

Structure, Function, and Physiology of Tendons and Muscles – A Review

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INTRODUCTION: The muscle-tendon-bone unit drives skeletal motion and maintenance of body posture. This movement and posture is conducted via muscle contractions that transmit force through tendons to bones (**Fig 1A**). Thus, tendons act as a "mechanical bridge" between muscles and bones and are responsible for holding muscle to bone. Skeletal muscles and tendons are soft, viscoelastic tissues. Skeletal muscles are more elastic than tendon, allowing greater deformation. Tendons have greater tensile strength than muscle, allowing muscles to transmit forces to bones without energy loss to tendon stretch. The muscle-tendon interface region is called the musculotendinous junction (MTJ) (**Fig 1B-C**) and is morphologically and compositionally specialized for force transmission [2].

Injuries to muscle and tendon tissues are either trauma or sports related, typically occurring near the MTJ in the extremities. If conservative approaches are unsuccessful, these injuries may be surgically addressed. Surgical interventions often result in permanent fibrous scarring with inferior mechanical properties as compared to native tendon and muscle [3]. Peritendinous scarring is a major complication of tendon repair surgeries [4, 5]. This complication often involves tangential muscle as a result of proximity to the repair and to the similar healing profiles of these tissues. Scarring can cause muscle weakness, pain, and can limit range of motion.

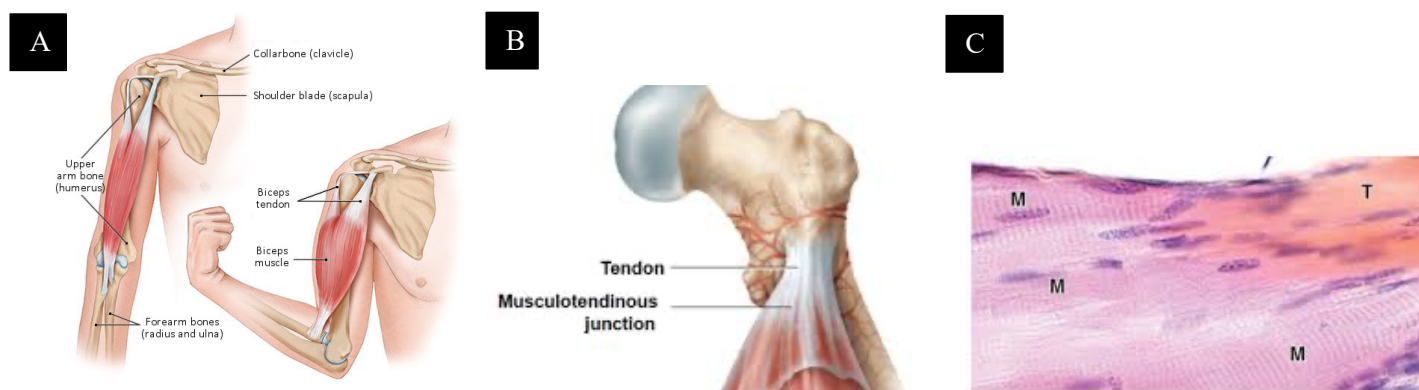


Fig 1. A) The skeletal muscle-tendon-bone unit that drives skeletal motion and maintenance of body posture; B) The musculotendinous junction (MTJ) illustrating the transition from tendon to muscle; C) Histological depiction of the MTJ where M denotes muscle tissue and T denotes tendon tissue.

CLASSIFICATION AND DISTRIBUTION OF TENDONS

Tendons are soft tissue structures interposed between muscles and bones, responsible for transmitting force from the generating muscle to the terminating bone, making movement possible. Healthy tendons are brilliant white in color and fibroelastic in texture. There are approximately 4,000 tendons in the human body, but the exact count depends on the person's size and muscle mass.

Tendons may vary considerably in shape and in the attachment to bone ranging from wide and flat tendons (rotator cuff, Achilles) to cylindrical (flexors, peroneal), fan-shaped (distal Biceps), and ribbon-shaped tendons (extensor). Muscles designed to create powerful, resistive forces, like the quadriceps and triceps brachii muscles, have short and broad tendons, while those that have to carry out subtle and delicate movements, like the finger flexors, have long and thin tendons. Cylindrical tendons respond equally to tensile loads with parallel collagen patterns while flat tendons can respond microanatomically in the form of

compression and shear forces as a result of longitudinal, oblique, and transverse collagen sequences [6].

