Facts About Metabolic Diseases of Muscle

What are metabolic diseases of muscle?

Metabolic diseases of muscle were first recognized in the second half of the 20th century. Each of these disorders is caused by a different genetic defect that impairs the body’s metabolism, the collection of chemical changes that occur within cells during normal functioning.

Specifically, the metabolic diseases of muscle interfere with chemical reactions involved in drawing energy from food. Normally, fuel molecules derived from food must be broken down further inside each cell before they can be used by the cells’ mitochondria to make the energy molecule ATP.

The mitochondria inside each cell could be called the cell’s “engines.” The metabolic muscle diseases are caused by problems in the way certain fuel molecules are processed before they enter the mitochondria, or by the inability to get fuel molecules into mitochondria.

Muscles require a lot of energy in the form of ATP to work properly. When energy levels become too low, muscle weakness and exercise intolerance with muscle pain or cramps may occur. In a few metabolic muscle disorders, symptoms aren’t caused so much by a lack of energy, but rather by unused fuel molecules that build up inside muscle cells. This buildup may damage cells, leading to chronic weakness.

Metabolic muscle diseases that have their onset in infancy tend to be the most severe, and some forms are fatal. Those that begin in childhood or adulthood tend to be less severe, and changes in diet and lifestyle can help most people with the milder forms adjust.

This fact sheet will cover 10 of the more common metabolic diseases of muscle (myopathies). Each one gets its name from the substance that's lacking:

- acid maltase deficiency (Pompe's disease)
- carnitine deficiency
- carnitine palmityl transferase deficiency
- debrancher enzyme deficiency (Cori's or Forbes' disease)
- lactate dehydrogenase deficiency
- myoadenylate deaminase deficiency
- phosphofructokinase deficiency (Tarui's disease)
- phosphoglycerate kinase deficiency
- phosphoglycerate mutase deficiency
- phosphorylase deficiency (McArdle's disease)
What causes Metabolic Diseases?

Nine of the diseases in this brochure are caused by defects in the enzymes that control chemical reactions used to break down food. Enzyme defects are caused by flaws in the genes that govern production of the enzymes.

The 10th disease, carnitine deficiency, is caused by lack of a small, naturally occurring molecule that's not an enzyme but is involved in metabolism.

Enzymes are special types of proteins that act like little machines on a microscopic assembly line, each performing a different function to break down food molecules into fuel. When one of the enzymes in the line is defective, the process goes more slowly or shuts down entirely.

Our bodies can use carbohydrates (starches and sugars), fats and protein for fuel. Defects in the cells' carbohydrate and fat-processing pathways usually lead to weakness in the voluntary muscles, but may also affect the heart, kidneys or liver. Although defects in protein-processing pathways can occur as well, these usually lead to different kinds of disorders that affect other organs.

A gene is a "recipe" or set of instructions for making a protein, such as an enzyme. A mistake (mutation) in the gene may cause the protein to be made incorrectly or not at all, leading to a deficiency in the amount of that enzyme. Genes are passed from parents to children. Therefore, gene defects can be inherited. (See "Does It Run in the Family?")

The metabolic muscle diseases aren't contagious, and they aren't caused by certain kinds of exercise or lack of exercise. However, exercise or fasting (not eating regularly) may bring on episodes of muscle weakness in a person who has the disease because of a genetic flaw.
What happens to someone with a Metabolic Disease?

**Exercise Intolerance**

The main symptom of most of the metabolic myopathies is difficulty performing some types of exercise, a situation known as exercise intolerance, in which the person becomes tired very easily.

The degree of exercise intolerance in the metabolic myopathies varies greatly between disorders and even from one individual to the next within a disorder. For instance, some people may run into trouble only when jogging, while others may have trouble after mild exertion such as walking across a parking lot or even blow-drying their hair. Each person must learn his activity limitations.

In general, people with defects in their carbohydrate-processing pathways tend to become very tired at the beginning of exercise but may experience a renewed feeling of energy after 10 or 15 minutes. On the other hand, those with carnitine palmitoyl transferase deficiency (CPT) may experience fatigue only after prolonged exercise.

