Traumatic muscle injury

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Abstract

Traumatic muscle injury represents a collection of skeletal muscle pathologies caused by trauma to the muscle tissue, and is defined as damage of the muscle tissue that can result in a functional deficit. Traumatic muscle injury can affect people across the lifespan and can result from high stresses and strains to the skeletal muscle tissue, often due to muscle activation while the muscle is lengthening resulting in indirect and non-contact muscle injuries (strains or ruptures), or from external impact resulting in direct muscle injuries (contusion or laceration). At a microscopic level, muscle fibres can repair focal damage, but must be completely regenerated after full myofiber necrosis. The diagnosis of muscle injury is determined from a combination of patient history and physical examination. Imaging may be indicated to eliminate differential diagnoses. The management of muscle injury has changed within the past five years from initial rest, immobilization and (over)protection to early activation and progressive loading using an active approach. A current challenge in muscle injury management is that numerous medical treatment options, such as medications and injections, are often used or proposed to try to accelerate muscle recovery despite very limited efficacy evidence. Muscle injury prevention represents current challenges, likely due to the multifactorial and complex nature of muscle injury.

[H1] Introduction

Traumatic muscle injury represents a collection of pathologies involving damage to the skeletal muscle tissue, caused by trauma, that can result in a functional deficit. Traumatic muscle injury is typically caused by indirect and non-contact trauma (strains and ruptures) or by direct contact (contusions or lacerations)[1].

The skeletal muscle consists of muscle fibre bundles separated by connective tissues: the epimysium surrounds the entire muscle, the perimysium surrounds the muscle fibre bundles, and the endomysium surrounds each muscle fibre (FIG. 1)[2]. The muscle fibre is the force-producing cell that constitutes the majority of the muscle tissue. Each muscle fibre contains hundreds of parallel myofibrils composed of contractile elements that extend the length of the fibre[2]. The region of a myofibril between two successive Z-discs is known as the sarcomere, which is the fundamental contractile unit of muscle[2]. The muscle fibre has many satellite cells arranged in its periphery that are involved in regeneration after injury[2]. At the muscle fibre end, the outer membrane becomes irregular and jagged to bind tightly to the connective tissue forming the myotendinous junction (MTJ)[3,4].

The skeletal muscle is the contractile organ system responsible, in tandem with the sensorimotor system, bones and connective tissues, for the motion of the musculoskeletal system, all components working together. It enables gross and fine motor movements such as locomotion, posture and gripping[2]. The muscle fibre can actively shorten from supra-threshold activation or passively be elongated, creating the force behind the motion of the musculoskeletal system[2,9,10].

When skeletal muscle is injured, a multi-stage natural process of repair (the response to focal damage, in which small regions of membrane or sarcomere elements are restored) and/or regeneration (the response to myonecrosis, in which the full myofibre is replaced) commences within the muscle[11,12]. Traumatic muscle injury may have negative consequences on movement (e.g., reduced walking velocity, asymmetrical stride) and posture (e.g., trunk or pelvic imbalance) due to muscle pain and/or loss of function. This may, depending on respective injury site, type and severity[13], lead to impairments in daily life, social life, physical or sports activities, with potential negative consequences on the quality of life and well-being[14].

Traumatic muscle injuries often occur in sports settings as strains (e.g., muscle activation while the muscle is lengthening such as during sprinting or tackle in football) or contusions and lacerations (e.g., impact from another person or object and stab wounds, respectively); however, they can affect all people across the lifespan and can also be the result of strains (e.g., slip with sudden lengthening, running to the bus) or contusions/lacerations (e.g. those caused by falls or motor accidents). These injuries may range from minor damage, not visible with medical imaging, to severe damage with total muscle rupture.

The diagnosis of muscle injury is typically made through a detailed patient history and physical examination; medical imaging can be indicated to eliminate differential diagnoses or when a precise diagnosis is needed. Muscle injury management has changed within the past five years from initial rest, immobilization and (over)protection, to early activation and progressive loading through an active approach that prepares the injured muscle and the patient to return to normal movement and activities[12,15,16]. Traumatic muscle injury mechanisms and aetiologies are multifactorial and complex, leading to difficulties in prevention.

In this Primer, we will provide a detailed overview of acute, traumatic skeletal muscle injury only, in isolation of other components of the musculoskeletal system, and will not include crush injuries by prolonged compression, delayed-onset muscle soreness (DOMS)[17,18], neuromuscular pathology (e.g., cerebral palsy[19], genetic diseases), or non-skeletal muscle pathologies (e.g., cardiac or smooth muscles). We will discuss the epidemiology, risk factors, pathophysiology and mechanisms, diagnosis, and management of muscle injuries, to translate latest basic and clinical research into clinical practice. We will also discuss the impact of muscle injuries on quality of life and the potential implications for future research and clinic. Most scientific data available is regarding traumatic muscle injuries occurring in the context of sports, however diagnosis and management principles can be applied to all traumatic muscle injuries.

[H1] Epidemiology

[H2] Traumatic muscle injury in the general population

In the general population, the burden of musculoskeletal pathologies have been rising more than 30% over the past three decades[20]. Musculoskeletal pathologies including traumatic muscle injuries can result in people being less active, which may interfere with the WHO

recommendations regarding physical activity for overall health[21]. However, it is difficult to determine the global prevalence, incidence, burden, rates and trends of traumatic muscle injuries for the general population, since muscle injuries are often combined with other musculoskeletal disorders, and minor traumatic muscle injuries not receiving medical attention may remain undetected (often self-managed and do not present in a health care setting)[20,22–28]. Traumatic muscle injuries can occur in all individuals across the lifespan irrespective of their physical condition. For example, traumatic muscle injuries can occur in children and adolescents[23,25,27], physical workers[23,24,26,28,29], elderly patients[22,30] and specific population groups (e.g., people living with genetic skeletal disorders and people living with cerebral palsy)[31], although there is limited detailed epidemiological data concerning traumatic muscle injuries in these populations[22–28,32]. In children and adolescents, muscle injuries represented a very small fraction of paediatric trauma encounters at the emergency departments[33,34]. Together with ligament and skin injuries in the soft tissue injury category, traumatic muscle injuries accounted for 35% of stair-related injuries of children younger than 5 years old[27], 13% of injury-related visits among children under 15 years old[25], and 38% of injuries among adolescent workers[23]. In adult workers, muscle and ligament injuries represented 40-50% of all injuries[24,28], and were the leading musculoskeletal pathologies sustained by firefighters[29]. In the elderly, muscle and ligament injuries represented 3.2% and 5.8% of fall-related injuries in men and women, respectively[22]. While fractures are a leading cause of morbidity in the elderly[22], the concomitant traumatic muscle injuries are often overlooked and may lead to challenges in the rehabilitation following fracture management. There is no information available about muscle injury rates in populations with decreased skeletal muscle tissue capacity (e.g., from sarcopenia, muscle disease).

[H3] Risk factors in the general population

In accordance with the scarce data on traumatic muscle injury rates in the general population, there is inadequate evidence for risk factors in the general population. Risk factors for musculoskeletal injury (including muscles, tendons, joints, ligaments, bone, nerves) include smoking, being overweight, physical inactivity, regular use of alcohol[35], and falls, slips and high impact trauma[32]. In the working population, risk factors such as age[36], manual occupations[37], pre-existing disease, cultural factors and adherence to occupational health and safety laws[38] may impact on the prevalence of musculoskeletal injury.

