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## Muscle

Robert L. Hall  
*Covance Laboratories, Inc.*

Holly Bender  
*Iowa State University, hbender@iastate.edu*

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### Abstract

Muscle diseases characterized by degeneration, necrosis, or inflammation with degeneration/necrosis may be detected with clinical chemistry techniques. The common feature of these conditions is disruption of muscle cell membranes and release of enzymes and cytoplasmic contents into surrounding blood and lymph. Muscular atrophy and neoplastic conditions not associated with cell membrane disruption usually do not cause changes in standard clinical chemistry tests.

### Disciplines

Veterinary Pathology and Pathobiology

### Comments

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Robert L. Hall, DVM, PhD  
Holly Bender, DVM, PhD

Muscle diseases characterized by degeneration, necrosis, or inflammation with degeneration/necrosis may be detected with clinical chemistry techniques. The common feature of these conditions is disruption of muscle cell membranes and release of enzymes and cytoplasmic contents into surrounding blood and lymph. Muscular atrophy and neoplastic conditions not associated with cell membrane disruption usually do not cause changes in standard clinical chemistry tests.

I. Serum enzymes of muscle origin

A. Creatine kinase (CK)

1. CK is critical to muscle energy production. CK makes adenosine triphosphate (ATP) available for muscle contraction by catalyzing the transfer of a high-energy phosphate bond from creatine phosphate to adenosine diphosphate (ADP). CK also catalyzes the reverse reaction when muscles are at rest. Muscle cells contain eight times more creatine phosphate than ATP, thereby providing a reservoir of high-energy phosphate bonds for contraction.
2. CK is primarily a cytosolic enzyme with highest activity in skeletal muscle, cardiac muscle, and brain. Liver has negligible CK activity.
3. CK is one of the most organ specific clinical enzymes, as most serum CK activity is of muscle origin.
4. CK is a dimeric enzyme with two subunits designated B for brain and M for muscle. Three principal isoenzyme types exist: CK-BB (CK<sub>1</sub>), CK-MB (CK<sub>2</sub>), and CK-MM (CK<sub>3</sub>).
  - a. CK isoenzymes can be separated electrophoretically, and the proportion of each determined. CK-BB is the most anodal.
  - b. CK isoenzymes may also be separated by species-specific immunological methods or by ion-exchange chromatography.
  - c. CK-BB is present in brain, peripheral nerves, cerebrospinal fluid, and viscera.
  - d. CK-MB is present in cardiac muscle with relatively low activity in other tissues.
  - e. CK-MM is present in both skeletal and cardiac muscle.
  - f. CK activity in serum is mostly CK-MM, followed by CK-BB, and very little, if any, CK-MB.
  - g. CK isoenzyme analysis has not been very informative in veterinary medicine and is rarely used in a clinical setting.
5. Erythrocytes contain very little CK, but enzymes and intermediates released from erythrocytes may affect assay reactions, causing falsely increased

activity when hemolysis is present. Hemolyzed serum specimens are unsatisfactory for determination of CK activity.

6. Dilution of serum samples to reduce CK activity to an acceptable range for measurement may paradoxically falsely increase enzymatic activity due to dilution of naturally occurring CK inhibitors.
7. Serum CK activity in healthy dogs varies with age and breed.
  - a. CK activity decreases with age; pups can have much higher CK activity than adult dogs.
  - b. Adult levels of CK activity are achieved by 7-12 months of age.
  - c. Small breeds of dogs tend to have higher activities.
8. Plasma CK half-life is short (< 3 hours in dogs, ~ 4 hours in cattle, < 2 hours in horses).
9. Specimens analyzed for CK activity should be processed quickly.
  - a. Reports vary concerning stability of CK activity in serum and plasma.
  - b. CK activity may diminish if a prolonged delay occurs between obtaining and analyzing the serum specimen (*e.g.*, transport via mail from the veterinary hospital to the laboratory).
  - c. If CK analysis must be delayed beyond 12 hours, serum or plasma should be frozen (-20°C) to minimize loss of activity.
  - d. Loss of activity can be partially reversed through the use of reducing agents in the assay system.
  - e. Serum CK activity is higher than plasma CK activity in the dog, and perhaps other species, due to release of CK from platelets during clot formation.