A person with exercise intolerance may also experience painful muscle cramps and/or injury-induced pain during or after exercising.

The exercise-induced cramps (actually sharp contractions that may seem to temporarily "lock" the muscles) are especially noted in many of the disorders of carbohydrate metabolism and, rarely, in myoadenylate deaminase deficiency. The injury-induced pain is caused by acute muscle breakdown, a process called rhabdomyolysis, which may occur in any metabolic muscle disorder and is particularly noted in CPT.

Episodes of rhabdomyolysis usually occur when a person with a metabolic myopathy "overdoes it" (sometimes unknowingly). These episodes, often described as "severe muscle pain," may occur during exercise or several hours afterward. In those with carbohydrate-processing disorders, rhabdomyolysis may be triggered by aerobic exercise (such as running or jumping) or isometric exercise (like pushing or pulling heavy objects, squatting or standing on tiptoes). In people with CPT, rhabdomyolysis is usually brought on by prolonged, moderate exercise, especially if an affected person exercises without eating. In CPT, rhabdomyolysis may also be triggered by illness, cold, fasting, stress or menstruation.

Because rhabdomyolysis is painful and can cause extensive kidney damage, many people with metabolic muscle diseases try to avoid triggering these episodes by modifying their physical activities or diet.

**Muscle Weakness**

In acid maltase deficiency, carnitine deficiency and debrancher enzyme deficiency, progressive muscle weakness, rather than exercise intolerance, is the primary symptom. Over time, people with acid maltase deficiency or debrancher enzyme deficiency may eventually need a wheelchair to get around and, as respiratory muscles weaken, may require ventilatory assistance to provide extra oxygen at night. All three of these disorders may be associated with heart problems.
It's important to realize that, although the metabolic muscle diseases characterized by exercise intolerance aren't generally prone to muscle weakness, some chronic or permanent weakness can develop in response to repeated episodes of rhabdomyolysis and to the normal loss of strength that occurs with aging. The degree of muscle weakness that develops in these disorders is extremely variable and may depend on such factors as genetic background and the number of episodes of rhabdomyolysis experienced. The diseases involving exercise intolerance don't usually progress to the degree that a wheelchair or any other mechanical assistance is needed.

**Special issues in Metabolic Disorders**

**Myoglobinuria:** Myoglobinuria refers to rust-colored urine caused by the presence of myoglobin (a muscle protein). When overexertion triggers acute muscle breakdown (rhabdomyolysis), muscle proteins like creatine kinase and myoglobin are released into the blood and ultimately appear in the urine. Myoglobinuria can cause severe kidney damage if untreated. Incidences of myoglobinuria should be dealt with as emergencies and may require intravenous fluids to avoid renal failure.

**Emergencies:** The metabolic muscle diseases are so rare that emergency room staffs are frequently unfamiliar with them. As a result, they may not treat episodes properly (with fluids and pain medications) or may give the patient food or anesthesia that could trigger further problems. People with these disorders may want to consider carrying a treatment "protocol" listing their doctor's phone number, the patient's current medications and dietary requirements, and guidelines for handling emergency situations. A MedicAlert bracelet can also be worn.

**Anaesthesia:** People with metabolic muscle disorders may be at higher risk for a potentially fatal reaction to certain common general anaesthetics (typically combinations of halothane and succinylcholine). This reaction, called malignant hyperthermia, can be avoided in planned surgeries by using lower-risk anaesthetics. However, it's a good idea to wear a MedicAlert bracelet stating this susceptibility in case of an emergency.

**Cardiac Care:** People with debrancher enzyme deficiency, carnitine deficiency and acid maltase deficiency may develop significant heart problems. In the case of primary carnitine deficiency, the only symptom may be heart failure; however, this disorder responds well to carnitine supplementation. If you're at risk for cardiac problems, a cardiologist who's familiar with your disorder should monitor your heart function.

**Respiratory Care:** Acid maltase deficiency and debrancher enzyme deficiency tend to weaken the respiratory muscles, those that operate the lungs, meaning that a person with one of these disorders may require supplemental oxygen at some point. If you're at risk for respiratory problems, your breathing should be monitored regularly by a specialist. Also, be conscious of symptoms such as unusual shortness of breath on exertion or morning headaches that may indicate that your breathing is compromised.
How are the Metabolic Diseases of muscle treated?