[H2] Traumatic muscle injury in sports

There is a wealth of epidemiological data on traumatic muscle injury in sports. In sporting populations, traumatic muscle injuries regularly contribute to the highest number, proportion, incidence and/or burden of injuries, although rates vary between sports[39–56]. Traumatic muscle injuries typically represent ~40% of all injuries in football (soccer) and athletics (track and field) championships, and ~20% of all injuries occurring during Olympic Games, Australian football, rugby, cricket, ice hockey, field hockey, basketball and gymnastics[39–44,47–62]. The rates of traumatic muscle injuries were stable or even increased over the past decades in Olympic Games[39,40,49,50], Australian football[44] and professional football[52,54], potentially due to increased demands of high-velocity running or density of playing schedule with a reduced rest-recovery balance. The rate of traumatic muscle injury recurrence ranged from 9 to 25% over the past three decades, highlighting the burdensome sequela[44,54,56]. All muscles of the body can be injured, but the location is often associated with the muscles used for specific motions. Hamstring muscles are mainly affected in sports with sprint and acceleration (~20% of all injuries)[44,51,52,54,56,63,64], lower leg muscles (i.e., calf) in sports with long-distance running (~20% of all muscle injuries)[51,63], groin muscles in sports with short bursts of multidirectional movement and directions changes[53], upper limb and shoulder muscles in upper-limb and throwing sports[60,62,65]. Muscles that span two joints (e.g., hamstring, rectus femoris, gastrocnemius muscles) are at an increased risk of injury, likely due to their relatively short fibres[1]. Hamstring muscle injuries are often reported as the most prevalent injured muscle in sports[44,51,54].

[H3] Risk factors in sports

During international athletics championships, overall traumatic muscle injury risk was almost 2-fold (relative risk 1.6, 95% CI 1.3-2.0) higher in male athletes compared with female athletes[66]. In collegiate athletics, the hamstring muscle injury rate was 2-fold (relative risk 1.9, 95% CI 1.1-2.6) higher in male athletes than female athletes[64]; however, quadriceps muscle injury rate was 3-fold (relative risk 3.0, 95% CI 2.5-3.8) higher in female athletes than male athletes for all sex-comparable sports[67]. In competitive athletes from different sport background, increased age was associated with a higher risk of hamstring (Standardised mean

differences = 1.6, 95%CI 0.6-2.6)[51,68,69] and calf[70] muscle injuries, but not with quadriceps muscle injuries[71]. An association between history of previous hamstring (relative risk = 2.7)[68], quadriceps, adductors[72] and calf[70] muscle injuries and future risk of these respective injuries has been reported[68,70–72]. Furthermore, history of any previous injuries (muscular or non-muscular) was also reported as a risk factor for hamstring[68], quadriceps[71], adductors[72] and calf[70] muscle injuries. No associations were found between anthropometrics (i.e., height, body mass, body mass index) and hamstring[68], quadriceps[71], or calf[70] muscle injuries (Supplementary Figure 1). No association has been identified between flexibility, mobility and range of motion and the risk of hamstring[68] and quadriceps[71] muscle injuries; however, hip rotational range of motion was 9° lower in male soccer players that sustained a subsequent acute adductor muscle injury[72]. Reduced hamstring strength, hamstring strength endurance, eccentric hamstring strength, isometric knee extensor strength and increased isometric:eccentric hamstring strength ratios were associated with higher hamstring muscle injury risk.[68] Reduced adductor strength in the injured muscle compared with the uninjured side was associated with a higher risk of acute adductor muscle injuries[72]. No association between strength and injury risk was reported for quadriceps muscle[71]. Increases in high-speed running exposure[73,74], sprinting running kinematics[75] and kinetics[76] were associated with higher hamstring muscle injury risk[68]. Playing position influenced hamstring muscle injury risk in team sports[68]. The dominant or kicking leg had an increased risk of quadriceps muscle injury compared with the non-dominant leg[71].

In collegiate sports, traumatic muscle injuries seem to predominantly occur in the preseason compared with the competition period[64,67]. In these student-athletes, a deconditioning after the season and semester break with possible decreased activity levels and an associated high relative training load in the preseason could contribute to these findings[64,67]. The pre-competition or preseason period was associated with a higher calf muscle injury risk compared with other season phases[70]. Higher muscle injury rates occurred during competition than during training in football and hockey[42,77]. During a football match, calf and hamstring injuries occurred more toward the end of a match, as well as quadriceps and hip/groin injuries more towards the last 15 minutes of a half which may be associated with fatigue[54,69]. Organisational sports conditions (e.g., travel, between-match time, competition level) were associated with hamstring muscle injuries[68] and climatic conditions with quadriceps muscle injury[71].

[H2] Traumatic muscle injury in military personnel

Another specific population prone to musculoskeletal injuries is military personnel. No data is currently available for muscle injury incidence rates or specific locations. While most studies summarized muscle injuries within a musculoskeletal injury category, epidemiological studies from US military personnel estimated that 20.4% of all sports- and activities-associated injuries were muscle injuries[78]. In this population, muscle injuries outside of military training mainly occurred during weight training (36.4% of all injuries) but were also seen in other activities, such as football (21.2% of all injuries), running (19.3% of all injuries), and basketball (18.8% of all injuries)[78]. Similar muscle injury rates occurred during basic combat training with 19.9% in male and 18.6% in female recruits[79]. When basic combat training was combined with advanced individual training for military police recruits, the muscle injury rates were 11.4% in male and 10.4% in female recruits[79].

[H3] Risk factors in military personnel

Age, overweight/obesity, prior injuries and low physical performance were associated with overall musculoskeletal injury risk[80]. However, these risk factors apply to overall musculoskeletal injuries in this population and not exclusively to military personnel.

[H1] Mechanisms/pathophysiology

[H2] Biomechanical injury mechanisms

At a macroscopic level, traumatic muscle injury mechanisms are divided into two main biomechanical injury mechanisms: indirect and non-contact muscle injuries and direct contact muscle injuries[1]. Indirect and non-contact muscle injuries (strains and ruptures) result from excessive stresses (the amount of force experienced per unit area of tissue) and strains (the relative length change of muscle tissue when stress is applied (i.e., strain is the measure of the deformation of the tissue)) on the skeletal muscle without direct impact at the injured site; the force that can be produced by the muscle or the external force imposed on the muscle exceeds the load-bearing capability of the muscle tissue, leading to damage[1,10,81] (FIG 2). Several contraction situations can lead to indirect and non-contact muscle injuries, but the most frequent

is when the muscle is contracting while being forced to rapidly lengthen, corresponding to an eccentric contraction[1,10,32,82–86]. In addition, strain magnitude is often highest in muscles that cross multiple joints (e.g., hamstring, gastrocnemius or rectus femoris)[87] due to the relatively short fibres in these muscles; thus, these muscles are very vulnerable to injury[1,88,89]. In direct contact injuries, muscle tissue damage results from compression, bruising, tearing or impact of the tissue, leading to contusion or laceration injuries; the external forces exceed the load-bearing capability of the skeletal muscle, leading to damage[1,10] (FIG. 2). Direct contact injuries result from an external direct impact at the injured site can be caused by another person (e.g., players in sports), a moving object (e.g., a road traffic accident), or a stationary object (e.g., ground during falls slips and trips).