#### B. Aspartate aminotransferase (AST) (see Chapter 7)

1. AST catalyzes the reversible transamination of L-aspartate and 2-oxoglutarate to oxaloacetate and glutamate. Oxaloacetate can enter the Krebs cycle. The enzyme was previously known as serum glutamic oxaloacetic transaminase (SGOT).
2. AST has cytosolic and mitochondrial isoenzymes, and AST activity is present in almost all cells, including red blood cells.
3. Serum AST activity is tissue-nonspecific, but muscle and liver are the major sources.
4. Plasma AST half-life is < 12 hours in cats, ~12 hours in dogs, ~18 hours in swine, and probably longer in horses and cattle.
5. Plasma AST half-life is longer than plasma CK half-life.
6. AST is relatively stable at room, refrigerator, and freezer temperatures.
7. Separate serum or plasma from cells immediately as imperceptible hemolysis may falsely increase AST activity.

#### C. Alanine aminotransferase (ALT) (see Chapter 7)

1. ALT catalyzes the reversible transamination of L-alanine and 2-oxoglutarate to pyruvate and glutamate. Pyruvate can be used for gluconeogenesis or enter the Krebs cycle. The enzyme was previously known as serum glutamic pyruvic transaminase (SGPT).
2. ALT is primarily a cytosolic enzyme considered liver-specific in dog and cat; however, increases in ALT activity have been reported with muscle diseases

such as X-linked muscular dystrophy or toxic myopathies.

3. ALT has been used as a muscle-specific enzyme in large animals because hepatic ALT activity in large animals is very low. Increased activity has been reported in myopathies of lambs, pigs, and horses.
4. Plasma ALT half-life in dogs is considered ~2.5 days. Plasma ALT half-life is likely greater than that for AST or CK in most species.

#### D. Lactate dehydrogenase (LDH)

1. LDH is a cytosolic enzyme present in all cells, and therefore all tissues, that catalyzes the reversible conversion of L-lactate to pyruvate.
2. Muscle, liver, and erythrocytes are usually the sources of high LDH activity in serum.
3. LDH is less useful than CK and AST for determining muscle damage because it lacks tissue specificity and is significantly affected by even mild hemolysis.
4. LDH is a tetrameric enzyme made up of two subunits, H and M, to form five isoenzymes, LDH<sub>1</sub> (H<sub>4</sub>), LDH<sub>2</sub> (H<sub>3</sub>M<sub>1</sub>), LDH<sub>3</sub> (H<sub>2</sub>M<sub>2</sub>), LDH<sub>4</sub> (H<sub>1</sub>M<sub>3</sub>), and LDH<sub>5</sub> (M<sub>4</sub>). In general, isoenzymes with mostly H subunits (LDH<sub>1</sub> and LDH<sub>2</sub>) predominate in aerobic tissue and those with mostly M subunits predominate in anaerobic tissue.
  - a. LDH isoenzymes can be separated electrophoretically, and the proportion of each determined. LDH<sub>1</sub> (H<sub>4</sub>) is the most anodal.
  - b. LDH<sub>1</sub> (H<sub>4</sub>) is heat stable; LDH<sub>2-5</sub> are inactivated in serum when heated at 65° C for 30 minutes.
  - c. LDH<sub>1</sub> (H<sub>4</sub>) is the principal isoenzyme in cardiac muscle and kidney.
  - d. LDH<sub>5</sub> (M<sub>4</sub>) is the principal isoenzyme in skeletal muscle and erythrocytes.
  - e. Liver contains primarily LDH<sub>4</sub> and LDH<sub>5</sub> (H<sub>1</sub>M<sub>3</sub> and M<sub>4</sub>) in many species, but the liver isoenzyme profile for cattle and sheep is more similar to heart.
  - f. All tissues contain variable amounts of the five LDH isoenzymes, and even with electrophoretic separation, the tissue source of increased serum LDH activity is often uncertain.
5. Separate serum or plasma from cells immediately as imperceptible hemolysis may falsely increase LDH activity.
6. LDH is unstable at freezer temperatures (-20°C), more stable at refrigerator temperatures (4°C).
7. Plasma LDH half-life varies for each isoenzyme with LDH<sub>1</sub> (H<sub>4</sub>) being longest and LDH<sub>5</sub> (M<sub>4</sub>) being shortest.