Tendons may also be classified according to their anatomy as sheathed, synovial-coated (digital flexors) or as non-sheathed, paratenon-coated (Achilles).

CLASSIFICATION AND DISTRIBUTION OF SKELETAL MUSCLES

Skeletal muscles are soft tissue structures that generate the forces required to maintain an upright posture and to produce movement. Skeletal muscles also play important roles in physiological processes such as thermogenesis [7], metabolism of proteins and carbohydrates [8] and in the secretion of peptides for communication with other tissues [9-11].

The human body has over 600 muscles, representing the largest tissue mass in the body constituting 40-45% of the total body weight. Muscle mass is sensitive to factors such as nutritional status, hormonal balance, physical activity/exercise,

and injury or disease. Muscle is a composite structure consisting of muscle cells, organized networks of nerves and blood vessels, and an extracellular connective tissue matrix.

Skeletal muscles may be classified by shape or by the movement generated by contraction (flexors vs extensors, abductors vs adductors, pronators vs supinators, internal vs external rotators). The skeletal muscles fibers are divided into two main types: slow twitch or fast twitch muscles.

Type I, red, or slow twitch muscles are dense tissues with capillaries rich in myoglobin and mitochondria, which appears red in color. Slow twitch muscles can contract for a long time without effort. Type I muscles can sustain aerobic activity using carbohydrates and fats as fuel.

Type II, fast twitch muscles contract rapidly and with great force. Contraction is strong but short-lived. Fast twitch muscles are responsible for muscle-strength and mass increase after periods of weight training.

MUSCULOTENDINOUS JUNCTION (MTJ)

The musculotendinous junction (MTJ), a complex, specialized region located at the muscle-tendon interface, is the primary site of force transmission [2]. The MTJ constitutes a dynamic and functional integrated unit that transduces muscle contraction force to the skeletal system. Despite different embryologic origins, muscle and tendon morphogenesis occurs in close spatial and temporal association. Structurally, the MTJ consists of actin microfilaments, actin filament bundling proteins, intracellular proteins that link the actin filament bundles to the sarcolemma, transmembrane protein complexes that connect cytoskeletal elements to basement membrane components, and proteins that link the basement membrane to the collagen fibrillar matrix. The morphology of the MTJ interface between a muscle fiber and the tendinous connective tissue looks like an adhesive joint [12, 13] (**Fig 2**). The tendinous collagen fibrils insert into the myocyte processes that transmits the forces to the collagen fibrils [14, 15]. In this region, the muscle increases the contact area with the tendon via deep interdigitations of the cell membrane, allowing the junction to resist to muscle contraction [2] to prevent fracture failure at the joint [12]. This resistance is so great that in situ muscle failure is not associated with a separation at the interface between muscle and tendon, but rather in the body of muscle cells, just proximal to the structurally defined MTJ [2].

MTJ ECM enables linking of muscle to tendon, plays a key role in transmission of force, and maintains tissue structure [1, 16]. Specifically, ECM proteins (e.g. collagens, laminins, thrombospondins) guides myofibers to attachment sites, mediates signaling between tenocytes and muscles, regulates MTJ maturation, and maintains tendons in response to mechanical force [17, 18].

STRUCTURE

The structure of tendons and muscles makes them uniquely suited to their respective roles. Similar to other soft tissues, tendons and skeletal muscles have a hierarchical structure (**Fig**

