

= Rhabdomyolysis =

Rhabdomyolysis is a condition in which damaged skeletal striated muscle breaks down rapidly . Breakdown products of damaged muscle cells are released into the bloodstream ; some of these , such as the protein myoglobin , are harmful to the kidneys and may lead to kidney failure . The severity of the symptoms , which may include muscle pains , vomiting , and confusion , depends on the extent of muscle damage and whether kidney failure develops . The muscle damage may be caused by physical factors (e.g. , crush injury , strenuous exercise , medications , drug abuse , and infections) . Some people have a hereditary muscle condition that increases the risk of rhabdomyolysis . The diagnosis is usually made with blood tests and urinalysis . The mainstay of treatment is generous quantities of intravenous fluids , but may include dialysis or hemofiltration in more severe cases .

Rhabdomyolysis and its complications are significant problems for those injured in disasters such as earthquakes and bombings . Relief efforts in areas struck by earthquakes often include medical teams with the skills and equipment to treat survivors with rhabdomyolysis . The disease was first described in the 20th century , and important discoveries as to its mechanism were made during the Blitz of London in 1941 . Horses may also develop rhabdomyolysis from a variety of causes .

= = Signs and symptoms = =

The symptoms of rhabdomyolysis depend on its severity and whether kidney failure develops . Milder forms may not cause any muscle symptoms , and the diagnosis is based on abnormal blood tests in the context of other problems . More severe rhabdomyolysis is characterized by muscle pain , tenderness , weakness and swelling of the affected muscles . If the swelling is very rapid , as may happen after someone is released from under a collapsed building , the movement of fluid from the bloodstream into damaged muscle may cause low blood pressure and shock . Other symptoms are nonspecific and result either from the consequences of muscle tissue breakdown or from the condition that originally led to the muscle breakdown . Release of the components of muscle tissue into the bloodstream causes electrolyte disturbances , which can lead to nausea , vomiting , confusion , coma or abnormal heart rate and rhythm . The urine may be dark , often described as " tea @-@ colored " , due to the presence of myoglobin . Damage to the kidneys may give rise to decreased or absent urine production , usually 12 to 24 hours after the initial muscle damage .

Swelling of damaged muscle occasionally leads to compartment syndrome ? compression of surrounding tissues , such as nerves and blood vessels , in the same fascial compartment ? leading to the loss of blood supply and damage or loss of function in the part (s) of the body supplied by these structures . Symptoms of this complication include pain or reduced sensation in the affected limb . A second recognized complication is disseminated intravascular coagulation (DIC) , a severe disruption in blood clotting that may lead to uncontrollable bleeding .

= = Causes = =

Any form of muscle damage of sufficient severity can cause rhabdomyolysis . Multiple causes can be present simultaneously in one person . Some have an underlying muscle condition , usually hereditary in nature , that makes them more prone to rhabdomyolysis .

= = = Common and important causes = = =

= = = Genetic predisposition = = =

Recurrent rhabdomyolysis may result from intrinsic muscle enzyme deficiencies , which are usually inherited and often appear during childhood . Many structural muscle diseases feature episodes of rhabdomyolysis that are triggered by exercise , general anesthesia or any of the other causes of

rhabdomyolysis listed above . Inherited muscle disorders and infections together cause the majority of rhabdomyolysis in children .

The following hereditary disorders of the muscle energy supply may cause recurrent and usually exertional rhabdomyolysis :

Glycolysis and glycogenolysis defects : McArdle 's disease , phosphofructokinase deficiency , glycogen storage diseases VIII , IX , X and XI

Lipid metabolism defects : carnitine palmitoyltransferase I and II deficiency , deficiency of subtypes of acyl CoA dehydrogenase (LCAD , SCAD , MCAD , VLCAD , 3 @-@ hydroxyacyl @-@ coenzyme A dehydrogenase deficiency) , thiolase deficiency

Mitochondrial myopathies : deficiency of succinate dehydrogenase , cytochrome c oxidase and coenzyme Q10

Others : glucose @-@ 6 @-@ phosphate dehydrogenase deficiency , myoadenylate deaminase deficiency and muscular dystrophies