#### E. Aldolase

1. Aldolase in muscle (also called aldolase A) is a cytosolic enzyme that catalyzes the cleaving of fructose-1,6-bisphosphate to form glyceraldehyde 3-phosphate and dihydroxyacetone phosphate in the glycolytic utilization of fructose for energy.
2. Aldolase has been used to investigate skeletal muscle disorders, but isoenzymes exist in multiple tissues, including liver and heart.
3. Aldolase is generally considered inferior to CK for diagnosis of skeletal muscle disorders because CK has better diagnostic sensitivity and greater

ease of measurement in the laboratory.

## II. Diagnostic significance of CK, AST, and LDH

A. Increased serum CK, AST and LDH activities occur with degenerative or necrotizing muscle injury. Diseases associated with increased serum activity of these enzymes are listed in Table 10.1.

1. CK is the most sensitive serum enzyme indicator of striated muscle damage.
  - a. CK is the enzyme of choice to detect skeletal muscle damage.
  - b. Serum CK activity increases within 4-6 hours after muscle injury and typically reaches maximum levels in 6-12 hours.
  - c. Serum CK activity returns to the reference interval within 48-72 hours once muscle injury abates.
  - d. Persistently high serum CK activity indicates continued muscle injury.
  - e. The magnitude of increased serum CK activity generally correlates with extent of muscle injury, but exceptions occur. Only marked (e.g., >5,000 IU/L) or moderate but persistent increases (e.g., >2000 IU/L) are considered clinically significant.
  - f. Minor increases of serum CK activity are considered more significant in cats because of smaller muscle mass and comparatively low CK activity in cat muscle. However, anorexic cats can exhibit increased serum CK activity in the absence of diseases directly affecting muscle.
2. Serum AST activity increases slower than serum activities of CK and LDH following muscle injury; increased serum AST activity may persist several days after muscle injury abates.
3. Serum LDH activity increases following muscle injury are less apparent than those for CK and AST and more difficult to assess because of the broad tissue distribution of LDH.

B. Serum CK and LDH isoenzymes have some tissue specificity.

1. Serum CK-MM and LDH5 (M4) activities increase in greater proportion following skeletal muscle injury.
2. Serum CK-MB and LDH1 (H4) activities increase in greater proportion following cardiac muscle injury. However, CK-MB has not proven effective for diagnosing equine cardiac muscle injury.
3. Serum LDH1 (H4) activity increases in hemolytic disease but also hemolyzed samples.
4. In general, determination of serum CK and LDH isoenzyme patterns have not proven valuable or practical for clinical veterinary medicine. Cardiac troponins are proving to be more sensitive, specific, and practical for assessing cardiac muscle injury.

C. Serum CK activity can be affected by minor muscle injuries unrelated to primary muscle disease.

1. Placement of electrodes for electromyography increases serum CK activity but usually not above the reference interval.
2. Intramuscular injections increase serum CK activity. Irritating drugs (e.g., ketamine) or drug vehicles can cause dramatic increases lasting up to 1 week.
3. Traumatic venipuncture, even in the absence of hemolysis, can increase

serum CK activity. Sample contamination with perivenous connective tissue or muscle can occur.