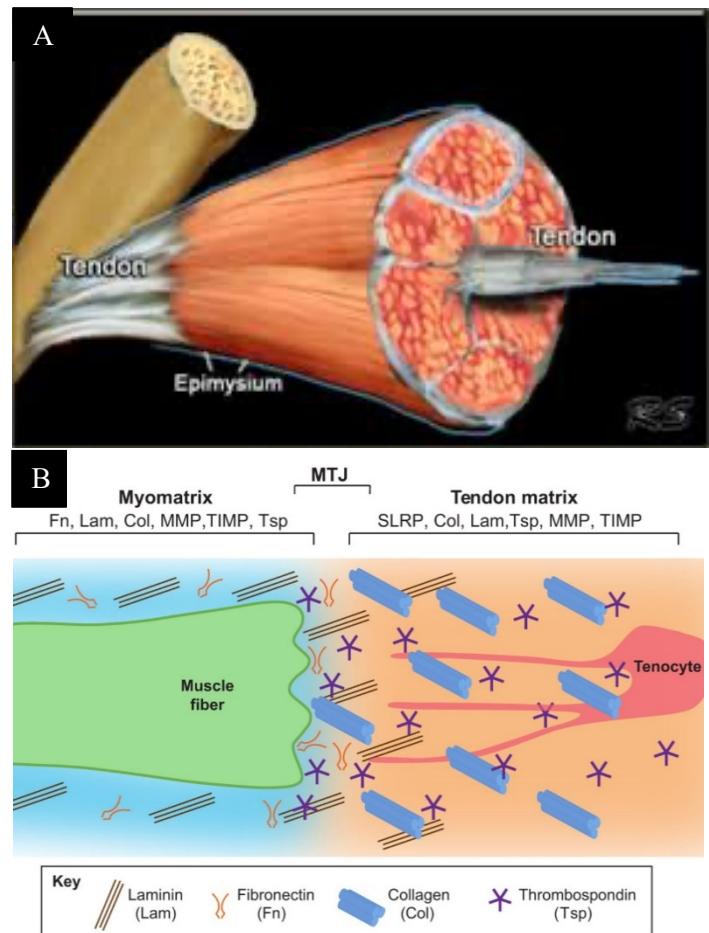


Fig 2. Composition of the ECM surrounding muscle, tendon and MTJ. A) Illustration of MTJ; B) A muscle fiber (green) secretes ECM components into its surroundings (the myomatrix). Some components overlap with those of the tendon ECM, which is secreted by tenocytes (red). Myomatrix is primarily composed of laminin and fibronectin. The tendon matrix is rich in collagen and thrombospondin. The myotendinous junction (MTJ) is the narrow zone in which ECM components of tendon and muscle interact [1].

3A-B). The fundamental building-block of the skeletal muscle is the sarcomere and that for tendon is collagen [19].

Tendons are composed of 55–70% (similar to muscles) water and 30–45% extracellular matrix (ECM), predominantly comprising of aligned Type I collagen fibers (65–80% dry weight) [20]. Collagen aggregates progressively from microfibrils to collagen fibrils. Several collagen fibrils form a collagen fiber, the basic unit of a tendon. Several collagen fibers form a primary fiber bundle (subfascicle), which group to form a secondary fiber bundle (fascicle). Fascicles are surrounded by a thin connective tissue sheath called endotenon (in tendons). This connective sheath binds secondary fiber bundles together to form tertiary bundles. Tertiary bundles comprise the tendon. The entire tendon is surrounded by a fine connective tissue sheath called epitenon. The epitenon contains the tendon's vascular, lymphatic, and nerve supply and aid in protecting and healing tendons [21].

Tendons that pass through tight fibro-osseous tunnels or around corners, such as those at the fingers, wrist and ankle are surrounded by a tendon sheath. The sheath provides an access

tunnel for tendon gliding at anatomic structures that might cause friction. The tendon sheath consists of an outer fibrotic layer and an inner synovial layer. The fibrotic layer is protective and supportive while the synovial layer secretes synovial fluid (e.g., hyaluronic acid) to enable tendon gliding [22]. In regions where friction is not expected the synovial sheath is replaced with paratenon, a thin layer of loose fatty connective tissue (e.g., Achilles) [20].

Skeletal muscle is a dynamic tissue composed of longitudinal, multinucleated cell bundles in a hierarchical arrangement similar to tendon collagen fiber bundles. The connective layers of the muscle (epimysium, perimysium, and endomysium) merge into a single organization to make contact with one or more fixed bone points. Muscles are composed of 75% water (similar to tendons), 20% protein, and 5% inorganic salts, minerals, fat, and carbohydrates. Collagen is the major structural protein in skeletal muscle ECM accounting for 1-10% of muscle mass dry weight [23]. Proteoglycans (PG) ubiquitously organize and lubricate collagen fiber bundles [20].