= = Mechanism = =

Damage to skeletal muscle may take various forms . Crush and other physical injuries cause damage to muscle cells directly or interfere with blood supply , while non @-@ physical causes interfere with muscle cell metabolism . When damaged , muscle tissue rapidly fills with fluid from the bloodstream , including sodium ions . The swelling itself may lead to destruction of muscle cells , but those cells that survive are subject to various disruptions that lead to rise in intracellular calcium ions ; the accumulation of calcium outside the sarcoplasmic reticulum leads to continuous muscle contraction and depletion of ATP , the main carrier of energy in the cell . ATP depletion can itself lead to uncontrolled calcium influx . The persistent contraction of the muscle cell leads to breakdown of intracellular proteins and disintegration of the cell .

Neutrophil granulocytes ? the most abundant type of white blood cell ? enter the muscle tissue , producing an inflammatory reaction and releasing reactive oxygen species , particularly after crush injury . Crush syndrome may also cause reperfusion injury when blood flow to decompressed muscle is suddenly restored .

The swollen , inflamed muscle may directly compress structures in the same fascial compartment , causing compartment syndrome . The swelling may also further compromise blood supply into the area . Finally , destroyed muscle cells release potassium ions , phosphate ions , the heme @-@ containing protein myoglobin , the enzyme creatine kinase and uric acid (a breakdown product of purines from DNA) into the blood . Activation of the coagulation system may precipitate disseminated intravascular coagulation . High potassium levels may lead to potentially fatal disruptions in heart rhythm . Phosphate binds to calcium from the circulation , leading to low calcium levels in the blood .

Rhabdomyolysis may cause kidney failure by several mechanisms . The most important is the accumulation of myoglobin in the kidney tubules . Normally , the blood protein haptoglobin binds circulating myoglobin and other heme @-@ containing substances , but in rhabdomyolysis the quantity of myoglobin exceeds the binding capacity of haptoglobin . Myoglobinuria , the presence of myoglobin in the urine , occurs when the level in plasma exceeds 0 @. @ 5 ? 1 @. @ 5 mg / dl ; once plasma levels reach 100 mg / dl , the concentration in the urine becomes sufficient for it to be visibly discolored and corresponds with the destruction of about 200 grams of muscle . As the kidneys reabsorb more water from the filtrate , myoglobin interacts with Tamm ? Horsfall protein in the nephron to form casts (solid aggregates) that obstruct the normal flow of fluid ; the condition is worsened further by high levels of uric acid and acidification of the filtrate , which increase cast formation . Iron released from the heme generates reactive oxygen species , damaging the kidney cells . In addition to the myoglobinuria , two other mechanisms contribute to kidney impairment : low blood pressure leads to constriction of the blood vessels and therefore a relative lack of blood flow to the kidney , and finally uric acid may form crystals in the tubules of the kidneys , causing obstruction . Together , these processes lead to acute tubular necrosis , the destruction of the cells of tubules . Glomerular filtration rate falls and the kidney is unable to perform its normal excretory

functions . This causes disruption of electrolyte regulation , leading to a further rise in potassium levels , and interferes with vitamin D processing , further worsening the low calcium levels .

= = Diagnosis = =

A diagnosis of rhabdomyolysis may be suspected in anyone who has suffered trauma , crush injury or prolonged immobilization , but it may also be identified at a later stage due to deteriorating kidney function (abnormally raised or increasing creatinine and urea levels , falling urine output) or reddish @-@ brown discoloration of the urine .