4. Strenuous exercise in dogs and horses increases serum CK and LDH activities.
  - a. Rarely more than three-fold baseline after light exercise.
  - b. Physical training minimizes post-exercise increases.
5. Animal shipping may cause increased serum CK activity.
- D. Cerebrospinal fluid (CSF) CK activity originates from the brain and may increase with central nervous system (CNS) disease.
  1. Increased CSF-CK activity does not affect serum CK activity.
  2. Increased serum CK activity associated with CNS disease likely originates from injury to muscle cells during convulsions (*e.g.*, involuntary muscle contractions or contusions) or prolonged recumbency.
- E. Increased serum LDH activity has been associated with canine lymphoma.
- F. Lymphoma in cattle is associated with high serum LDH activity in about 70% of affected animals.
  1. Serum LDH activities overlap between clinically healthy and affected cattle.
  2. Serum LDH activity is not elevated for cattle with persistent lymphocytosis.
- G. CK, AST, and LDH activities are used to diagnose skeletal muscle disease in birds.
  1. As in mammals, serum CK activity is the most muscle-specific indicator.
  2. Hemolysis markedly increases avian serum LDH activity.

### III. Other laboratory findings in muscle disease

#### A. Troponins

1. Troponins are globular proteins bound to tropomyosin that help modulate the interaction between actin and myosin within the myofibril of striated muscle.
  - a. Three troponin proteins form a regulatory complex: troponin I, troponin T, and troponin C.
  - b. Troponin I and T have genetically distinct cardiac isoforms and are therefore useful for evaluating cardiac muscle injury.
  - c. Cardiac troponins I and T (cTnI and cTnT) are considered the markers of choice for acute cardiac injury in humans, replacing CK-MB.
  - d. cTnI and cTnT are highly conserved in mammalian species and many human immunoassays cross-react with cardiac troponins in animals.
  - e. Many functional assay systems exist for cTnI. The cTnT assay is limited to one vendor and less available.
  - f. There is no clear diagnostic advantage measuring both cTnI and cTnT.
2. Cardiac troponins are released into blood by degenerating/necrotic cardiac muscle cells.
3. Serum cardiac troponin concentrations are normally very low, and increases are apparent within a few hours of cardiac muscle injury.
4. Cardiac troponins have short half-lives (hours) so serum levels decrease quickly (1 or 2 days) unless cardiac muscle injury is ongoing.
5. Increased serum cardiac troponin concentrations have also been observed with strenuous exercise in horses and renal failure.

#### B. Natriuretic peptides

1. Two natriuretic peptides, atrial or A-type (ANP) and brain or B-type (BNP) have been studied as markers for cardiac muscle function/dysfunction.
2. Natriuretic peptides are released as prohormones from cardiac muscle in response to mechanical stress or cardiac muscle stretching, most often due to increased pressure.
3. The prohormones are cleaved into inactive N-terminal fragments (NTproANP or NTproBNP) and active C-terminal fragments (ANP and BNP).
4. Active ANP and BNP contribute to cardiovascular homeostasis by inhibiting the renin-angiotensin-aldosterone system, promoting vasodilatation, increasing natriuresis and diuresis, and decreasing arterial blood pressure.
5. Assays have been developed for the inactive N-terminal fragments and active C-terminal fragments.
  - a. BNP and NTproBNP are used in human medicine as sensitive but nonspecific markers for congestive heart failure.
  - b. Human BNP and NTproBNP assays do not cross-react well with animal peptides so development of species-specific assays has limited use of these markers until recently.
  - c. Half-lives for the inactive active fragments may be longer than those for active fragments, making the inactive fragments (NTproANP and NTproBNP) more attractive as potential markers of heart disease.

