

## Skeletal Muscle - Structure and Function (Salford).

Supporting notes.

The number in the left-hand column represents the slide to which the notes refer.

Slide No.	Notes.
1	Title Slide
2	<p>Skeletal muscle, as the name suggests, is usually associated with the skeletal system. It is also called striated muscle because of the presence of alternating dark and light bands along the length of its fibres, or voluntary muscle because it is subject to voluntary control (although involuntary, reflex contractions and spontaneous, automatic movements also occur).</p>
3	Need we say more ???
4	<p>Mature skeletal muscle cells are long and slender and may extend from one end of a muscle to the other, in some cases reaching a length of as great as 30cm. Since their length is much greater than their width, these cells are called fibres. Each muscle fibre is multinucleated and is surrounded by an electrically polarized membrane - the sarcolemma . The nuclei are usually located just under the sarcolemma.</p> <p>The entire muscle consists of a number of bundles of muscle fibres known as fasciculi. Surrounding each fibre and filling in the space between fibres within a fasciculus is a delicate connective tissue called the endomysium. Each fasciculus is bounded by a stronger connective tissue sheath, the perimysium, which in turn is continuous with a tough connective tissue, the epimysium, enveloping the whole muscle.</p> <p>Skeletal muscle has regular striations due to transverse alternating dark and light bands. Myofibrils are the contractile units of the fibre, and the striations arise from the arrangement</p>

	<p>of its subunits into thick and thin filaments. The thick filaments are composed largely of myosin, the thin filaments of three proteins - actin (the principal one), tropomyosin, and troponin. The dark, or A band of the myofibril corresponds to the thick filaments, overlapped on either end with thin filaments. The light, or I band, corresponds to the region where there are only thin filaments.</p> <p>The Z line, a narrow band in the central region of the I band represents a structure to which the thin filaments are attached, and the H zone, a lighter region, located in the central portion of each A band, into which the thin filaments do not penetrate. The area between two adjacent Z lines, the sarcomere, represents the repeating unit of a myofibril, each about 2.5 micrometers long in resting muscle.</p>
5	<p>The myofibrils are surrounded by structures made up of membranes in the form of vesicles and tubules. These structures form two systems:</p> <ul style="list-style-type: none"><li>T (for transverse) tubules, which are actually invaginations of the membrane of the muscle fibre.</li><li>The sarcoplasmic reticulum, consists of tubules running parallel to the myofibrils.</li></ul> <p>Each T tubule runs between a pair of sacs formed by fusion of the sarcoplasmic reticulum. These three transverse structures make up what is known as a triad. The triad is important functionally because, although there is no open continuity between the sarcoplasmic reticulum and the T tubules at the triad, the close association of the two systems at this site enables the T tubules to function as a conduit for transmission of the electrical impulse to the sarcoplasmic reticulum.</p> <p>The arrival of the electrical impulse activates the release from the sarcoplasmic reticulum of calcium, the triggering agent for muscle contraction.</p>

	<p><b>Excitation of Skeletal Muscle.</b></p> <p>Muscle fibres possess the property of being excitable. Any force affecting this excitability is called a stimulus, which, in muscle tissue, is usually conveyed by nerve fibres. The stimulus is an electrical impulse transmitted from a nerve fibre branch to a muscle fibre at a junctional region called the neuromuscular junction. At the junction a gap, the synaptic cleft, exists between a nerve branch terminal and a recess on the surface of the muscle fibre. A nerve impulse reaching the neuromuscular junction causes the release of acetylcholine, a neurotransmitter stored in synaptic vesicles within the nerve terminal. Acetylcholine crosses the gap and acts on the membrane of the muscle fibre, causing it to generate its own impulse, which travels along the muscle fibre in both directions at a rate of about 5 meters per second and is conducted to the sarcoplasmic reticulum via the T system.</p>
6	<p>A single nerve fibre innervates about 150 muscle fibres. All of these fibres and the single nerve fibre innervating them are called a motor unit because muscle fibres of the unit are always excited simultaneously and contract in unison. It is important to note that terminal divisions of a motor neuron are distributed throughout the muscle belly. Stimulation of a single motor unit, therefore, causes weak action in a broad area of muscle rather than a strong contraction at one specific point.</p> <p>Muscles controlling fine movements are characterized by the presence of a few muscle fibres in each motor unit, i.e. the ratio of nerve fibres to muscle fibres is high. For instance, each motor unit present in the ocular muscle contains less than 10 muscle fibres. On the other hand, gross movements, e.g. major limb muscles, may be governed by motor units containing 1000 or more muscle fibres.</p>
7	<p>The generally accepted conception of how muscle contracts is known as the 'sliding filament model'. According to this model, the contraction is brought about by the sliding of the thin filaments at each end of a sarcomere toward each other between the stationary thick filaments. This draws the Z lines closer together,</p>