Skeletal muscle sarcomeres aggregate to form myofibrils (**Fig 3A**). Myofibrils are composed of filamentous proteins: thick (myosin) and thin (actin) filaments, troponin and tropomyosin. Several myofibrils are parallelly arranged to form a muscle fiber which is the structural unit of the skeletal muscles. Each muscle fiber is wrapped with a connective tissue sheath called endomysium, composed of Type I, III, IV, V collagen [19]. A muscle fiber is a single, multinucleated cell called a myocyte that is vascularized and innervated. The muscle fiber is surrounded by the sarcoplasmic reticulum, a membranous structure where calcium is stored for use during contraction [24].

Bundles of muscle fibers form a muscle fascicle surrounded by another connective tissue sheath, the perimysium, composed of Type I, III and V collagen [19]. Groups of fascicles bundled together, form the whole muscle belly. The whole muscle is coated by a layer of dense, irregular connective tissue sheath named epimysium. This membrane is primarily made of large collagen filaments (Type I and III).

The terminal side of the muscle progressively changes composition, transitioning from cellular to collagenous [24]. The perimysium surrounding the muscle fascicles join and become continuous with tendon [25]. The tendon and perimysium both contain primarily type I collagen, and decorin proteoglycan (PG) [23]. Because of loading conditions, collagen in tendon becomes much more organized than in perimysium.

The fibrils in tendons and the epimysium in muscles have a structural characteristic waviness called crimp (**Fig 3B**) [26]. This specialized structure explains non-linear tissue behavior; as tension increases the collagen fibers progressively un-crimp, or elongate, until all fibers are nearly linear, maintaining smooth movement under normal circumstances.

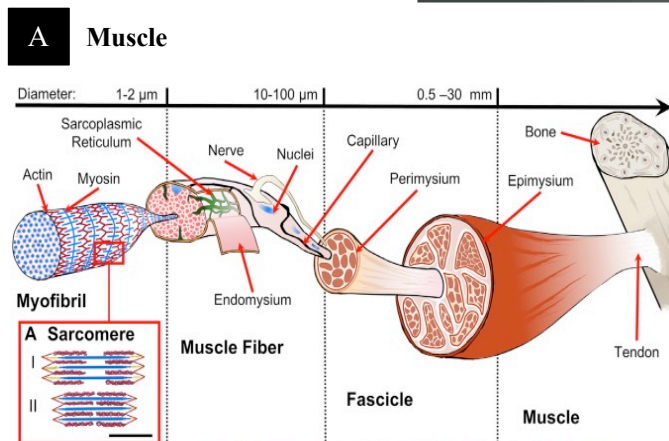


Fig 3A A schematic diagram of the structural hierarchy of a skeletal muscle [27].

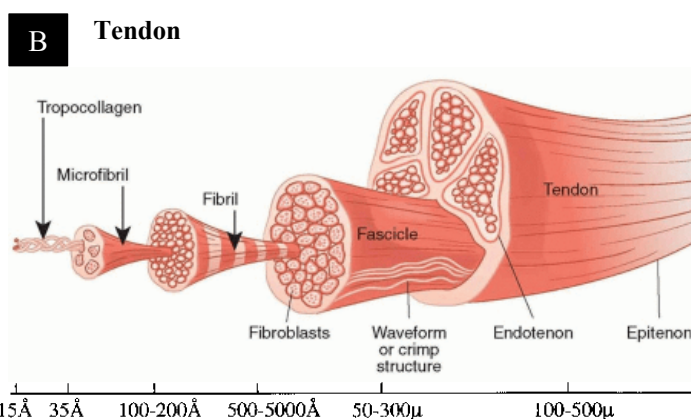


Fig 3B. A schematic diagram of the structural hierarchy of a tendon (Adapted from Kastelic et al., 1978)

FUNCTION: MUSCLE CONTRACTION AND TRANSMISSION OF FORCE

Skeletal muscle is under voluntary control, although maintaining posture or balance can be subconscious. The main function of skeletal muscles is to generate force by contraction. Excitation–contraction (EC) coupling is the coordination of the required processes for force generation. EC couples the transmission of the nerve stimulus and calcium release with the interaction of actin and myosin cross-bridges.