= = = General investigations = = =

The most reliable test in the diagnosis of rhabdomyolysis is the level of creatine kinase (CK) in the blood . This enzyme is released by damaged muscle , and levels above 5 times the upper limit of normal (ULN) indicate rhabdomyolysis . Depending on the extent of the rhabdomyolysis , concentrations up to 100 @,@ 000 U / l are not unusual . CK concentrations rise steadily for 12 hours after the original muscle injury , remain elevated for 1 ? 3 days and then fall gradually . Initial and peak CK levels have a linear relationship with the risk of acute kidney failure : the higher the CK , the more likely it is that kidney damage will occur . There is no specific concentration of CK above which kidney impairment definitely occurs ; concentrations below 20 @,@ 000 U / l are unlikely to be associated with a risk of kidney impairment , unless there are other contributing risk factors . Mild rises without kidney impairment are referred to as " hyperCKemia " . Myoglobin has a short half @-@ life , and is therefore less useful as a diagnostic test in the later stages . Its detection in blood or urine is associated with a higher risk of kidney impairment . Despite this , use of urine myoglobin measurement is not supported by evidence as it lacks specificity and the research studying its utility is of poor quality .

Elevated concentrations of the enzyme lactate dehydrogenase (LDH) may be detected . Other markers of muscle damage , such as aldolase , troponin , carbonic anhydrase type 3 and fatty acid @-@ binding protein (FABP) , are mainly used in chronic muscle diseases . The transaminases , enzymes abundant in both liver and muscle tissue , are also usually increased ; this can lead to the condition being confused with acute liver injury , at least in the early stages . The incidence of actual acute liver injury is 25 % in people with non @-@ traumatic rhabdomyolysis ; the mechanism for this is uncertain .

High potassium levels tend to be a feature of severe rhabdomyolysis . Electrocardiography (ECG) may show whether the elevated potassium levels are affecting the conduction system of the heart , as suggested by the presence of T wave changes or broadening of the QRS complex . Low calcium levels may be present in the initial stage due to binding of free calcium to damaged muscle cells .

Urinalysis by urine test strip may reveal a positive result for " blood " , even though no red blood cells can be identified on microscopy of the urine ; this occurs because the reagent on the test strip reacts with myoglobin . The same phenomenon may happen in conditions that lead to hemolysis , the destruction of red blood cells ; in hemolysis the blood serum is also visibly discolored , while in rhabdomyolysis it is normal . If kidney damage has occurred , microscopy of the urine also reveals urinary casts that appear pigmented and granular .

= = = Complications = = =

Compartment syndrome is a clinical diagnosis , i.e. , no diagnostic test conclusively proves its presence or absence , but direct measurement of the pressure in a fascial compartment , and the difference between this pressure and the blood pressure , may be used to assess its severity . High pressures in the compartment and a small difference between compartment pressure and blood pressure indicate that the blood supply is likely to be insufficient , and that surgical intervention may be needed .

Disseminated intravascular coagulation , another complication of rhabdomyolysis and other forms

of critical illness , may be suspected on the basis of unexpected bleeding or abnormalities in hematological tests , such as a decreasing platelet count or prolongation of the prothrombin time . The diagnosis can be confirmed with standard blood tests for DIC , such as D @-@ dimer .

= = = Underlying disorders = = =

If an underlying muscle disease is suspected , for instance if there is no obvious explanation or there have been multiple episodes , it may be necessary to perform further investigations . During an attack , low levels of carnitine in the blood and high levels of acylcarnitine in blood and urine may indicate a lipid metabolism defect , but these abnormalities revert to normal during convalescence . Other tests may be used at that stage to demonstrate these disorders . Disorders of glycolysis can be detected by various means , including the measurement of lactate after exercise ; a failure of the lactate to rise may be indicative of a disorder in glycolysis , while an exaggerated response is typical of mitochondrial diseases . Electromyography (EMG) may show particular patterns in specific muscle diseases ; for instance , McArdle 's disease and phosphofructokinase deficiency show a phenomenon called cramp @-@ like contracture . There are genetic tests available for many of the hereditary muscle conditions that predispose to myoglobinuria and rhabdomyolysis .

Muscle biopsy can be useful if an episode of rhabdomyolysis is thought to be the result of an underlying muscle disorder . A biopsy sample taken during an episode is often uninformative , as it will show only evidence of cell death or may appear normal . Taking the sample is therefore delayed for several weeks or months . The histopathological appearance on the biopsy indicates the nature of the underlying disorder . For instance , mitochondrial diseases are characterized by ragged red fibers . Biopsy sites may be identified by medical imaging , such as magnetic resonance imaging , as the muscles may not be uniformly affected .