[H2] Muscle injury and repair at the cellular and molecular levels

At a microscopic level, in general, muscle fibres can repair focal damage (i.e., minor cytoskeletal and membrane focal damage) intrinsically via myonuclei[90], but must be completely rebuilt after full myofiber necrosis by regeneration through adult regenerative myogenesis[91] within the original basement membrane[92] (TABLE 1, FIG 3). Upon formation of new myofibres, the original basement membrane is replaced[92,93], involving fibroblasts, satellite cells, and some myonuclei[94], illustrating the coordinated support of many resident cell types to complete muscle repair. Satellite cell depletion studies in animals have confirmed their unequivocal requirement for muscle regeneration[95]. In the absence of satellite cells, muscle repair is characterised by the accumulation of fat and connective tissue in the place of muscle fibres[96]. Importantly, satellite cells do not act alone but are guided by cues from other cell types such as vessel-associated cells[97] and immune cells. Specifically, pro-inflammatory macrophages stimulate satellite cell proliferation and, subsequently, anti-inflammatory macrophages stimulate satellite cell differentiation and fusion[98]. Another major muscle cell type is the fibroblast, or fibro-adipogenic precursor (FAP)[99]. This is a heterogeneous population of cells with the ability to differentiate into fibrogenic cells or adipocytes and are therefore relevant during tissue injury and repair when fatty infiltration and fibrosis may occur[100]. FAPs are relatively new cell players to the field so our understanding of their roles in muscle repair is still developing[99]. We do know that at least some FAP populations expand in number

following injury[101], and are important for satellite cells differentiation and fusion[96,102]. Together, the activity of FAPs, immune cells, and vessel cell types is in line with the presence of a highly pro-inflammatory, fibrogenic, and angiogenic injury exudate (fluid accumulated at the site of injury) containing high levels of the pro-inflammatory cytokines and growth factors TNF-α, IL-6, IL-8, IL-15 and VEGF-A[103].

Currently there is a major gap between insight from animal and human models of muscle injury and real-life muscle injuries. Much of the knowledge has been gained from experimental animal models with different muscle injury approaches[10,104,105]. These allow to better understand the repair and regeneration mechanisms for focal damage and full myofiber necrosis, respectively (TABLE 1, FIG 3)[10,104,105]. They also reflect the biomechanical muscle injury mechanisms: laceration or contusion for focal damage, and strains induced by toxin or electrically stimulated eccentric contractions for full myofibre necrosis (TABLE 1, FIG 3)[10,104,105]. Experimental models have also been developed in humans and, when combined with tissue biopsy sampling, have proven valuable in mapping the slower repair time course compared to rodents subjected to the same injury[92]. A major hurdle to advancing the understanding of human muscle injury repair is however the lack of insight into the actual site of tissue disruption at the ultrastructural level. Two of the most widely used animal models (i.e., eccentrical contraction injury model and contusion model) have taught us most of what we now know about how muscle repairs, therefore their insights are more detailed here.

[H3] Eccentric contraction muscle injury model

Muscles subjected to eccentric (lengthening) contractions are more easily injured compared with other types of contractions: concentric (shortening) and isometric (muscle length stays the same)[108,109]. During eccentric contractions, the myosin cross-bridges, which form the myosin filaments within the sarcomere, increase the strength of their connection with actin filaments[110] and then bear a high force. This high force, combined with lengthening (high strain) can result in injury[10,111,112]. Based on the biophysics of myosin cross-bridge interaction with actin filaments, muscles produce lower forces when shortening (concentric) and higher forces when forced to lengthen (eccentric).

One of the classic signs of a muscle injury is observed from electron micrographs of muscles in which the natural striation pattern is disrupted[10] The normal striation pattern in muscle (FIG

1) results from the regular interdigitation of contractile proteins (including actin and myosin) in series and parallel across the muscle[2]. The striation pattern can be disrupted in any location, but Z-disk disruption occurs earliest and is; therefore, considered the "weak link" of eccentric contraction-induced injury[113]. It is hypothesised that the most mechanically vulnerable portions of a sarcomere are the "connecting" proteins that connect the contractile sarcomere with adjacent sarcomeres, with specialized proteins at the sarcolemma (muscle fibre membrane) such as dystrophin and the dystroglycan complex[114] and with the muscle-tendon junction via proteins such as talin[115]. When the genes that code for these proteins are mutated, dystrophy occurs[116]. In the same way, desminopathies occur when the intermediate filament protein desmin is disrupted[2]. Desmin disruption seems to be one of the earliest signs of muscle injury and can occur after just a few minutes of eccentric contraction in animal models[117,118]. When desmin disruption occurs, the sarcomere becomes mechanically unlinked from the rest of the muscle fibre. Desmin not only interconnects adjacent sarcomeres, but it connects myonuclei to the rest of the fibre cytoskeleton[119]. Desmin deletion has the functional effect of decreasing the stress generated by the muscle, disconnecting myonuclei from the sarcomere lattice and decreasing the phosphorylation of the immediate early genes that ultimately serve to remodel the muscle. It is hypothesised that, during an eccentric contraction, desmin acts as a mechanical "circuit breaker" to disconnect the muscle sarcomere from the rest of the fibre to enable remodelling to occur after injury[120]. Interestingly, when desmin is deleted in a transgenic mouse model, less muscle injury occurs due to eccentric contraction[121]. Less remodelling also results from this lighter injury, so that the net result is that a muscle never actually becomes "trained" and; therefore, resistant to eccentric contraction-induced injury[120].

[H3] Contusion injury model

Based on the contusion model, the healing process of the skeletal muscle tissue was described into three separate phases: destruction, repair and remodeling[122].

During the destruction phase, myofibre rupture is associated with the rupture of adjacent blood vessels. Ruptured myofibres contract to create a space that is subsequently filled by a hematoma[122]. Due to the rupture of blood vessels, hypoxia in turn causes the muscle to necrose; the necrosis then spreads along the injured myofibres from the rupture site[122]. The spread of the necrosis is demarcated within the injured myofibres by the formation of new membrane called

contraction band (a cap of densely aggregated or hypercontracted myofilaments) that reseals the plasma membrane[123] formed within first hours after the injury[123]. Due to rich vasculature and subsequent large hematoma formation, the skeletal muscle injuries induce a robust inflammatory response[124,125]; the inflammatory cells, in particularly macrophages invade the injured site and induce macrophages to destroy necrotized tissue material via phagocytosis.[124]. Phagocytosis also delineates the transition from the pro-inflammatory phase of the inflammatory response to the recovery phase and ensures tissue reconstruction (the process is called as efferocytosis)[124].

During the repair phase, the injured area is rapidly revascularized by angiogenic capillaries, which can be seen using micro-angiography, invading to the injured area three days after the injury[126]. Also, during this phase, macrophages secrete growth factors (e.g., vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-13) to direct tissue regeneration in the hypoxic environment[124]. These growth factors keep the skeletal muscle´s own stem cells (satellite cells) alive in hypoxic conditions and activate them. These satellite cells begin the repair along the injured myofibre. Two distinct satellite cell populations exist and participate in the repair: committed satellite cells differentiate immediately into myoblasts, whereas undifferentiated stem satellite cells proliferate to replenish the satellite cells stocks for potential future bouts of injury, as well as contributing myoblasts for the regeneration[127]. These myoblasts then fuse together to form multi-nucleated myotubes[128]. The regenerating myotubes replace the necrotized part of the ruptured myofibre inside the intact basal lamina, which are preserved in hypoxia and provide guidance to steer regenerative effort to the right direction[128]. Simultaneously with the myofibre regeneration, the activated fibroblasts follow angiogenic capillaries and fill the hematoma formed at the rupture site. They lay out the early connective tissue called granulation tissue (a new connective tissue and microscopic blood vessels). Granulation tissue is rich in extracellular matrix components such as fibronectin, tenascin-C, as well as collagen type III[122]. Fibronectin and tenascin-C possess elastic modules that can be stretched several times their resting length in response to mechanical loading placed upon them, and provide strength and elasticity for the granulation tissue to withstand the contraction forces created by injured skeletal muscle[122]. Granulation tissue can also be viewed as a provisional matrix filling the area caused by tissue injury; it is an evolutionarily conserved process aimed at the reconstitution of tissue integrity

promptly after an injury[122]. Regenerating myofibres try to re-establish skeletal muscle tissue at the site of the rupture and pierce into the granulation tissue, establishing a cone-like form at the invasion front and do not attach to the surrounding connective tissue[122]. Instead, they enhance their adhesion on their lateral sides both in the intact and regenerating parts of the myofibres by dynamic redistribution of α7β1-integrin along the lateral sarcolemma[129].