Briefly, action potentials trigger calcium release from the sarcoplasmic reticulum. As calcium levels rise a series of molecular events exposes the active site of the actin filament allowing the binding of myosin which subsequently forms cross-bridges. These cross-bridges initiate contraction such that myosin ATP facilitates the detachment of myosin from actin (a cross-bridge formed in a previous contraction) and the formation of a new cross-bridge. This sliding of actin and myosin filaments generates force [10].

Two pathways are involved in transmitting force from muscle fibers to the tendon: the longitudinal transmission, in which force is transmitted through the myotendinous junctions; and lateral

transmission, in which force is transmitted laterally from myofibers to the extracellular matrix (ECM), and then to the tendon [26, 28-30].

SKELETAL MUSCLE AND TENDON INJURIES

Overstretched tendons and muscles can lead to tears and to injury [31, 32] (**Fig 4**). Injuries such as lacerations, contusions, or strains can lead to functional impairment [11, 33, 34]. The most common injury is strain which can occur (1) within the muscle, (2) near the MTJ, and/or (3) in the tendon.

While tendons anchor every muscle of the body to bone, the most common injuries involve the rotator cuff tendons, Achilles

tendon, and flexor tendons of the hand. Muscle injuries commonly occur during excessive loading of the muscle; that is, when the muscle is contracting while it is elongating (e.g., pushing off during a sprint or changing directions during racquetball), the force across the MTJ unit can be so great that tissues tear, either partially or completely. Muscles most susceptible to sport injury are listed in **Table 2**.

Primary surgical interventions include removal of intramuscular hematoma(s), muscle-tendon reinsertion, and reinforcement [35] of a complete (III degree) or of a partial (II degree) strain or tear [36, 37].