	<p>shortening the sarcomere.</p> <p>As a sarcomere shortens, the I band of each myofibril (the region containing only thin filaments bisected by a Z line) narrows as the thin filaments move toward the centre of the sarcomere, while the A band (representing the length of the thick filaments) is unaltered.</p>
8	No additional notes
9	<p>Myosin (thick) filaments have a globular head and linear tail. They can be split into two subunits. One, called heavy meromyosin, contains the globular head and a linear tail section; the other, called light meromyosin, is an all-linear tail segment. The head of heavy meromyosin can combine with actin, and contains ATP-splitting enzymes. The linear light meromyosin subunits have a self-combining property (they stick together).</p> <p>Thick filaments are assembled by tail-to-tail aggregation of myosin molecules so that in each half of the filaments the heads, which form the ends of the cross-bridges, face opposite directions . This built-in directionality explains how thin filaments at opposite ends of a sarcomere can be pulled inward toward the centre of the thick filaments.</p>
10	<p>The thin filament is an assembly of three proteins: actin, the principal one, tropomyosin, troponin.</p> <p>Actin consists of two strands of spherical molecules coiled around one another. On the surface of each strand of actin is a filamentous tropomyosin.</p> <p>Troponin is a complex of three subunits positioned at regular intervals along the thin filament. The largest subunit of troponin, designated Tn-T, binds to tropomyosin. Another, Tn-I (the inhibitory subunit), reversibly binds to actin; when bound, the troponin complex, linked to tropomyosin and actin, seems to act as a latch, holding tropomyosin in a position that blocks the myosin</p>

	<p>binding site on actin.</p> <p>The latch is released when calcium binds the smallest subunit, Tn-C, causing the troponin complex to undergo a change in conformation which breaks the link between the Tn-I subunit and actin.</p>
11	<p>The sequence of events leading to the contraction:</p> <ol style="list-style-type: none"> <li>1. The electrical impulse travelling along the membrane of a muscle fibre reaches the sarcoplasmic reticulum via the T tubules.</li> <li>2. Stimulates the release of calcium, which combines with the Tn-C subunits and induces conformational change of the troponin molecules.</li> <li>3. Tropomyosin moves away from the myosin binding sites on actin, and the myosin heads, charged with ATP, combine with actin.</li> <li>4. When actin and myosin interact, the energized myosin complex breaks down, providing the energy for the propulsive force (probably a swivelling of the myosin heads) for pulling the thin filaments toward the centre of the sarcomere.</li> <li>5. Successive cycles, involving binding of ATP to myosin heads, detachment of myosin heads from actin, and reattachment in a new position on actin, followed by the power stroke that moves the thin filaments, result in the continued sliding of the thin filaments.</li> <li>6. Contraction ends when calcium returns to the sarcoplasmic reticulum.</li> </ol>
12	<p><b>Rigor Complex.</b></p> <p>The detachment of the myosin cross-bridges from actin after ATP is split can take place only after a new ATP binds to the myosin beads. The low energy complex between actin and myosin without bound ATP is called a rigor complex. Rigor complexes, unlike active actin-myosin complexes, can form in either the absence or presence of calcium.</p> <p>The depletion of ATP after death results in the formation of rigor complexes and accounts for the development of rigor mortis.</p>