For many people with metabolic muscle diseases, the only treatment needed is to understand what activities and situations tend to trigger attacks of rhabdomyolysis. A small percentage of adults with metabolic disorders may experience painful muscle cramps that have no obvious triggers; painkillers and meditation techniques may be effective under these circumstances.

In addition, some people with metabolic disorders have benefited from dietary changes. There's evidence that those with carbohydrate-processing problems may be helped by a high-protein diet, while those with difficulty processing fats may do well on a diet high in carbohydrates and low in fat. Carnitine supplements are usually given for carnitine deficiency and can be very effective in reversing heart failure in this disorder.

Please consult your doctor before undertaking any special diets. Your neurologist can help you design a specific plan suited for your metabolic disorder and your individual needs.

There's also emerging evidence that people with some carbohydrate-processing disorders, such as McArdle's disease, may benefit from light exercise. Researchers believe that people who are physically fit are better able to use alternative fuel sources to make energy. Because overexertion can trigger muscle breakdown, you should only undertake an exercise program under the supervision of a doctor who's familiar with your disorder.

It's unclear whether regular exercise is beneficial in the fat-metabolizing disorders, such as carnitine palmityl transferase deficiency. Note that because of their rarity, the characteristics of several of these diseases aren't known well.

Enzyme replacement therapy has recently become available for acid maltase deficiency.
What are the symptoms and characteristics of each type of disease?

### Carbohydrate-Processing Disorders
These disorders affect the breakdown of glycogen or glucose (complex and simple carbohydrates) and are also called glycogenosis disorders.

#### Acid Maltase Deficiency
- **Also called:** Glycogenosis type 2, Pompe's disease (infantile form), lysosomal storage disease
- **Onset:** Infancy to adulthood
- **Inheritance:** Autosomal recessive
- **Symptoms:** Causes slowly progressive weakness, especially of the respiratory muscles and those of the hips, upper legs, shoulders and upper arms. Enlargement of the tongue occurs in the infantile form, but rarely in the older forms. Cardiac involvement may occur in the childhood form, but is less common in adults. The childhood and adult-onset forms are less severe than the infantile form, but may require use of mechanical ventilation for breathing support as the disease progresses. The infantile form of Pompe’s disease often leads to death by age 2. An infant with this condition usually requires mechanical ventilation and a feeding tube to help with nourishment. If your infant's condition has been diagnosed as Pompe's disease, your neuromuscular doctor will keep you abreast of ongoing clinical trials for the disease and work with you to make the best decisions for care.

#### Debrancher Enzyme Deficiency
- **Also called:** Cori's or Forbes' disease, glycogenosis type 3
- **Onset:** Childhood to adulthood
- **Inheritance:** Autosomal recessive
- **Symptoms:** Principally affects the liver, causing swelling of the liver, slowing of growth, low blood sugar levels and, sometimes, seizures. In children, these symptoms often improve around puberty. Muscle weakness may develop later in life, and is most pronounced in the muscles of the forearms, hands, lower legs and feet. Weakness is often accompanied by loss of muscle bulk. The heart can be affected as well, and heart function should be monitored closely.

#### Phosphorylase Deficiency
- **Also called:** Myophosphorylase deficiency, McArdle's disease, glycogenosis type 5
- **Onset:** Childhood to adulthood
- **Inheritance:** Autosomal recessive
- **Symptoms:** Causes exercise intolerance, cramps, muscle pain and weakness shortly after the beginning of exercise. A person with this disorder may tolerate light-to-moderate exercise such as walking on level ground, but strenuous exercise will usually bring on symptoms
quickly. Resting may lead to a "second wind," in which activity is then better tolerated. Isometric exercises that require strength, such as lifting heavy objects, squatting or standing on tiptoe, also may cause muscle damage.

The symptoms of McArdle's disease vary in severity among people and even within the same person from day to day. Symptoms usually don't persist between attacks, although fixed weakness later in life is possible.