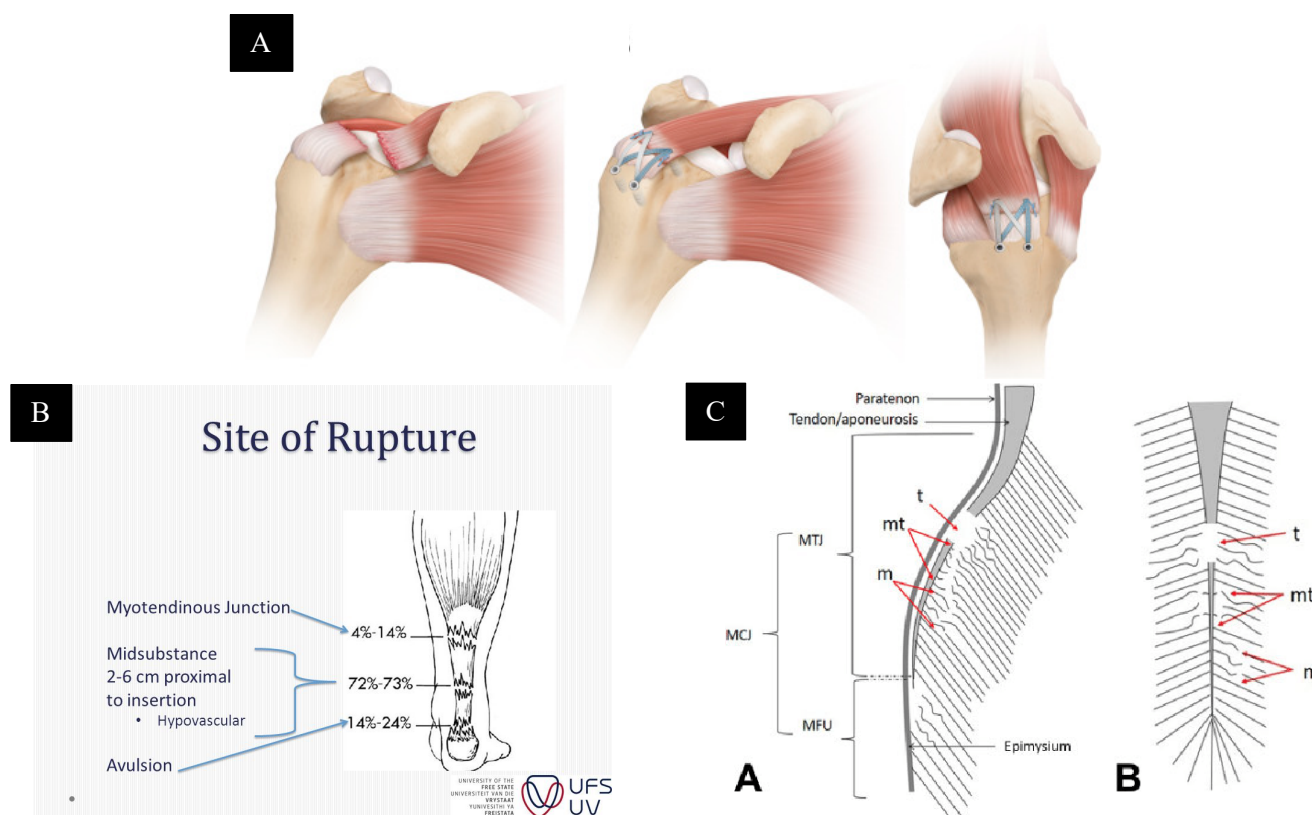


Fig 4. Musculotendinous junction (MTJ) injuries. A) Rotator cuff injury and repair area; B) Achilles / calf muscle injuries near the MTJ; C) Schematic of MTJ injuries. m, muscular; MFU, myofascial union; mt, musculotendinous; t, tendinous [38]

HEALING PROFILE

Acute injury to a muscle or tendon is followed by rapid initiation of a general wound healing process. This process is subdivided into three chronological phases: inflammation, proliferation, and remodeling [39-41]. In addition to these broad phases, skeletal muscles may also undergo complex repair that includes a degenerative phase prior to the inflammatory phase and a regenerative phase involving fibrosis prior to the remodeling phase (**Fig 5**) [34]. Revascularization

and innervation are achieved after muscle repair or regeneration.

Degeneration and Inflammatory Stage: The inflammatory stage of tendon and muscle healing begins immediately after acute injury with formation of hematoma in the damaged tissue. In muscles, the initial event is muscle fiber necrosis triggered by disruption of local homeostasis and by unregulated influx of calcium through sarcolemma lesions [42]. Excess cytoplasmic calcium causes proteases and hydrolases activation that contribute to muscle damage. The initial inflammatory phase

Table 1. Key similarities and differences between tendons and skeletal muscles

Similarities		
1	Material: Soft tissue of the skeletal system	
3	Function: Provide mechanical strength by transmitting tensile load	
4	Structure: Hierarchical structure	
5	Mechanical Behavior: Nonlinear and viscoelastic	
6	Healing Profile: General wound healing process	
9	Challenges: Susceptible to scarring and tissue tethering	
Differences		
	Tendon	Skeletal Muscles
1	Transmits force	Generates force
2	Fibrous tissue	Cellular tissue
3	ECM matrix consists of 65-80% collagen fibrils	ECM matrix consists of 1-10% collagen fibrils
4	Healing: Inflammation, Proliferation, Remodeling	Healing: Degeneration, Inflammation, Regeneration, Fibrosis, Remodeling
5	Approximately 4000 tendons in human body	Approximately 600 muscles in human body
6	Basic structural unit is collagen	Basic structural unit is sarcomere
7	High tensile strength	Low tensile strength
8	Commonly injured tendons are rotator cuff, Achilles and flexor tendons of the hand	Commonly injured muscle is hamstring and pectoralis major
9	Avascular, acellular and low innervation	Composite structure consisting of contractile proteins, vascularization, cellular, innervated
10	Limited healing capability, No regeneration	Ability to regenerate
Concluding Remarks		
Tendon and muscles exhibit similar basic structure and healing profile. The ECM of tendons and muscles interface at the musculotendinous junction (MTJ) where most injuries occur. Therefore, differences between the tissues do not impact the treatment approach for tendon and muscle injuries.		