= = Treatment = =

The main goal of treatment is to treat shock and preserve kidney function . Initially this is done through the administration of generous amounts of intravenous fluids , usually isotonic saline (0 @. @ 9 % weight per volume sodium chloride solution) . In victims of crush syndrome , it is recommended to administer intravenous fluids even before they are extracted from collapsed structures . This will ensure sufficient circulating volume to deal with the muscle cell swelling (which typically commences when blood supply is restored) , and to prevent the deposition of myoglobin in the kidneys . Amounts of 6 to 12 liters over 24 hours are recommended . The rate of fluid administration may be altered to achieve a high urine output (200 ? 300 ml / h in adults) , unless there are other reasons why this might lead to complications , such as a history of heart failure .

While many sources recommend additional intravenous agents to reduce damage to the kidney , most of the evidence supporting this practice comes from animal studies , and is inconsistent and conflicting . Mannitol acts by osmosis to enhance urine production and is thought to prevent myoglobin deposition in the kidney , but its efficacy has not been shown in studies and there is a risk of worsening kidney function . The addition of bicarbonate to the intravenous fluids may alleviate acidosis (high acid level of the blood) and make the urine more alkaline to prevent cast formation in the kidneys ; evidence suggesting that bicarbonate has benefits above saline alone is limited , and it can worsen hypocalcemia by enhancing calcium and phosphate deposition in the tissues . If urine alkalinization is used , the pH of the urine is kept at 6 @. @ 5 or above . Furosemide , a loop diuretic , is often used to ensure sufficient urine production , but evidence that this prevents kidney failure is lacking .

= = = Electrolytes = = =

In the initial stages , electrolyte levels are often abnormal and require correction . High potassium levels can be life @-@ threatening , and respond to increased urine production and renal replacement therapy (see below) . Temporary measures include the administration of calcium to

protect against cardiac complications , insulin or salbutamol to redistribute potassium into cells , and infusions of bicarbonate solution .

Calcium levels initially tend to be low , but as the situation improves calcium is released from where it has precipitated with phosphate , and vitamin D production resumes , leading to hypercalcemia (abnormally high calcium levels) . This " overshoot " occurs in 20 ? 30 % of those people who have developed kidney failure .

= = = Acute kidney impairment = = =

Kidney dysfunction typically develops 1 ? 2 days after the initial muscle damage . If supportive treatment is inadequate to manage this , renal replacement therapy (RRT) may be required . RRT removes excess potassium , acid and phosphate that accumulate when the kidneys are unable to function normally and is required until kidney function is regained .

Three main modalities of RRT are available : hemodialysis , continuous hemofiltration and peritoneal dialysis . The former two require access to the bloodstream (a dialysis catheter) , while peritoneal dialysis is achieved by instilling fluid into the abdominal cavity and later draining it . Hemodialysis , which is normally done several times a week in chronic kidney disease , is often required on a daily basis in rhabdomyolysis . Its advantage over continuous hemofiltration is that one machine can be used multiple times a day , and that continuous administration of anticoagulant drugs is not necessary . Hemofiltration is more effective at removing large molecules from the bloodstream , such as myoglobin , but this does not seem to confer any particular benefit . Peritoneal dialysis may be difficult to administer in someone with severe abdominal injury , and it may be less effective than the other modalities .

= = = Other complications = = =

Compartment syndrome is treated with surgery to relieve the pressure inside the muscle compartment and reduce the risk of compression on blood vessels and nerves in that area . Fasciotomy is the incision of the affected compartment . Often , multiple incisions are made and left open until the swelling has reduced . At that point , the incisions are closed , often requiring debridement (removal of non @-@ viable tissue) and skin grafting in the process . The need for fasciotomy may be decreased if mannitol is used , as it can relieve muscle swelling directly .

Disseminated intravascular coagulation generally resolves when the underlying causes are treated , but supportive measures are often required . For instance , if the platelet count drops significantly and there is resultant bleeding , platelets may be administered .