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<thead>
<tr>
<th>Phosphofructokinase Deficiency</th>
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<tr>
<td><strong>Also called:</strong> Glycogenosis type 7, Tarui's disease</td>
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<tr>
<td><strong>Onset:</strong> Childhood to adulthood</td>
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<tr>
<td><strong>Inheritance:</strong> Autosomal recessive</td>
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<tr>
<td><strong>Symptoms:</strong> Causes exercise intolerance, with pain, cramps and, occasionally, myoglobinuria. Symptoms are very similar to those of phosphorylase deficiency, but people with this disorder are less likely to experience the &quot;second wind&quot; phenomenon. A carbohydrate meal typically worsens exercise capacity in this condition by lowering blood levels of fats, which are the major muscle energy fuels for those with the disorder. A partial deficiency of phosphofructokinase in the red blood cells results in the breakdown of those cells and an increase in blood levels of bilirubin, though the person usually experiences no symptoms.</td>
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<tr>
<th>Phosphoglycerate Kinase Deficiency</th>
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<tr>
<td><strong>Also called:</strong> Glycogenosis type 9</td>
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<tr>
<td><strong>Onset:</strong> Infancy to early adulthood</td>
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<tr>
<td><strong>Inheritance:</strong> X-linked recessive</td>
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<tr>
<td><strong>Symptoms:</strong> May cause anaemia, enlargement of the spleen, mental retardation and epilepsy. More rarely, weakness, exercise intolerance, muscle cramps and episodes of myoglobinuria also occur.</td>
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<tr>
<th>Phosphoglycerate Mutase Deficiency</th>
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<tr>
<td><strong>Also called:</strong> Glycogenosis type 10</td>
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<tr>
<td><strong>Onset:</strong> Childhood to early adulthood</td>
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<tr>
<td><strong>Inheritance:</strong> Autosomal recessive</td>
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<tr>
<td><strong>Symptoms:</strong> Causes exercise intolerance, cramps, muscle pain and, sometimes, myoglobinuria. Permanent weakness is rare.</td>
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<tr>
<th>Lactate Dehydrogenase Deficiency</th>
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<tr>
<td><strong>Also called:</strong> Glycogenosis type 11</td>
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<tr>
<td><strong>Onset:</strong> Early adulthood</td>
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<tr>
<td><strong>Inheritance:</strong> Autosomal recessive</td>
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Symptoms: Causes exercise intolerance and episodes of myoglobinuria. A skin rash is common, probably because skin cells need lactate dehydrogenase.

### Fat-Processing Disorders

#### Carnitine Deficiency

<table>
<thead>
<tr>
<th>Onset:</th>
<th>Childhood</th>
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<tr>
<td>Inheritance:</td>
<td>Autosomal recessive</td>
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<tr>
<td>Symptoms:</td>
<td>This slowly progressive disorder causes cardiac disease and muscle weakness in the hips, shoulders, and upper arms and legs. The neck and jaw muscles may also be weak. Carnitine deficiency may occur secondary to other metabolic diseases (secondary carnitine deficiency) or in response to a genetic mutation (gene defect) in the protein responsible for bringing carnitine into the cell (primary carnitine deficiency). Primary carnitine deficiency can often be treated successfully with carnitine supplements.</td>
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#### Carnitine Palmitoyl Transferase Deficiency

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<tr>
<th>Onset:</th>
<th>Childhood to early adulthood</th>
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<tr>
<td>Inheritance:</td>
<td>Autosomal recessive</td>
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<tr>
<td>Symptoms:</td>
<td>Symptoms are usually brought on by prolonged and intense exercise, especially in combination with fasting, but may not appear for several hours after activity stops. Short periods of exercise usually don’t provoke symptoms. Symptoms can also be brought on by illness, cold, stress or menstruation. This disorder causes muscle pain, stiffness and tenderness, while weakness is less common. Breakdown of muscle tissue during an attack can cause myoglobinuria.</td>
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#### Disorder Affecting ATP Recycling

#### Myoadenylate Deaminase Deficiency

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<th>Onset:</th>
<th>Adulthood</th>
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<tr>
<td>Inheritance:</td>
<td>Autosomal recessive</td>
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<tr>
<td>Symptoms:</td>
<td>Interferes with the recycling of the major energy molecule of the cell (called ATP). It may cause exercise intolerance, cramps and muscle pain, although, in many cases, people with deficiencies in this enzyme may experience no symptoms.</td>
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How are the metabolic diseases of muscle diagnosed?