#### C. Myoglobin

1. Myoglobin is a heme protein responsible for transporting and storing oxygen within muscle cells. Myoglobin is normally absent in serum.
2. Myoglobin is considered a specific and sensitive indicator of muscle necrosis.
  - a. Myoglobin released from muscle enters blood immediately.
  - b. CK and AST first enter lymph, delaying increased serum activity.
  - c. Serum myoglobin falls rapidly once muscle injury abates.
3. Myoglobin is a low molecular weight monomer that, unlike hemoglobin, does not bind significantly to plasma proteins.
4. Myoglobin readily passes through the glomerulus, and plasma may not become discolored.
5. Both myoglobin and hemoglobin cause a positive urine occult blood reaction on urinalysis test strips (see Chapter 9) and pink to red to brown urine depending on concentration and degradation/oxidation.
  - a. An ammonium sulfate precipitation test to differentiate myoglobin from hemoglobin is unreliable (in theory, hemoglobin precipitates in an 80% ammonium sulfate solution, but myoglobin does not.)
  - b. Myoglobinuria is typically associated with other evidence of muscle injury, normal plasma color, and normal hematocrit.
  - c. Hemoglobinuria is typically associated with other evidence of hemolysis (e.g., low hematocrit), pink to red plasma, and no supporting evidence for muscle injury.
6. Myoglobin can be measured in serum or urine by a variety of immunoassays but they are used infrequently in clinical veterinary medicine.

#### D. Potassium

1. Intracellular fluid contains much more potassium than extracellular fluid.

2. Degeneration or necrosis of a large muscle mass may release enough potassium to cause hyperkalemia.
    - a. Correlation between hyperkalemia and increased muscle serum enzyme activity may be poor.
    - b. Hyperkalemia is more commonly associated with disorders of acid-base and electrolyte balance (see Chapter 5).
  3. Hyperkalemic periodic paralysis in Quarter horses is due to skeletal muscle sodium channel defects and often results in hyperkalemia.
    - a. Hyperkalemia is present during or immediately following clinical signs of disease (*e.g.*, muscle fasciculations, collapse) but not between episodes.
    - b. Serum CK activity may be mildly increased or within the reference interval.
  4. Hypokalemic polymyopathy may occur in cats with chronic renal failure or fed acidifying diets. Hypokalemia and increased serum CK activity are typical.
- E. Lactate (see Chapters 5 and 6)
1. Lactate is a byproduct of anaerobic glycolysis produced primarily by skeletal muscle, erythrocytes, brain, skin, and renal medulla.
  2. Blood lactate concentration reflects a balance between lactate production, metabolism by the liver (used for gluconeogenesis), and elimination in urine.
  3. Plasma lactate increases markedly after exercise in dogs with exercise-induced mitochondrial and lipid storage myopathies and Labrador Retrievers with hereditary myopathy.
  4. Meticulous sample acquisition and handling are essential for lactate analysis in whole blood or plasma.
    - a. Blood should be collected into tubes containing sodium fluoride and potassium oxalate, chilled, and centrifuged within 15 minutes. Fluoride inhibits anaerobic glycolysis and lactate production by erythrocytes.
    - b. Blood lactate can increase if the patient struggles during venipuncture (muscle activity) or if the vein is held off for a prolonged period (venous stasis and local hypoxia).
    - c. Blood lactate can also increase after a meal.
- F. Dystrophin and muscular dystrophy
1. Dystrophin is a cytoplasmic cytoskeleton protein that helps reinforce the sarcolemma and is part of a transmembrane protein complex that connects the muscle fiber to extracellular matrix.
  2. An X-linked inherited deficiency of dystrophin causing muscular dystrophy has been described in dogs and cats. The disorder is characterized by progressive muscle degeneration/necrosis, with hypertrophy of some muscle groups, and increased serum muscle enzyme activities.
  3. Dystrophin in muscle can be assessed by immunocytochemistry or immunoblot techniques.
  4. Cases of canine muscular dystrophy without dystrophin deficiency have been reported.
- G. Acetylcholine receptor antibodies and myasthenia gravis
1. Immunoprecipitation tests are used to detect circulating autoantibodies to

acetylcholine receptors in dogs and cats with immune-mediated myasthenia gravis.

2. Antibodies are absent in congenital (non-immune-mediated) myasthenia gravis.

H. Erythrocyte glutathione peroxidase activity and selenium deficiency

1. Decreased erythrocyte glutathione peroxidase activity is associated with selenium deficiency because selenium is a cofactor for the enzyme.