= = Prognosis = =

The prognosis depends on the underlying cause and whether any complications occur . Rhabdomyolysis complicated by acute kidney impairment in patients with traumatic injury may have a mortality rate of 20 % . Admission to the intensive care unit is associated with a mortality of 22 % in the absence of acute kidney injury , and 59 % if kidney impairment occurs . Most people who have sustained kidney impairment due to rhabdomyolysis fully recover their kidney function .

= = Epidemiology = =

The exact incidence of rhabdomyolysis is difficult to establish , because different definitions have been used . In 1995 , hospitals in the U.S. reported 26 @, @ 000 cases of rhabdomyolysis . Up to 85 % of people with major traumatic injuries will experience some degree of rhabdomyolysis . Of those with rhabdomyolysis , 10 ? 50 % develop acute kidney injury . The risk is higher in people with a history of illicit drug use , alcohol misuse or trauma when compared to muscle diseases , and it is particularly high if multiple contributing factors occur together . Rhabdomyolysis accounts for 7 ? 10 % of all cases of acute kidney injury in the U.S.

Crush injuries are common in major disasters , but especially so in earthquakes . The aftermath of the 1988 Spitak earthquake prompted the establishment , in 1995 , of the Renal Disaster Relief Task Force , a working group of the International Society of Nephrology (a worldwide body of kidney experts) . Its volunteer doctors and nurses assisted for the first time in the 1999 Izmit earthquake in Turkey , where 462 people received dialysis , with positive results . Treatment units are generally established outside the immediate disaster area , as aftershocks could potentially injure or kill staff and make equipment unusable .

= = History = =

The Bible may contain an early account of rhabdomyolysis . In Numbers 11 : 4 - 6 , 31 - 33 , the Pentateuch says that the Jews demanded meat while traveling in the desert ; God sent quail in response to the complaints , and people ate large quantities of quail meat . A plague then broke out , killing numerous people . Rhabdomyolysis after consuming quail was described in more recent times and called coturnism (after Coturnix , the main quail genus) . Migrating quail consume large amounts of hemlock , a known cause of rhabdomyolysis .

In modern times , early reports from the 1908 Messina earthquake and World War I on kidney failure after injury were followed by studies by London physicians Eric Bywaters and Desmond Beall , working at the Royal Postgraduate Medical School and the National Institute for Medical Research , on four victims of The Blitz in 1941 . Myoglobin was demonstrated in the urine of victims by spectroscopy , and it was noted that the kidneys of victims resembled those of patients who had hemoglobinuria (hemoglobin rather than myoglobin being the cause of the kidney damage) . In 1944 Bywaters demonstrated experimentally that the kidney failure was mainly caused by myoglobin . Already during the war , teams of doctors traveled to bombed areas to provide medical support , chiefly with intravenous fluids , as dialysis was not yet available . The prognosis of acute kidney failure improved markedly when dialysis was added to supportive treatment , which first happened during the 1950 - 1953 Korean War .

= = Other animals = =

Rhabdomyolysis is recognized in horses . Horses can develop a number of muscle disorders , many of which may progress to rhabdomyolysis . Of these , some cause isolated attacks of rhabdomyolysis (e.g. , dietary deficiency in vitamin E and selenium , poisoning associated with pasture or agricultural poisons such as organophosphates) , while others predispose to exertional rhabdomyolysis (e.g. , the hereditary condition equine polysaccharide storage myopathy) . 5 - 10 % of thoroughbred horses and some standardbred horses suffer from the condition equine exertional rhabdomyolysis ; no specific cause has been identified , but an underlying muscle calcium regulation disorder is suspected .

Rhabdomyolysis affecting horses may also occur in outbreaks ; these have been reported in many European countries , and later in Canada , Australia , and the United States . It has been referred to as " atypical myopathy " or " myoglobinuria of unknown etiology " . No single cause has yet been found , but various mechanisms have been proposed , and a seasonal pattern has been observed . Very high creatine kinase levels are detected , and mortality from this condition is 89 % .

= = Etymology and pronunciation = =

The word rhabdomyolysis (/ ˈræbdəˈmaɪəˌlɪsɪs /) uses the combining forms rhabdo- + myo- + -lysis , yielding " striated muscle breakdown " .