Table 2. Sports related skeletal muscle injuries

Activity	Skeletal Muscle	Region of injury	Case study references
Weightlifting, Weight training, Wrestling, Rugby, Waterskiing	Pectoralis major	Insertion tendon injuries (55%), muscle belly or muscular-tendon insertion (35%)	[43]
Skydiving and Wakeboarding	Biceps brachii	Tendon portion, more often the long proximal head and to a lesser extent the distal end that inserts into the muscle belly	[44, 45]
Tennis, Badminton	Gastrocnemius	Rupture of the distal MTJ – Tennis leg	[46]
Soccer	Quadriceps femoris	Tear at the proximal MTJ	[47]
Sprinting, Running	Hamstring (most common)	proximal or distal MTJ, muscle belly, the proximal and distal tendon insertion	[48]

continues with neutrophil and macrophage removal of necrotic debris and with stimulation of fibroblast/fibromyoblast proliferation during the first 24-72 h [41].

The repair/proliferative phase: Muscle repair is a competitive process involving regeneration of functional myofibers and production of fibrous scar tissue, depending on the severity of the injury and the size of muscle gap [49]. As in general wound healing, the repair phase lasts a few weeks and is characterized by expansion of the ECM including glucosaminoglycans, increased cellularity, and deposition of fibrovascular scar by fibroblasts [3, 31, 39, 50, 51]. Insulin-like growth factor-I (IGF-I) and transforming growth factor- β (TGF- β) expression remains high, continuing to attract fibroblasts to the site and to increase ECM production [34, 52, 53]. The fibrous tissue thus formed contains a high proportion of type III collagen. In its initial phase, the fibrotic response is beneficial, stabilizing the tissue and acting as a scaffold for myofiber regeneration in muscles.

Muscle regeneration initiates within 4–5 days, peaks at 2 weeks, and then gradually diminishes 3 to 4 weeks after injury. The regeneration process includes activation and proliferation of satellite cells, repair and maturation of damaged muscle fibers, and connective tissue formation. A delicate balance

between these mechanisms is essential for recovery of contractile muscle function [34].

Remodeling Phase: The *remodeling phase* begins about 6 weeks following injury. The fibrous repair tissue becomes less cellular, glycosaminoglycan concentrations decrease, and the proportion of type I collagen increases. For tendons, during this period, the repaired tissue changes to fibrous tissue, which again changes to tendon-like tissue after 10 weeks. Eventually the collagen fibers and tenocytes/fibrocytes align with the direction of stress to increase the repaired tensile strength. In muscles, the regenerated muscle fibers and connective tissue align parallel to the line of action if appropriate stresses are allowed [54]. The remodeling phase can last several months. The repaired tissue (scar) is inferior in strength and is prone to tears and re-ruptures [39, 55].

SCARRING IN TENDONS AND MUSCLES

Scarring is a result of an exaggerated inflammatory response to an injury or surgical procedure. Specifically, this inflammatory response involves the over-production of fibroblastic cells and an increase in the deposition of extracellular matrix proteins, encouraging fibrotic cellular