During remodelling phase, regenerating myofibres penetrate only a short distance into the granulation tissue and then adhere to it by forming new MTJs[129,130]. The contraction of large granulation tissue to small scar tissue is driven by contraction capable fibroblast population called myofibroblasts. The myofibroblast are transformed from the fibroblast population that previously laid down the granulation tissue. Tenascin-C disappears from granulation tissue, but forms similar band-like structures as in the normal MTJs at the end of myofibres once they establish neo-MTJs[122]. Fibronectin, tenascin-C and collagen type III are replaced by a mechanically strong collagen type I in the scar tissue[122]. This transition to collagen type I improves mechanical strength of the scar tissue, to a large extent due to the formation of multiple interfibrillar cross-links between collagen type I fibres[122]. The skeletal muscle forms finger-like projections into the tendinous tissue at the MTJ[122]. The attachment of myofibres to neo-MTJs is mediated by integrin- and dystrophin-associated adhesion protein complexes, which accumulate again at the newly-formed MTJs when the regenerating myofibres there[122]. The expression of α7β1-integrin shifts towards a splice variants that can implement firm adhesion[131].

[H3] Restoration of muscle-tendon interface integrity after injury

In contrast to our solid understanding of muscle fibre regeneration, as described above, MTJ repair mechanisms in humans after muscle injury are still largely unknown. Collagen type XXII[132], talin[133], desmin[134], and dystrophin[135] have been recognised to be involved in the MTJ. From 2020, attempts to map the composition of the MTJ revealed a previously unrecognised specialisation in protein composition[136,137] and gene expression[94,138]. The attachment of the muscle to the tendon is achieved through two transmembrane linkage complexes; the dystrophin-associated glycoprotein complex and the vinculin-talin-integrin complex, with the myofibre basement membrane component laminin acting as a common component in both systems[139,140]. However, it is not known whether it is possible to re-establish the natural linkage

of muscle to the tendon in the adult state once it has been disrupted. While the formation of scar tissue may be the second-best outcome; it is unknown whether a muscle-scar-tendon construction has the capacity to resist the high forces that caused the initial injury.

The majority of muscle injuries in humans occur at the MTJ (e.g., 52% in hamstring muscle injuries[141]). The MTJ invaginated structure creates greater surface area contact between the two tissues that have dissimilar mechanical properties, and thus results in force distribution that keeps stress low[3,4]. One pressing unanswered question in this field is where precisely the MTJ/aponeurosis injuries occur in humans at the ultrastructural level. Elegant studies on frog semitendinosus muscle have revealed that, in the activated state, when stretched to failure, the site of failure was the basement membrane[115]. In contrast, when the muscle was in a relaxed state, the tissue failed at the level of the sarcomere, at the Z-discs[115]. Data in humans are lacking and vital to our fundamental understanding of the nature of muscle injuries, and to develop the optimal clinical management to ensure complete repair and resistance to subsequent injury.

[H1] Diagnosis, screening and prevention

[H2] Diagnosis

The signs and symptoms presented by patients with a traumatic muscle injury are mainly a pain located regarding the injured muscle associated with the function impairment of the respective muscle. Patients commonly experience an acute/sudden onset or very rapid progressive onset of pain in the muscle, but can experience a gradual onset and worsening of pain with cumulative load. The diagnosis of a traumatic muscle injury can, in most cases, be made through a detailed patient history and thorough physical examination (BOX 1). During the physical examination, patients often present with pain upon stretching, resistance testing and palpation of the injured muscle. Based on the injury mechanisms, traumatic muscle injuries are differentiated into strain muscle injuries (including rupture) resulting from indirect and non-contact *vs.* contusion or laceration muscle injuries resulting from direct contact[1,142] (TABLE 2). This diagnostic work-up provides information on injury characteristics that may guide the management and estimate prognosis. It also aims to assess the potential differential diagnoses of acute muscle-tendon-

bone-complex-related injuries. Traumatic muscle injuries are likely underdiagnosed since people often do not seek medical advice for these injuries and often self-manage them.

[H3] Differential diagnosis

Two important differential diagnoses presenting similar signs and symptoms, that should be considered because their management and prognosis can differ from traumatic muscle injuries, are complete tendon ruptures and apophyseal avulsion fractures (i.e., fractures of the secondary ossification centre in the apophysis (tendon-bone insertion) only seen in children and adolescents with immature skeletal)[143] (TABLE 2). Other differential diagnoses are broad and may include the muscle-tendon-bone complex with gradual onset (such as delayed onset muscle soreness[17,18], muscle cramps/spasms, myositis ossificans[144], compartment syndrome, tendinopathy[145], traction apophysitis, joint injury), neural (e.g., radiculopathy, peripheral nerve entrapment), vascular (e.g., peripheral arterial disease[146], thrombophlebitis, venous thrombosis[147], post-thrombosis syndrome), bone (e.g., bone stress injuries[148], bone tumours[149,150]), and joint (e.g., referred pain from adjacent joints, bursitis) pathologies.

[H3] Imaging

In most cases, imaging is not required for a traumatic muscle injury diagnosis. Imaging can be considered in suspected cases of complete tendon rupture (ultrasonography or MRI, FIG. 4), in suspected cases of apophyseal avulsion fracture (plain radiograph, FIG. 4), if the diagnosis is not clear after patient history and physical examination, or when recovery is not progressing as expected. In elite sports, ultrasonography or MRI is often performed to improve estimations of recovery time and/or re-injury risk[151]. However, the current scientific literature does not provide enough evidence to support the routine use of imaging for prognostic purposes[152].

[H3] Grading and classification

In practice, clinical and imaging-based classifications are often used to grade traumatic muscle injuries. A range of classification and grading systems exist, each with unique strengths and weaknesses[153]. The most commonly used classification systems are presented in FIG. 5[142,154–157]. None of the classification systems have been shown to effectively estimate prognosis[153], they are currently used to describe injury anatomy and support communication and education in clinical practice.

[H3] Prognosis and sequalae

After sustaining a traumatic muscle injury, most patients inquire about their prognosis, expected recovery times and return to activities times. There are substantial differences in recovery times between contusions, lacerations, strains, and severe complete ruptures (TABLE 2)[158,159]. Findings in the diagnostic work-up may guide a prognosis; however, providing an accurate prognosis for a patient remains challenging. Many factors can be used to estimate a prognostic in terms of recovery times, such as the number of days with impairments due to the traumatic muscle injury in daily life, degree of muscle function loss, physical activity performed by the patient and/or physical examination (pain provocation, flexibility deficit, strength deficits and functional impairments)[160,161]. Follow-up examinations and reassessment during the recovery period will enable a more accurate determination of recovery time and time to return to activities[160]. Other influencing factors to consider are patient-related (e.g., age, sex, fitness, previous injuries) or activity-related (e.g., type of occupation/sport, level) factors[162]. The prognosis should be a driver to guide muscle injury management with an estimated timeline and with all stakeholders having the same level of information, and not used as an immutable deadline of expected recovery time.

Finally, although rare, traumatic muscle injury can lead to complications and/or sequelae, such as chronic or recurrent pain, compressive hematoma (compressive to the adjacent tissue/structure), encysted hematoma (encysted collection of old blood with tissue shell around it), long-term muscle strength deficit, complex regional pain syndrome, muscle fibrosis, myositis ossificans (heterotopic calcification that occur at the site of the injury) or thrombophlebitis (inflammation of a vein related to a thrombus)[144].