2. Serum vitamin E and selenium concentrations can also be measured.

I. Thiamine (vitamin B<sub>1</sub>) deficiency

1. Although infrequent to rare, thiamine deficiency may cause myocardial necrosis as well as CNS disease.

2. Increased serum CK activity may not be apparent.

Table 10.1 Diseases with high serum enzyme activity (CK, LDH, AST) of muscle origin (conditions with severe disruption of muscle cell membranes may present with myoglobinuria).

Inflammatory myopathies

Infectious

Bacterial

- Clostridial myositis
- Immune-mediated *Streptococcus equi* infections
- Leptospira icterohaemorrhagiae*
- Pasteurella multocida* myositis (cats)
- Staphylococcal and streptococcal myositis (dogs)

Parasitic

- Hepatozoon canis*
- Neospora caninum*
- Otobius megnini* (equine ear tick) associated muscle cramping
- Sarcocystis* spp.
- Toxoplasma gondii*
- Trypanosoma cruzi*

Viral

- Blue tongue
- Bovine ephemeral fever
- Bovine virus diarrhea
- Equine herpesvirus 1
- Equine infectious anemia
- Equine influenza virus A2
- Malignant catarrhal fever

Noninfectious

- Dermatomyositis (dogs)
- Eosinophilic myositis (dogs, cattle)
- Immune-mediated polymyositis (dogs and cats)
- Masticatory muscle myositis (dogs)

Traumatic myopathies

Accidental

- CNS disease (especially with seizures)
- Extreme exercise
- Post-operative
- Post-cardiac resuscitation
- Prolonged recumbency of large animals (downer animals)
- Intramuscular injections of irritating substances
- Gastrocnemius rupture (horses)
- Secondary to joint diseases
- Tourniquet syndrome

Degenerative myopathies

- Inherited or congenital

Lysosomal alpha-1,4-glucosidase deficiency (dogs, Shorthorn and Brahman cattle)

Debranching enzyme deficiency (dogs and foals)

Hyperkalemic periodic paralysis (horses)

Mitochondrial myopathy

Decreased cytochrome C oxidase (sheep dogs)

Respiratory chain defect (Arabian horses)

Muscular dystrophy (cattle, sheep, dogs, cats, chickens)

Myophosphorylase deficiency (cattle)

Myotonia (dogs, goats, horses)

Chloride-channel myotonia (goats)

Phosphofructokinase deficiency (English Springer Spaniels)

Lysosomal alpha-polysaccharide storage myopathy (horses)

Metabolic or unknown cause

Acquired equine motor neuron disease

Anesthesia (horses, swine)

Canine exertional rhabdomyolysis in racing greyhounds

Capture myopathy

Equine rhabdomyolysis (paralytic myoglobinuria, azoturia, Monday morning disease, tying-up syndrome)

Hyperadrenocorticism (dogs, horses)

Hypokalemic polymyopathy (cats)

Hypothyroidism (dogs, horses)

Malignant hyperthermia (swine, dogs)

Porcine stress syndrome

Toxic

Blister beetle toxicosis

Bracken fern (myocardial necrosis in horses)

*Cassia* sp. (coffee weed, castor bean, sicklepod) toxicosis (cattle, horse)

Copper poisoning (sheep)

Gossypol toxicosis (cattle, horse)

Horsetail (*Equisetum arvense*) (horses)

Ionophore-induced myocardial and skeletal muscle degeneration from monensin, lasalocid, maduramicin, or salinomycin (horse, ruminants, turkey)

Organophosphate toxicosis

Nutritional

Anorexia (cats)

Thiamine (vitamin B<sub>1</sub>) deficiency

Destruction of thiamine in heat (> 100°C) processed diets (dogs, cats)

Excessive thiaminase ingestion

Bracken fern (horses)

Horsetail (*Equisetum arvense*) (horses)

Vitamin E / selenium deficiency (calves, lambs, yearling cattle, foals, kids, swine, dogs, ostriches)

Ischemic myopathies

Aortic thrombosis (cats)  
Bacterial endocarditis  
Dirofilariasis  
Iliac thrombosis (horses, calves)

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