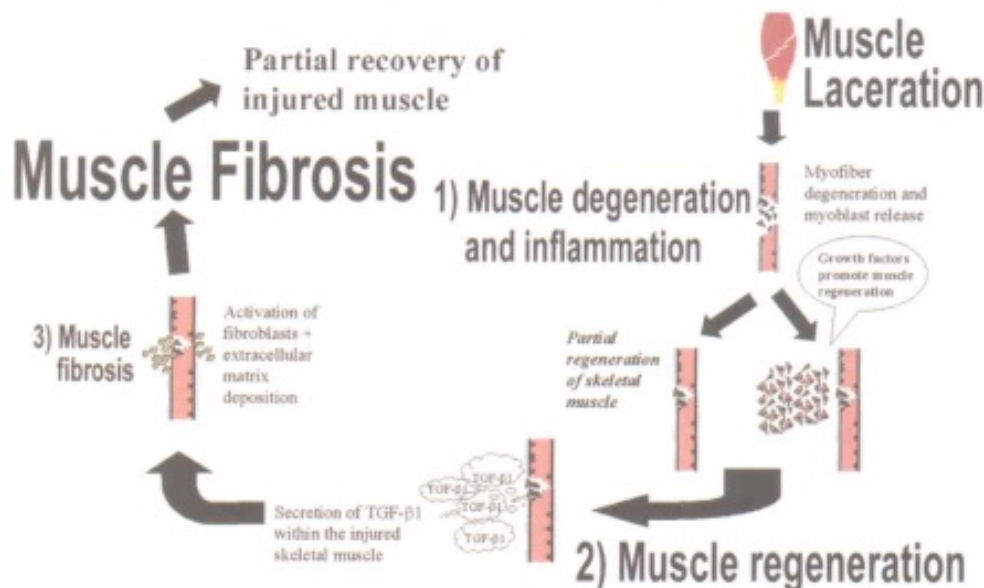


Fig 5. Sequential cycle of muscle healing phases following laceration injury. Muscle injuries induce myofiber degeneration and inflammation. Infiltrating lymphocytes release growth factors that activate myoblasts to proliferate and to differentiate into myotubes and myofibers enhancing muscle regeneration. The release of transforming growth factor- β 1 (TGF- β 1) within the injured site stimulates ECM deposition and triggers the formation of fibrosis [11].

deposition. This scarring often causes tissues to tether that would otherwise be separate. Unnatural tissue tethering almost inevitably produces functional disability by causing pain and by limiting range of motion. Tendon healing within the synovial sheath (e.g. digital flexor tendons) is invariably associated with scar formation [4, 5, 41].

Scarring within muscles can cause muscle weakness, pain, and a limited range of motion. Like other scar tissue in the body, tethering in muscle tissue results from the body's self-healing mechanisms. Failure of the regeneration pathway owing to an injury results in incomplete healing and fibrosis. Even small, micro-injuries in muscles cause muscle tissue to stick together. Consequently, tension may be placed on tendons or other muscles that are not suited to handle the stress, and nerves may become pinched. Pinched nerves can lead to a cascade of other problems, such as tingling, weakness, and numbness.

Hamstring syndrome is one such example resulting from entrapment of sciatic nerve by the hard-fibrotic tissues at the insertion site of hamstring muscles to ischial tuberosity [56]. Surgical treatment includes isolating tendons, debriding the ischial tuberosity, reinserting tendons with bone anchors and if necessary, neurolysis of the sciatic nerve.

THERAPY MODALITIES

Restoration of tendon and muscle function is challenging. The healing process is slow and fibrotic [57]. Most muscle injuries can be successfully treated non-surgically while severe muscle injuries need surgical repair. Current therapies to prevent postoperative tethering focus on the use of mechanical barriers and antiadhesive adjuvants [5, 58-60].

Recently, several strategies have been proposed to modulate the inflammatory response to enhance skeletal muscle repair, many of them involving the use of biological (mainly decellularized porcine ECM) [61] or biomaterial-based scaffolds [62]. Injectable hydrogels, polymeric biomaterials that form 3D networks with high water content and permeability, can be applied via minimally invasive technique. While some are made of natural biomaterials, e.g., alginate or chitosan, and others are made of synthetic ones [63, 64].

CONCLUSIONS

The muscle-tendon-bone unit drives skeletal motion and maintenance of body posture. Muscle contractions transmit force via tendons to move or to stabilize bone. This transmission from muscle to tendon occurs via the musculotendinous junction (MTJ). The MTJ is characterized by intertwining collagen of muscle layers with tendon fibers, designed for energy conservation and force transmission efficiency.

Skeletal muscles and tendons are susceptible to overstretch or tear, especially in the extremities. The most common muscle/tendon injuries occur near the MTJ, where there is weaker tissue proximal or distal to the intertwined collagen of the muscle-tendon matrix. While skeletal muscle is capable of repair, traumatic injury is often sufficient to disrupt this regenerative capacity, resulting in excessive fibrosis and tethering. Orthopedic treatment to restore the normal mechanical function of muscles and tendons remains challenging, typically requiring surgical intervention. This intervention may initiate exaggerated inflammation responsible for unwanted scarring. Peritendinous scarring and muscle fibrosis is a common complication of tendon,

muscle, and joint repair procedures. Current therapies to prevent postoperative tendon and muscle tethering focus on the use of mechanical barriers and antiadhesive adjuvants [5, 58, 60, 63-65].

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