[H2] Screening

The screening for traumatic muscle injury is usually based on the identification of individual risk factors (e.g., sex, age, previous injuries, strength, flexibility) using questionnaires or physical tests at the start of or regularly within an activity (e.g., beginning of a sporting season or an employment)[163]. This may enable modification of some risk factors via the implementation of specific appropriate and individualized measures[163]. Muscle injury screening is predominantly performed in competitive/professional sports, and is much less common in the non-sporting population and mainly done prior to employment.

The common research practice of evaluating single risk factors neglects the multifactorial aetiology of muscle injury and the inter-relationship between risk factors[164–166] as well as their potential variability over time[76,167–169]. The knowledge is primarily restricted to some sports and specific muscles[68,70–72,170,171]. The identification of individuals at higher injury risk, in general, does not predict injury with certainty[163,172]; in reality, people deemed to be high risk might never sustain a muscle injury and conversely, those deemed to be low risk may go on to sustain an injury[163].

Despite the challenges of screening, evaluations of muscle force, flexibility, function, cardiovascular and psychological health can help to evaluate the current muscle status and establish baseline levels of performance and function[173]. This may help to implement a regular routine for longitudinal analysis and build a relationship between clinicians and individuals to guide load management and a possible return to activity. Improvement in muscle injury screening strategies represents an important perspective of muscle injury management improvement.

[H2] Prevention

Traumatic muscle injury prevention is elusive for health professionals, researchers, and individuals at risk of muscle injury.

Numerous studies have investigated the effect of preventive measures/strategies on traumatic muscle injuries, predominantly in male athletes, and with the majority of studies focussing on hamstring muscles[174–181]. Transferring prevention strategies identified in one population at one particular muscle to other populations or muscle locations might not be appropriate, since, each muscle has variable morphology, function, and properties[182]. Muscle injury prevention measures predominantly target muscle strengthening, multiple components approach, proprioceptive, balance/coordination, and stretching[174–181]. Improving the muscle capacity to resist mechanical constraints through strengthening has been demonstrated as an effective strategy to reduce muscle injury risk, in particular through slow eccentric contraction modes, mainly in football, reducing of ~40-50% the risk of hamstring and adductor muscle injuries[177–179,183,184]. Efficacy of other scientifically evaluated measures is still inconclusive: stretching before exercise[185–189], core stability training[190], balance training[191,192], weekly frequency and load progression of exercises[193].

Evidence-based approaches to muscle injury rehabilitation[16,194,195] could also help to inform content and techniques to be implemented for uninjured persons to reduce their muscle injury risk.

Traumatic muscle injury prevention strategies may represent an important goal for traumatic muscle injury management. This could be achieved through including and evaluating other physical and non-physical measures (e.g., psychological[196,197] or environmental[198,199] factors), better exposing individuals to the demand-specifics and capacity required by the muscle during potentially injurious activities, as these vary with activities[63,84,200], improving the implementation of prevention measures and increasing the adherence[177,201–203]. There is a need to extend scientific evidence to other populations and muscles. Leading an active lifestyle may be a method of prevention muscle injury in the general, non-athletic population.

[H1] Management

[H2] General guidelines

Most traumatic muscle injuries can be treated conservatively with promotion of healing, graded exercise therapy and return to activity, and addressing any predisposing factors. There is mixed evidence about how the extent of the injury affects recovery[204,205], there are substantial differences in recovery times between contusions, lacerations, strains, and severe complete ruptures that should be taken into account in management and rehabilitation planning (TABLE 2)[158,159]. Progression through rehabilitation of an individual patient should not be solely based on a predefined fixed timeline (time based), but mainly guided by progress in symptoms and functional performance (criteria based). This is due to 1) the substantial variation in recovery times within muscle injury types (e.g., a hamstring strain injury in professional football takes a median of 2 weeks to recover, but with a large variation of 80% recovering between a few days and 5 weeks), and 2) the inability of an accurate estimation of the recovery time for an individual patient after sustaining the muscle injury[206]. So, it is preferable to rely on the clinical presentation of the patient as to the speed of progression through the phases of rehabilitation.

The cornerstone of traumatic muscle injury management is early activation and progressive loading through an active approach. In the past five years, scientific evidence supports a shift from a management approach based on initial rest, immobilization and (over)protection to this

early activation and progressive loading through rehabilitation[12,15,16]. One randomised controlled trial (RCT) published in 2017 reported that patients with traumatic muscle injuries receiving early exercise therapy (2 days after injury) had a significantly decreased time to return to sport compared to those with delayed exercise therapy (9 days after injury) (median time of 62.5 days *vs.* 83.0 days, respectively)[16]. This supported evidence from animal study reported significantly increased muscle recovery in active compared to sedentary rats[15]. The aim of this management approach is twofold: optimize traumatic muscle injury recovery in a timely manner and reduce the risk of traumatic muscle injury recurrence by preparing the injured muscle and the patient for the functional demands before returning to activities. The challenge is to find the optimal balance in mechanical stimuli to enable proper functional recovery but avoid injury aggravation; however, there is a lack of scientifically proven indicators to guide this balance. Pain is an indicator commonly used in clinical practice and scientific studies, with the aim to maintain a pain-free or limited pain status in all activities (e.g., rehabilitation programme, exercises, physical activities, sporting activities) during the recovery process from traumatic muscle injury[207,208]. One RCT reported no differences in time to return to activities and muscle injury recurrence when using pain-free (i.e., rehabilitation programme was performed without any pain: 0 on a 0-to-10 numeric rating scale) or pain-threshold (i.e., rehabilitation programme was performed with an accepted pain scored up to 4 on a 0-to-10 numeric rating scale) approaches to guide the rehabilitation programme[208]. Using pain as an indicator to perform exercises and activities and to guide the balance between mechanical stimuli and avoiding injury aggravation seems most optimal if 1) pain is not masked by analgesic (e.g., paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), or another analgesia), and 2) the patient is educated about the pain as an indicator and can implement this in their injury management.

Traumatic muscle injury management should not be limited to only targeting the injured muscle, but also targeting synergistic muscles to limit the work placed upon the injured muscle, address potential (pre-existing) risk factors, and avoid patient deconditioning (e.g., other muscles, musculoskeletal system, cardio-pulmonary system)[194,209]. Traumatic muscle injury management can be broadly divided into managing the early acute/sub-acute, repair/regeneration and functional phases as well as managing activities during recovery, medical treatments as an adjunct to rehabilitation, and return to activities/sports (FIG. 6).

[H2] Acute and sub-acute phases

The acute phase is related to immediate management when traumatic muscle injury occurs. The first aim is to protect the patient to avoid any subsequent accident, by removing the patient from injury causing situation. The second aim is to protect the muscle to avoid any injury aggravation, by stopping the injury causing activity, if applicable. In severe muscle injuries, with total functional impairment, protected weight- or load-bearing can be suggested, with additional treatment to reduce thrombophlebitis risk. But in most cases, load-bearing is allowed. Then, measures are proposed that limit the muscle damage consequences (i.e., hematoma, oedema, pain) and prepare the tissue healing.

The sub-acute phase concerns the first days after the injury. It was initially recommended to follow the RICE "rest, ice, compression, and elevation) approach[122]. Such an approach progressively evolved by adding protection (PRICE), and changing rest into optimal load (POLICE[210,211]) and, further evolved in 2020, by avoiding anti-inflammatories and adding education, psychological approach, physical conditioning and exercises (PEACE & LOVE[212]). The level of scientific evidence for all these approaches is low, and is mainly based on the understanding of the pathophysiological mechanisms (muscle tissue damage including hematoma, sweeling, oedema) and the clinical signs (pain and functional impairment), and experiences from patients and clinicians, aimed at reducing consequences, aggravation and deconditioning risks. Importantly, the sub-acute phases shifted, in the past five years[12,16,212], from a management approach including refraining movements and exercises and recommending immobilization to a management approach including early activation and mobilization through early and appropriate rehabilitation. This shift is based on scientific evidence from fundamental[12,15,126] and clinical[16] studies, consistent with the concept of mechanotherapy[126,213–216]. Thus, the sub-acute phase of traumatic muscle injury management usually requires adaptation to the load rather than stopping all movements and exercises. There is now a need for indicators to guide this early activation and mobilization process with the challenging balance between mechanical stimuli and avoiding injury aggravation.