It's important to get an accurate diagnosis of a specific metabolic myopathy so the affected person can modify diet and exercise and monitor potentially serious disease effects. Because these diseases are rare, many people with metabolic disorders of muscle have spent some time trying to find out what caused their muscle weakness, myoglobinuria or other symptoms. The diagnostic process usually begins with a careful medical history, a physical exam and a neurological exam to test reflexes, strength and the distribution of weakness.

Several specialized tests are used to confirm a suspected diagnosis of metabolic disease:

- **Blood tests** can be used to detect the presence of certain chemicals in the blood that may indicate some metabolic diseases.

- **An exercise test** is used to monitor a person's response to intense or moderate exercise. Blood samples are taken during exercise for testing.

- **Electromyography (EMG)** uses small needle electrodes to measure the electrical currents in a muscle as it contracts. While an EMG can't definitively diagnose metabolic disease, it can be used to rule out a number of other types of neuromuscular disease that cause similar patterns of weakness.

- **A muscle biopsy** requires the removal of a small piece of muscle tissue for microscopic analysis. The procedure is done either surgically, with an incision to expose the target muscle, or with a needle. A skin biopsy is also sometimes performed.

- Other tests that may be needed include an **electrocardiogram** to test heart function, and **brain imaging studies** such as CT or MRI scans.

- **Genetic tests**, using a blood sample, can analyze the person's genes for particular defects that cause metabolic disease, but these tests often aren't necessary for diagnosis or for determining treatment.
Does it run in the family?

On being told they have a genetic disorder such as a metabolic muscle disease, bewildered patients often ask, “But it doesn't run in the family, so how could it be genetic?”

Metabolic myopathies can run in a family, even if only one person in the biological family has it. This is because of the ways in which genetic diseases are inherited.

Most of the metabolic diseases of muscle are inherited in an autosomal recessive pattern, meaning that a person needs two defective genes in order to have the disease. One copy is inherited from each parent, neither of whom would normally have symptoms.

Thus, the disease appears to have occurred “out of the blue,” but in reality, both parents may be carriers, silently harboring the genetic mutation (a flaw in the gene). Many parents have no idea they're carriers of a disease until they have a child who has the disease.

Other metabolic disorders have X-linked or autosomal dominant patterns of inheritance, each of which carries different risks for transmission to children. In some cases, a single disorder is associated with more than one pattern of inheritance.

Finally, metabolic disorders actually can occur "out of the blue" when a new mutation appears with a baby’s conception. These are called spontaneous mutations, and, after they occur, they can be passed on to the next generation.

The risk of passing on a metabolic myopathy to your children depends on many circumstances, including exactly which type of metabolic disease has been diagnosed.

A good way to find out more about these risks is to talk to your neuromuscular physician or ask to see a clinical geneticist or genetic counselor at the neuromuscular clinic. Also, see MDA’s fact sheet, "Genetics and Neuromuscular Diseases," or visit the Centre for Genetics Education website (www.genetics.com.au).
Search for a treatment or cure

Scientists are pursuing a number of promising leads in their quest to understand the causes of the metabolic diseases of muscle.

To date, scientists have isolated all of the genes involved in the metabolic myopathies described in this brochure, and their genetic codes have been unraveled, offering insight into how particular gene defects lead to disease. In addition, isolation of genes has allowed researchers to begin experiments with gene therapy, a potential cure for some metabolic diseases.

The knowledge researchers are obtaining about the mechanisms by which metabolic gene defects cause disease may lead to other strategies for prevention and treatment.

Targets now being pursued in research include:

- better diagnosis of metabolic diseases, to allow better identification of at-risk individuals and earlier treatment
- continued examination of the benefit of exercise in metabolic disease
- development of animal models of metabolic diseases, both to improve understanding of the diseases and to test possible treatments
- development of enzyme replacement therapy for an increasing number of diseases
- development of gene therapy for acid maltase deficiency and phosphorylase deficiency