	<p>Muscle also has its own glycogen stores. When exercise is strenuous, a point is reached when the oxygen supply is insufficient to meet the energy needs of active muscle. When this occurs (estimated as an energy expenditure of approximately 220 calories per minute per kilogram of body weight), glycolysis provides a sizable portion of the energy needs.</p> <p>Far less ATP is produced by the anaerobic process than by the aerobic process. The lactic acid produced during glycolysis is released from the muscles into the blood stream to be subsequently taken up by the liver (where it is converted to glucose and glycogen).</p>
13	<p>ATP is a direct source of energy for muscular contraction. ATP is synthesised during the aerobic breakdown of glucose and the fatty acid component of fat, to carbon dioxide and water. During glycolysis, the anaerobic breakdown of glucose (or glycogen) to lactic acid also produces ATP.</p> <p>ATP must be continuously resynthesised in muscle, since its reserves are very small. Muscle contains a small auxiliary source of high energy phosphate in the form of creatine phosphate.</p> <p>Creatine phosphate can be utilised during muscular contraction for the rapid re-synthesis of ATP by phosphate transfer to ADP. When muscle is at rest, the reverse reaction, phosphate transfer from ATP to creatine, rebuilds the reserves of creatine phosphate.</p> <p>Oxygen debt - defined as the amount of oxygen consumed above the resting level during the post-exercise period. If the exercise was moderate, the oxygen consumption returns to normal within a few minutes and the debt is small.</p> <p>Oxidation of fatty acids and glucose during this brief period replenishes the approximately half-depleted stores of ATP and creatine phosphate. Strenuous exercise results in a large oxygen debt, and the return to resting oxygen consumption is slow</p>

	<p>(requiring an hour or more). The large debt is incurred because a portion of the glycogen stores as well as possibly all of the stores of ATP and creatine phosphate must be replaced. Furthermore, glycolysis continues during the recovery period in order to contribute to the replenishment of ATP and creatine phosphate. Since the glycogen used during this period must also be replaced, this adds to the debt.</p>
14	<p>Traditionally, certain muscles have been described on the basis of appearance and speed of contraction as either; red, slow-contracting, and having a preponderance of small-diameter reddish fibres, or white, fast-contracting, and having a preponderance of large-diameter, pale fibres.</p> <p>Most muscles fall somewhere between the two extremes, and the proportions of the two basic fibre types vary considerably from one muscle to another.</p> <p>Motor units of a muscle can be distinguished on the basis of contraction times and other characteristics. Fibres of fast contracting units, which also fatigue rapidly, are of large diameter, have few capillaries and mitochondria, and contain an abundance of glycogen. Their dependence upon anaerobic glycolysis could explain their rapid fatigue.</p> <p>Large-diameter fibres also have an extensive sarcoplasmic reticulum, allowing rapid release and uptake of large amounts of calcium ions, it is consistent with their faster contraction.</p> <p>Fibres of slow-contracting, fatigue resistant units have small diameters, a rich capillary supply, many mitochondria and little glycogen. This profile suggests a high capacity for aerobic energy pathways. Small-diameter fibres also contain large amounts of the oxygen carrying protein myoglobin. This characteristic and the presence of cytochromes in the abundant mitochondria, as well as the vascularity of these fibres, account for the description of small fibres as red, as distinguished from the large, white fibres.</p>

	<p>The fibres of a third group of motor units, described as fast-contracting and fatigue-resistant, are of variable diameter and liberally supplied with capillaries. Their glycogen and mitochondrial content suggests utilization of both aerobic and anaerobic pathways.</p>
15	<p>Dystrophies are a subgroup of myopathies characterised by muscle degeneration and regeneration. Clinically, muscular dystrophies are typically progressive, because the muscles' ability to regenerate is eventually lost, leading to progressive weakness, often leading to use of a wheelchair, and eventually death due to respiratory complications, eg duchenne muscular</p> <p>Myotonia is characterised by the slow relaxation of the muscles after voluntary contraction or electrical stimulation. Generally, repeated effort is needed to relax the muscles, and the condition improves after the muscles have warmed-up. However, prolonged, rigorous exercise may also trigger the condition. Individuals with the disorder may have trouble releasing their grip on objects or may have difficulty rising from a sitting position and a stiff, awkward gait. Symptoms of myotonia are more frequently experienced in women during pregnancy.</p> <p>Myotonia is not always a disease-related or abnormal phenomenon. Humans and other animals (such as the fainting goat) often display myotonia when placed in situations of extreme stress or fear; a resultant increase in 'fight-or-flight' hormones such as adrenaline and cortisol may cause increased muscle tension throughout the body. <i>Watch goat video.</i></p> <p>People suffering from disorders involving myotonia can have a life threatening reaction to certain anaesthetics, eg" Malignant Hyperthermia ". Anaesthesiologists cannot diagnose this condition until the patient is under anaesthetic so this condition is very life threatening</p> <p>The congenital myopathies do not show evidence for either a progressive dystrophic process (i.e., muscle death) or</p>