[H2] Repair/regeneration and functional phases

These phases aim to guide physiological muscle repair and regeneration, limit muscle injury complications, and prepare the patient to return to their activities. It is often performed through interdisciplinary rehabilitation[217] supervised by a physiatrist or physiotherapist. It can also be performed autonomously by the patient following prescribed exercises, if the patient is able to understand and perform the exercises and if the muscle tissue damage (e.g., size of the muscle lesion) and impairments (e.g., muscle function, participation in activities) are low. Adequate rehabilitation or exercises should start as soon as possible[16].

Return to optimal capacity requires appropriate mechanical loading (constraints by mechanical stresses and strains on the muscle) of the injured muscle and the potentially deconditioned patient. Mechanical loading is essentially the only method of communication with the muscle about the required strength of the repair, the structure of the muscle fibres, and the required capacity of the muscle[12]. Delays in adequate loading can be detrimental to recovery and return to function[16]. Appropriate and gradually progressed loading also ensures that the patient is ready to cope with the demands of daily, occupational and sporting activities[194,218]. This period is also an optimal time to address any factors that might have predisposed the patient to a muscle injury[194,209].

Rehabilitation should be adapted to the goal and progression. It may be useful to consider the required capacity of the patient to complete their activities and to structure the rehabilitation backwards from there. Rehabilitation is a continuous process from the injury until the return to initial and/or expected activities[217,219], with a progressive increase in variation and complexity, volume and intensity of the exercises. When designing an exercise program, it is important to consider the stage of tissue healing, the outcomes to be achieved by the exercises, and the adaptation required to meet the specific needs of the patient. The programme should include the restoration of adequate strength through isometric or isotonic exercises to reduce muscle inhibition, restore motor recruitment and pain-free motion[220], and eccentric exercises[221,222] since they promote greater morphological and neuromuscular adaptations than other contraction modes[223] and to restore tissue capacity and muscle fibre length and to minimize the risk of recurrence[220]. In addition, regaining the neuromuscular control of the injured muscle and of the patient's movements is also essential through sensorimotor training of the central nervous

system's ability to fine-tune muscle activation and coordination with different movement velocities and lengths[224]. Finally, progressively including exercises and activities targeting the function and the demand-specific of the expected activity, and preparing the return to activities is important[194].

[H2] Management of activities during the healing process

During the healing process, it is important to avoid any risk of injury aggravation, but also to prevent unnecessary deconditioning. Limiting activities that can lead to adverse stresses/strains on the injured muscle is ideal. This can be achieved by continuing only pain-free activities or limiting to 'acceptable' pain and increasing their volume and intensity progressively. Thus, activities can be adapted, particularly sporting activities, rather than stopped, so that patients continue to follow the WHO recommendations on physical activities[21]. This can mean stopping the usual activity and doing another activity which does not involving the injured muscle. This may also mean decreasing the intensity of the exercise and/or limiting body weight impact (e.g., changing activity from running to walking or altered-gravity treadmill running). Another approach could be cross-education and gaining neural adaptation patterns in the injured limb through unilateral training of the uninjured limb[225–227].

In older adults, sarcopenia (the declining effect of age on muscle mass)[228], and accompanying factors of systemic inflammation and decreased functional muscle strength over the lifespan may be a major predisposing factor for acute muscle injuries[229]. Sarcopenia may be associated with inadequate muscle healing and chronic maladaptation during recovery after muscle injury in the elderly population[229]. Since physical activity has strong evidence promoting diminished decline and enhancement of physical function with few adverse events, especially for the elderly population[230–233], this supports promoting physical activity continuation within muscle injuries, especially in older adults.

In a global health approach, the period of the injury can also be used to educating the patients to protect their health with appropriate lifestyle (e.g., physical activities, nutrition, and sleep)[234].

[H2] Adjuncts to exercise rehabilitation

[H3] Surgery

Surgery should be used only in extreme circumstances[235], such as some complete muscle or tendon ruptures, in which surgical fixation may be indicated[235], although data indicate that even complete avulsion ruptures such as proximal hamstring-muscles avulsion ruptures can heal by conservative treatment to a similar level as surgical re-attachment of the muscles[236,237]. Decision modifiers for surgical intervention include the presence or absence of agonist muscles, distance of retraction, desired physical activity level (e.g., high-demanding sports or occupations) and patient preference[237].

[H3] Hematoma aspiration

After contusions, the formation of large hematomas may occur. Aspiration may be suggested in clinical practice to help the healing process or decrease the risk of compressive hematoma, encysted hematoma, muscle fibrosis, or myositis ossificans; however, there is no scientific evidence to support that this improves recovery[238,239].

[H3] Medications

There is a large diversity of treatment modalities as an adjunct to rehabilitation offered in clinical practice. Based on the current scientific literature, their use in traumatic muscle injury treatment cannot be recommended, as none have been sufficiently proven efficacious in clinical studies and for some, there are even concerns for a possible detrimental effect on muscle healing. Current supporting evidence is predominantly based on pre-clinical studies in animal models and non-controlled clinical case series. Rigorously conducted RCTs are available for the use of NSAIDs[240] and platelet-rich plasma (PRP) injections[241–243] in acute muscle injuries. Many other treatment modalities have been proposed to treat muscle injuries, including Actovegin® (deproteinized calf serum)[244], corticosteroids[245], hyperbaric oxygen therapy[246], losartan[247], stem cell therapy, extracorporeal shockwave therapy[248] and therapeutic ultrasonography[249], but without rigorous conducted clinical trials to support their use as treatments for traumatic muscle injuries.

Treatment with NSAIDs aims to inhibit pro-inflammatory activity in the early phase after muscle injury and provide an analgesic effect. Administration of oral NSAIDs in particular is common clinical practice. Numerous studies have demonstrated the potency of NSAIDs in

animal and human experimental settings,[250–253] although it remains unknown whether these results can be generalized to patients with acute traumatic muscle injuries. In the only RCT evaluating NSAIDs in patients with muscle strain injuries (n=44), no benefit of NSAIDs use over placebo was found on pain and muscle strength recovery in the short 7-day study period[240]. Given the strong effects of NSAIDs at the cellular level, together with the complexity of temporal events after injury, an increase in RCTs is needed to fully evaluate the role of NSAID administration in tissue repair after strain injury.

There is growing interest in (sports) medicine for "regenerative medicine" to facilitate muscle healing. Arguably, the most popular biological treatment approach for muscle injuries in the past 10 years is the injection of PRP. PRP is derived from centrifuging autologous blood to separate the plasma high in platelet concentration[254,255]. Growth factors released upon platelet activation are assumed to promote muscle regeneration[254,255]. Despite the promising regenerative benefits reported in early basic research and apparent widespread clinical use, a meta-analysis with pooled data of three RCTs showed no superiority of PRP over placebo, or no injection, in treating acute hamstring muscle injuries[241–243,256].

