and serum creatinine.
# Rhabdomyolysis in the Hospital*

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Poly / Dermatomyositis

- The ANA positive diseases
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Sjogren’s syndrome
  - Scleroderma
  - Poly / Dermatomyositis
Clinical Features

- Symmetrical proximal muscle weakness
- Elevated muscle enzymes
  - CPK, aldolase, transaminases, LDH
- Myopathic EMG abnormalities
- Typical changes on muscle biopsy
- Typical rash of dermatomyositis
Heliotrope Rash

**Heliotrope rash**

Violaceous discoloration and puffiness of the eye lids
<table>
<thead>
<tr>
<th>Lesion Steps</th>
<th>EMG</th>
<th>Normal</th>
<th>Neurogenic Lesion</th>
<th>Myogenic Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertional Activity</td>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Spontaneous Activity</td>
<td>Fibrillation</td>
<td>Positive Wave</td>
<td>Fibrillation</td>
<td>Positive Wave</td>
</tr>
<tr>
<td>Motor Unit Potential</td>
<td>0.5-1.0 mv</td>
<td>5-10 msec</td>
<td>Large Unit</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Limited Recruitment</td>
<td>Normal</td>
<td>Early Recruitment</td>
<td>Early Recruitment</td>
</tr>
<tr>
<td>Interference Pattern</td>
<td>Full</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Full</td>
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Pathology of PM / DM
The Elevated CK in the Clinic
Asymptomatic Elevation of CK

- Why did I order this test????????
Asymptomatic Elevation of CK

It may be normal*

- Redefining elevated CK as 1.5 time beyond Upper Limit of Normal
- Adjust for ethnicity and gender
  - White women – 325 IU/L
  - White men – 504 IU/L
  - Black women – 621 IU/L
  - Black men – 1,200 IU/L

*European Academy of Neurology
Physical Activity Raises CK

- CK levels rise after heavy exercise or heavy manual labor
  - The P90X exercise program
Physical Activity Raises CK

- CK levels rise more in those who are couch potatoes
Physical Activity Raises CK

- CK levels rise more in those who are couch potatoes
  - If minimally elevated - Repeat 7 days after forced couch potato activity
Look for Non-neuromuscular Causes of elevated CK

- Take a careful history and review the chart for:
  - Illicit drugs & ETOH
  - Prescription drugs
- Order TSH/Free T4
- Macro CK
  - 1% of population
  - Atypical high molecular weight mass with reduced clearance
  - CK electrophoresis required
Look for Neuromuscular Causes of elevated CK

- Consider more Invasive studies
  - EMG / NCT
  - Muscle Biopsy
- When to biopsy?
  - CK more than 3 times Upper Limit of Normal
  - Age less than 25
  - Exercise intolerance
  - Abnormal EMG
What is the Yield of Invasive Testing in Asymptomatic Hyper-CK-emia

- Likelihood of specific diagnosis is 28%
- Diagnoses
  - Muscular dystrophies
  - Rare metabolic myopathies
  - Rare noninflammatory myopathies
Idiopathic hyper-CK-emia*

- Defined as persistent elevation of CK despite:
  - No family history of neuromuscular disease
  - No clinical evidence of neuromuscular disease
  - Normal EMG, NCT and muscle biopsy

- 7 Year follow-up
  - 10% Malignancy
  - 10% Neuromuscular disorder
  - 80% No new condition

Thank You for Your Attention
Corticosteroid Myopathy

- Prox muscle weakness
- Normal muscle enzymes
- Normal EMG
- Type II fiber atrophy
He has been in the unit for 10 days and largely immobile...

Is there anything we can do to prevent ICU-related weakness?
Critical Illness
Myopathy/Polyneuropathy

Who?
- Critically ill ICU
- Mechanically ventilated > 7 days
- Risk factors
  - Sepsis
  - Multiorgan failure
  - SIRS
  - High dose steroids?
  - Neuromuscular blockers

Clinical Features
- Flaccid quadriplegia (proximal)
- Failure to wean from mechanical ventilation
- Facial muscle weakness
- Relative sparing of cranial nerves*
- Decreased DTRs*
- Loss of peripheral sensation*

*CIP only
Critical Illness
Myopathy/Polyneuropathy

**CIP**
- Reduced nerve excitability
- Axon degeneration
- Inactivation of sodium channels

**CIM**
- Selective loss of myosin
- Atrophy of type 2 > type 1 fibers
Critical Illness
Myopathy/Polyneuropathy

Clinical Evaluation

- Muscle strength testing*  
- Sensory examination*  
- CK usually ↑ in CIM  
- Electrodiagnostic testing*  
  - EMG  
    - Low motor amplitudes  
    - Fibrillations  
  - NCT  
    - Low motor and sensory amplitudes

*Require alert, cooperative patient
Critical Illness
Myopathy/Polyneuropathy
Management/Prognosis