	<p>inflammation, but instead characteristic microscopic changes are seen in association with reduced contractile ability of the muscles.</p>
16	<p><b>Duchenne muscular dystrophy (DMD)</b> is a severe recessive X-linked form of muscular dystrophy that is characterized by rapid progression of muscle degeneration, eventually leading to loss in ambulation, paralysis, and death. This affliction affects one in 3500 males, making it the most prevalent of muscular dystrophies. In general, males are only afflicted, though females can be carriers.</p> <p>The disorder is caused by a mutation of a gene located X chromosome, coding for the protein dystrophin, an important structural component within muscle tissue.</p> <p>Symptoms usually appear in male children before age 6 and may be visible in early infancy. Progressive proximal muscle weakness of the legs and pelvis associated with a loss of muscle mass is observed first. Eventually this weakness spreads to the arms, neck, and other areas. Early signs may include enlargement of calf muscles, low endurance, and difficulties in standing unaided or inability to ascend staircases.</p> <p>As the condition progresses, muscle tissue experiences wasting and is eventually replaced by fat and fibrotic tissue. By age 10, braces may be required to aide in walking but most patients are wheelchair dependent by age 12.</p> <p>Later symptoms may include abnormal bone development leading to skeletal deformities, including curvature of the spine. Due to progressive deterioration of muscle, loss of movement occurs eventually leading to paralysis. Intellectual impairment may also be present but does not progressively worsen as the child ages. The average life expectancy for patients afflicted with DMD varies from early teens to mid 30s. There have been reports of DMD patients surviving past the age of 40 and even 50.</p> <p>A positive Gower's sign reflects the more severe impairment of</p>

	<p>the lower extremities muscles. The child helps himself to get up with upper extremities: first by rising to stand on his arms and knees, and then "walking" his hands up his legs to stand upright.</p> <p><b>Treatment</b> - There is no known cure for DMD although recent stem-cell research is promising in replacing damaged muscle tissue. Treatment is generally aimed at control of symptoms to maximize the quality of life, and include the following.</p> <ul style="list-style-type: none"> <li>• Corticosteroids increase energy and strength and defer severity of some symptoms.</li> <li>• Mild, non-jarring physical activity such as swimming is encouraged. Inactivity can worsen the muscle disease. Physical therapy is helpful to maintain muscle strength, flexibility, and function.</li> <li>• Orthopedic appliances (such as braces and wheelchairs) may improve mobility and the ability for self-care. Form-fitting removable leg braces that hold the ankle in place during sleep can defer the onset of contractures.</li> <li>• Appropriate respiratory support as the disease progresses is important</li> </ul> <p><b>Prognosis</b>- Duchenne muscular dystrophy eventually affects all voluntary muscles and involves the heart and breathing muscles in later stages. The life expectancy can range from the late teens to the age of 35, However there have been people with duchennes who made it to age 40 and beyond.</p> <p>Becker MD is a similar form, but much milder</p>
17	<p>A disorder of unknown cause in which connective tissue and muscle are replaced by bone. The more common type (myositis ossificans circumscripta), only one area is affected, with ossification noted following injury to the part. This usually occurs in the arm or thigh. And develops in 10% to 20% of thigh contusions.</p> <p>In the rare progressive type (myositis ossificans progressiva), group after group of muscles become ossified, until the individual</p>

is completely rigid. Breathing and swallowing become difficult, and fatal respiratory infections may occur.