[H2] Return to normal activity levels

Returning to the level of activity required by the patient is often the goal of the patient but does not always correspond to the final stage of the recovery after traumatic muscle injury[219,257]. Before this, the patient should have completed the components of the final demand-specific activity goal[219,258]. At work, this typically occurs with the patient returning to their initial occupation on modified hours or duties and gradually progressing as capacity increases[218]. In sports, there is commonly a return to partial activities, first returning to adapted training to limit the constraints on the injured muscle and then a progressive increasing in participation, volumes and intensities[219,258]. Such graduated return to sports enables the preparation of the body globally and the injured muscle for demand-specific sporting activities[219,258]. This promotes the transition from "control to chaos", from a controlled environment to "chaotic" circumstances during return to activities[258].

The return to activity period is a challenging period during which the balance between a 'quick' return versus the risk of recurrence should be individually discussed. In sports, and especially for hamstring muscle injuries, return-to-sport criteria (e.g., strength, pain, functional

performance, flexibility, medical clearance) are recommended to be achieved by the patient before being eligible to return[259]. Since the muscle injury recurrence risk is high in the first days/weeks after return to activities/sports[54,257,260], caution and special attention are required in the acute phase of return to activities/sports. Importantly and consequently, the rehabilitation process should continue for a period after return to activity.

[H1] Quality of life

Traumatic muscle injuries in their manifold appearance can negatively affect the quality of life in various domains. Associated pain and loss of muscle function can lead to impairment in usual musculoskeletal system function. This could negatively affect various areas of daily life, and thus lead to participation impairment or loss in social, occupational, physical or sporting activities, depending on injury site, type and severity[13]. This can consequently lead to a decreased quality of life and well-being. For example, in an analysis of health-related quality of life in uninjured and injured adolescent athletes (including muscle injuries), the Short Form–36 Health Survey Questionnaire (SF-36) and Paediatric Outcomes Data Collection Instrument (PODCI) showed lower scores for physical functioning (SF-36: 55.1 *vs.* 57.1), limitations due to physical health problems (SF-36: 49.5 *vs.* 56.6), pain and comfort (SF-36: 45.1 *vs.* 54.2; PODCI: 31.7 *vs.* 48.5), as well as social functioning (SF-36: 51.0 *vs.* 56.4), concluding at a lower health-related quality of life in injured adolescent compared to uninjured peers[14]. Traumatic muscle injury can negatively affect mental health such as causing uncertainty, apprehension, depression or anxiety[196,261]. This can affect the return to active life if not adequately managed. There is, however, scarce research investigating quality of life and the psychological and social effects of muscle injury[262]. Muscle injury also represents a cause of interruption or even cessation of physical activity and sport, recommended to promote health[21]. This is associated with the inherent consequences of physical inactivity or even a sedentary lifestyle on health[261,263,264]. As such, it seems that traumatic muscle injuries lead to two side-effects on health: direct tissue injury, and indirect physical and psychological effects caused by physical inactivity or possible sedentary behaviours. The prevention and appropriate diagnosis and management of traumatic muscle injuries, and communication between different stakeholders in the health care system, are important to reduce muscle injury impact.

Outlook

Improving traumatic muscle injury prevention strategies may represent an important perspective for muscle injury management in sporting and non-sporting populations as well as patients with underlying muscle pathologies. This can be helped by a better understanding of the underlying conditions of traumatic muscle injuries that are highly multifactorial and complex. There is a need to extend the understanding of the factors and mechanisms, and their interactions, that are involved in the occurrence of traumatic muscle injuries. This should include several perspectives and domains, at the macroscopic and microscopic levels and integrating several domains (e.g., anatomical, biomechanical, and biological, as well as psychological and environmental factors), in addition to the demands of activities (including daily life, occupation and sports participation). This could enable the proposal of new muscle injury primary, secondary and tertiary prevention measures.

A better basic and translational understanding of the mechanisms of skeletal muscle injury and repair/regeneration is still needed. Currently, the most pressing question is pinpointing the actual site of tissue disruption at the ultrastructural level (e.g., is there separation of myofibre basement membrane from the tendon collagen matrix?). Without knowledge regarding the nature of the tissue (e.g., myofibre or tendon) damaged during injury, it is difficult to guide rehabilitation programmes to achieve improved outcomes. Tissue and fluid sampling from injured individuals for nanometre scale imaging (e.g., electron microscopy) and molecular analysis (e.g., proteomics or single nuclei RNA-sequencing) is the only way to answer this question, and then perhaps, appropriate experimental animal or organoid models can be developed to take this research further.

For traumatic muscle injury management, physical therapy including exercise is the current gold standard. Improvements in basic knowledge on skeletal muscle injury and repair/regeneration would be advantageous for improving traumatic muscle injury management. Clearer and scientifically proven guidelines and indicators to guide this process, the increase in exercise modalities, volume and intensity, the patients' autonomy, and the return to activities are still needed. After a traumatic muscle injury, the prognosis for time to return to activities is a clinical requirement by the patients and their entourage, and the health professionals involved. This represents the subject of ongoing and future research to improve the ability to provide our patients with accurate prognoses. Some medications are used without proven efficacy, we thus need rigorously conducted RCTs to evaluate whether (new)

medications/therapies provide benefits in patients with muscle injuries. New regenerative medicine (e.g., stem cell) or gene therapy may provide other opportunities to accelerate and/or improve muscle repair. However, this raises ethical questions, as exercise therapy normally provides good results on the return to activities and the consequences and impairment of muscle injuries probably do not legitimate such approaches.

Finally, it is of interest to extend the current scientific evidence to other skeletal muscles involved in common muscle injuries and to larger populations particularly non-sporting general populations as well as patients with underlying muscle diseases or sarcopenia. This would enhance development of comprehensive, integrated approaches of muscle injury prevention and management.

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Acknowledgements

The authors would like to that Dr Sylvain Grange (Department of Radiology, University Hospital of Saint-Etienne, France) for providing imaging of muscle injuries.

Author contributions

Introduction (P.E.); Epidemiology (K.H. and P.E.); Mechanisms/pathophysiology (A.M., R.L., and T.G.); Diagnosis, screening and prevention (G.R., PE., T.P. and T.G.); Management (P.E., T.P., G.R., T.A.J. and T.G.); Quality of life (T.G. and P.E.); Outlook (P.E.); All authors critically revised all aspects of the article. P.E. and K.H. were responsible for overall handling of the manuscript.

Competing interests

G.R. reports an institutional grant from Arthrex for a previously performed randomized clinical trial on efficacy of PRP in hamstring injuries and non-financial support to his institution from Arthrex (Heittich centrifuge on loan) for a previously performed randomized clinical trial on efficacy of PRP in ankle osteoarthritis.

The other authors declare no competing interests.

Tables:

Table 1: Experimental animal and human models of muscle injury[10,104,105]. This table provides an overview of commonly used models of muscle injury in both animals and humans. Events and features of each model are provided to highlight key differences and similarities, including the extent of the damage (focal damage or full myofiber necrosis), which in turn are associated with the injury mechanism (direct or indirect) and with repair and regeneration outcomes. For example, one of the major differences is whether scar tissue is formed. Scar tissue rarely resolves so full tissue repair is unlikely.

Injury mechanisms	Extent of damage	Repair / regeneration	Experimental animal models	Species	Inflammatory cell activity	Myogenesis	Vascular component	Basement membrane damage	Scar tiss
Direct muscle injury (laceration)	Focal damage	Repair	Laceration	Animal	Yes	Yes	Yes	Yes	Yes
Direct muscle injury (contusion)	Focal damage	Repair	Contusion	Animal	Yes	Yes	Yes	Yes	Yes
Indirect muscle injury (strain)	Full myofibre necrosis	Regeneration	Toxin (e.g., cardiotoxin)	Animal	Yes	Yes	Yes	No	No
Indirect muscle injury (strain)	Full myofibre necrosis	Regeneration	Electrical stimulation for eccentric contraction	Animal / Human	Yes	Yes	Yes	No	No
Indirect muscle injury (strain)	Depends on location	Depends on location	Strain	Animal	Yes	Unknown	Yes	No	Yes

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Table 2: Traumatic muscle injury diagnosis and important differential diagnosis to consider.

Injury type	Direct contact, indirect non-contact or differential diagnosis	Injury mechanism	Clinical examination	Additional imaging	Recovery prognosis
Strain or rupture / indirect muscle injury	Indirect non-contact	Muscle contraction or stretch	Sharp twinge felt during contraction (eccentric, concentric or isometric) or stretch Triad of pain: upon stretch, resistance testing and palpation	Usually not required for diagnosis	Several days up to 3 months, large variation according to clinical presentations
Contusion or laceration / direct muscle injury	Direct contact	A direct blunt external force compressing the muscle tissue	Painful swelling Stretch test: marked pain and loss of range of motion	Usually not required for diagnosis. May be used in severe cases for hematoma management/monitoring.	From few days up to 2-3 weeks, bu with large variation according to tissular damages
Complete tendon rupture	Differential diagnosis	Excessive forced stretch/lengthening of the muscle-tendon complex	Substantial or complete loss of muscle strength	MRI or ultrasonography to confirm or rule out and guide treatment decision making	>3 months up to a year

			Marked pain provocation and functional deficit		
			Deformation of the tendon-muscle contour (gap and/or bulging)		
			Extended bruising may be present		
		High energetic trauma mechanism			Possible persistent functional deficits
		May not be remarkable and can occur in similar situations to the common strain			Requiring adapted rehabilitation and in some cases surgical intervention[158]
Apophyseal avulsion fracture	Differential diagnosis	Often not remarkable and similar to a common strain	In skeletally immature patient (i.e., children and adolescents, in who the apophysis is the weakest link in the muscle-tendon-bone complex in the skeletally immature)	Plain radiograph is the first-line imaging modality to confirm or rule out and guide treatment decision making (FIG. 4)	>3 months up to a year
			Substantial or complete loss of muscle strength		

			Marked pain provocation at the apophysis		

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Figures:

Fig. 1: Structural organization of the skeletal muscle.

Skeletal muscle consists of muscle fibre bundles, separated by connective tissues (epimysium, perimysium, and endomysium)[2]. These connective tissue come together to join to the tendon that unites the muscle to the bony skeleton. The myofibrils, found within each muscle fibre, consist of alternating A- (Anisotropic band, containing myosin and part of actin myofilaments) and I-bands (Isotropic, containing only actin myofilaments) with the Z-discs located in the middle of the I bands. The region of a myofibril between two successive Z-discs is known as the sarcomere: the fundamental contractile unit of muscle composed primarily of the contractile proteins actin and myosin[2]. A third filament, titin, extends from the middle of the A-band to the Z-disc[5]: Titin is the major passive load-bearing protein within a sarcomere but does not bear significant passive load at the whole muscle level in which loads are borne primarily by connective tissue[6,7]. The skeletal muscle is biomechanically organized in contractile (i.e., the sarcomeres) and elastic components (i.e., the connective elements)[8].

Fig. 2: Pathophysiology of muscle injury.

Direct or indirect and non-contact trauma lead to stresses (the amount of force experienced per unit area of tissue) and strains (the relative length change of muscle tissue when stress is applied (i.e., strain is the measure of the deformation of the tissue)) to the skeletal muscle. When stresses and strains to the skeletal muscle exceed the load-bearing capability of the skeletal muscle, this results in muscle damage[10]. The muscle damage can be repaired, leading to similar muscle load-bearing capability; however, when muscle injury repair is incomplete muscle load-bearing capability is decreased. When muscle does not reach complete repair there may be negative sequelae, such as chronic/recurrent pain or long-term muscle strength deficit. When stresses and strains to the skeletal muscle are lower to their load-bearing capacity, this can result in increasing the muscle load-bearing capability (e.g., in case of strengthening).

Fig. 3: Molecular mechanisms of muscle injury.

Muscle injury can be broadly categorised according to whether there is focal damage (to small segments of the myofibre and its basement membrane) or full necrosis of myofibres, which is also linked to the injury mechanism: direct or indirect muscle injuries, respectively (TABLE 1). Both share an infiltration of immune cells, creating a pro-inflammatory environment, rich in signalling molecules, such as cytokines and growth factors, to force satellite cells to re-enter the cell cycle and proliferate[98]. Ultimately, some of these satellite cells fuse to form myotubes to replace damaged segments, or completely reform a necrotic myofibre. The shift from a pro-inflammatory, to anti-inflammatory, environment is essential for progression to the fusion stage[98]. Fibroblasts also play an important role in stimulating myogenic cell fusion[102,106]. In real-life muscle injuries, the administration of NSAIDs may play in role in regulating the inflammatory environment although data from injury models and inconsistent and further work is required. Lastly, the basement membrane plays a key role as it acts as a scaffold for regeneration, so if the basement membrane is damaged along with myofibres, the regeneration is delayed[107].

Fig. 4: Imaging modalities for exemplary muscle injuries and differential diagnosis.

a: Ultrasonography of the posterior leg showing a lesion at the interface between the muscle and connective tissues of the gastrocnemius medialis muscle (arrow and crosses) from the soleus muscle. B: MRI axial section with T2FatSat sequence of the thigh showing a hyperintense signal in the left vastus medialis muscle (arrow) corresponding to a muscle oedema inside the muscle and a grade 1 at the Peetrons classification system. C-d: MRI coronal © and axial (d) sections showing an injury of the right hamstrings (long head of the biceps femoris muscle and semimembranosus muscle). The high signal intensity on these fluid sensitive sequences indicates oedema and hematoma in the injured area (arrow). e: IRM sagittal section of the thigh with T2 sequence showing a proximal avulsion tendon injury of the semimembranosus muscle with retraction of the proximal tendon (arrow). F: IRM axial section with T2FatSat sequence of the thigh showing a hyperintense signal in the left long head of the

biceps femoris muscle regarding the myotendinous junction (arrow), corresponding to a grade 2 at the Peetrons classification system. g: Plain radiograph showing an avulsion fracture of the right trochanter minor (arrow) corresponding to the muscle iliopsoas insertion in an adolescent athlete.

Fig. 5. Overview of commonly used classification systems for muscle injuries.

Numerous grading systems for muscle injuries have been proposed. The classification system from the American Medical Association[154] is the most used, since it is based on clinical evaluation. When using imaging, the Modified Peetrons[155] is widely used, and in sports context the British athletics system[156] was proposed in 2014 based on MRI. In sports context, the Munich consensus system[142] in 2013 and Barcelona system[157] in 2017 have also been suggested based on clinical and imaging evaluations.

Fig. 6: Exemplary management workflow for a common type of injury, from the muscle injury and its diagnosis to the return to activities, with expected timelines.

Timelines are an indication to see the range of possible times, but timelines widely vary according to muscle injury diagnosis (e.g., location, severity).

Boxes:

Box 1: General guidelines for patient history and physical examination when diagnosing muscle injuries.

Patient History

- Patient-related factors
  - Age
  - Skeletal maturity
  - History of previous muscle injuries
  - Type and level of activity

- Injury-related factors
  - Injury mechanism
    - Indirect (strain) *vs.* direct (contusion)
    - active contraction *vs.* passive stretch
  - Site of pain
  - Pain mode of onset
  - Pain intensity
  - Function loss
  - Progress symptoms over time

Clinical examination

- Inspection
  - Bruising/hematoma
  - Deformation of the muscle contour: swelling, gap and/or bulging
- Stretch testing
  - Flexibility deficit
  - Pain intensity
- Resistance/strength testing
  - Strength deficit
  - Pain intensity
- Palpation
  - Gap, oedema
  - Pain location and intensity