The cause of myositis ossificans is unknown. It most commonly develops within a muscle that has sustained a severe contusion (bruise), usually from direct contact. The muscle is usually crushed between the underlying bone and an object (another player's helmet, a knee or elbow, or a ball).

**Common Signs and Symptoms**

- Pain, tenderness, swelling, and warmth of the injured extremity
- Feeling of fullness deep in the injured extremity
- Discoloration and bruising of the skin
- Restricted activity (stiffness of the joints) of the injured extremity, including loss of motion of the knee (thigh) or elbow (arm), depending on the area injured

**Treatment** - ice, and compression. Stretching, maintaining strength or muscle control of the injured extremity, and modifying activity help restore function to the extremity. These may help reduce the incidence of myositis ossificans. NSAIDs may also reduce the formation of bone of the haematoma (clot). Most people function well. Surgery to remove the bone of myositis ossificans is considered only if symptoms (pain) persist, loss of joint motion persists, or the bone is unusually large; it is done only after the bone is fully mature (at least 6 to 12 months after the injury).

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A common nonarticular rheumatic syndrome characterized by myalgia and multiple points of focal muscle tenderness to palpation (trigger points). Muscle pain is typically aggravated by inactivity or exposure to cold. This condition is often associated with general symptoms, such as sleep disturbances, fatigue, stiffness, headaches, and occasionally depression. There is significant overlap between fibromyalgia and the chronic fatigue syndrome. Fibromyalgia may arise as a primary or secondary

disease process. It is most frequent in females aged 20 to 50 years.

**Signs and symptoms** - The defining symptoms of fibromyalgia are chronic, widespread pain and allodynia. Other symptoms can include moderate to severe fatigue, needle-like tingling of the skin, muscle aches, prolonged muscle spasms, weakness in the limbs, nerve pain, functional bowel disturbances, and chronic sleep disturbances. Many patients experience cognitive dysfunction (known as "brain fog" or "fibrofog"), which may be characterized by impaired concentration.

Other symptoms often attributed to fibromyalgia that may possibly be due to a comorbid disorder include myofascial pain. Although fibromyalgia is classified based on the presence of chronic widespread pain, pain may also be localised in areas such as the shoulders, neck, low back, hips, or other areas. Many sufferers also experience varying degrees of facial pain and have high rates of comorbid TMJ disorder

Eye problems such as eye pain, sensitivity to light, blurred vision, and fluctuating visual clarity, can also be a symptom of the condition. They can become more or less tolerable throughout daily or yearly cycles; however, many people with fibromyalgia find that, at least some of the time, the condition prevents them from performing normal activities such as driving a car or walking up stairs. The disorder does not cause inflammation as is characteristic of rheumatoid arthritis, although some non-steroidal anti-inflammatory drugs may temporarily reduce pain symptoms in some patients. Their use, however, is limited, and often of little to no value in pain management.

There is still debate over what should be considered essential diagnostic criteria. The difficulty with diagnosing fibromyalgia is that, in most cases, laboratory testing appears normal and that many of the symptoms mimic those of other rheumatic conditions such as arthritis or osteoporosis.

	<p>The most widely accepted set of classification criteria for research purposes was elaborated in 1990 by the Multicenter Criteria Committee of the the American College of Rheumatology. These criteria, which are known informally as "the ACR 1990," define fibromyalgia according to the presence of the following criteria:</p> <ol style="list-style-type: none"> <li>1. A history of widespread pain lasting more than three months— affecting all four quadrants of the body, i.e., both sides, and above and below the waist.</li> <li>2. Tender points—there are 18 designated possible tender or trigger points (although a person with the disorder may feel pain in other areas as well). During diagnosis, four Kg of force is exerted at each of the 18 points; the patient must feel pain at 11 or more of these points for fibromyalgia to be considered. Four Kg of force is about the amount of pressure required to blanch the thumbnail when applying pressure.</li> </ol> <p>It should be noted that the number of tender points that may be active at any one time may vary with time and circumstance.</p>
19	No additional notes
20	No additional notes
21	No additional notes