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Acute hamstring injuries – diagnosis and prognosis

DISSERTATION FROM THE NORWEGIAN SCHOOL OF SPORT SCIENCES • 2018

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ASPETAR ORTHOPAEDIC SPORTS MEDICINE HOSPITAL IN DOHA, QATAR

THE DATA COLLECTION WAS PERFORMED AT ASPETAR

Sport has the power to change the world.

It has the power to inspire.

It has the power to unite people in a way that little else does.

It speaks to youth in a language they understand.

Sport can create hope where once there was only despair.

It is more powerful than government in breaking down racial barriers.

Nelson Mandela, from the speech '*Power of sport'* in 2006

الرياضة لديها القدرة على تغيير العالم.

لديها القدرة على الإلهام.

لديها القدرة على توحيد الناس بطريقةٍ قلّما تتوفر في غيرها.

إنها تتحدث إلى الشباب بلغةٍ يفهمونها.

الرياضة يمكنها أن تخلق الأمل حيث لم يكن هناك سوى اليأس.

إنها أشد قوة من الحكومات في تحطيم الحواجز العنصرية.

نيلسون مانديلا، من خطاب "قوة الرياضة" عام 2006

Occurrences in this domain are beyond the reach of exact prediction because of the variety of factors in operation, not because of any lack of order in nature

Albert Einstein

Table of contents

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Arnlaug Wangensteen

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List of Papers

This dissertation is based on the following original research papers, which are referred to in the text by their Roman numerals:

I. Wangensteen A, Bahr R, Van Linschoten R, Almusa E, Whiteley R, Witvrouw E, Tol JL. MRI appearance does not change in the first 7 days after acute hamstring injury - a prospective study. 2017 Jul;51(14):1087-1092. doi: 10.1136/bjsports-2016-096881. Epub 2016 Dec 28.

II. Wangensteen A, Almusa E, Boukarroum S, Farooq A, Hamilton B, Whiteley R, Bahr R, Tol JL. MRI does not add value over and above patient history and clinical examination in predicting time to return to sport after acute hamstring injuries: a prospective cohort of 180 male athletes. Br J Sports Med. 2015 Dec;49(24):1579-87. doi: 10.1136/bjsports-2015-094892. Epub 2015 Aug 24.

III. Wangensteen A, Tol JL, Roemer FW, Bahr R, Dijkstra HP, Crema MD, Farooq A, Guermazi A. Intra- and interrater reliability of three different MRI grading and classification systems after acute hamstring injuries. Eur J Radiol. 2017 Apr;89:182-190. doi: 0.1016/j.ejrad.2017.02.010. Epub 2017 Feb 11.

IV. Wangensteen A, Guermazi A, Tol JL, Roemer FW, Hamilton B, Alonso JM, Whiteley R, Bahr R. New MRI muscle classification systems and associations with return to sport after acute hamstring injuries. European Radiol. 2018. Published online 19 February 2018.

V. Wangensteen A, Tol JL, Witvrouw E, Van Linschoten R, Almusa E, Hamilton B, Bahr R. Hamstring Reinjuries Occur at the Same Location and Early After Return to Sport: A Descriptive Study of MRI-Confirmed Reinjuries. Am J Sports Med. 2016 Aug;44(8):2112-21. doi: 10.1177/0363546516646086. Epub 2016 May 16.

Abbreviations

ANOVA	Analyses of variance
BAMIC	British Athletics Muscle Injury Classification
BF	Biceps femoris
CI	Confidence interval
CSA	Cross sectional area
ECM	Extracellular connective-tissue matrix
ETL	Echo train length
FOV	Field of view
IQR	Interquartile range
κ	Cohen's kappa
MRI	Magnetic resonance imaging
MTJ	Musculotendinous junction
NSMP	National Sports Medicine Program
QSL	Qatar Star League
PD-w	Proton density-weighted
PD-w FS	Proton density–weighted fat-suppressed
PPP	Platelet-poor plasma
PRP	Platelet-rich plasma
RCT	Randomised controlled trial
ROM	Range of motion
RTS	Return to sport
SLR	Straight leg raise
SM	Semimembranosus
SPSS	Statistical Package for the Social Sciences
ST	Semitendinosus
T	Tesla
TE	Time to echo
TR	Time to repetition
VAS	Visual analogue scale

Summary

Introduction

Acute hamstring injury is one of the most common non-contact muscle injuries in sports. The incidence remains high, causing a significant loss of time from training and competition, and a substantial risk of sustaining a reinjury. However, there is still a lack of knowledge and consensus regarding the diagnosis and prognosis for time to return to sport (RTS). The overall aim of this thesis was therefore to investigate aspects related to diagnosis and prognosis of acute hamstring injuries in male athletes, based on baseline clinical examinations and magnetic resonance imaging (MRI).

Methods

This thesis is based on two separate study projects. Male athletes (18-50 years) with acute hamstring injury were recruited in the outpatient department at the study center and underwent standardised baseline clinical and MRI examinations. The MRIs were scored by one or two experienced radiologists using standardised scoring forms. In the first project (Paper I), athletes with positive MRI ≤1 day after injury were prospectively included (between January 2014 and December 2015), and consecutive MRIs were then obtained daily throughout the subsequent week. One radiologist scored the MRIs in order to describe the day-to-day changes in the extent of the oedema, and to investigate the optimal timing for fiber disruption. The second project (Papers II-V) is a prospective cohort with pooled data from 180 athletes included in a previous randomised controlled trial or an ongoing prospective case series (between January 2011 and June 2014). Clinical examinations and MRI were obtained ≤5 days and the athletes were followed up until RTS. In Paper II, two multiple regression models were created to analyse the predictive value of clinical examinations alone, and the additional value of MRI, for time to RTS (in days). To examine the prognostic value of three different MRI grading and classification systems, the intra- and interrater reliability of the modified Peetrons grading system, the Chan acute muscle injury classification (Chan) and the British Athletics Muscle Injury Classification (BAMIC) was first assessed in 40 selected athletes (Paper III). Then, agreement between each of the MRI systems and their associations with RTS were analysed (Paper IV). In Paper V, athletes with MRI confirmed reinjury ≤365 days after RTS were included. The MRIs of the reinjury were compared with the MRIs of the index injury, to describe and analyse reinjury characteristics.

Main results

For the 12 athletes included, there were no significant day-to-day changes in the extent of oedema for any of the oedema measures. Fibre disruption (tear) present in 5 of the athletes, was detectable from day 1, with small and insignificant changes (Paper I). In the first regression model including only patient history and clinical examination, the final model explained 29% of the total variance in time to RTS. By adding MRI variables, the second final model increased the adjusted R^2 values from 0.290 to 0.318. Thus, the additional MRI explained only 2.8 % of the variance in RTS (Paper II). For the grading and classification systems, we observed 'substantial' to 'almost perfect' intra- and interrater reliability for severity gradings, overall anatomical sites and overall classifications for the three MRI systems (Paper III). Among all athletes included in paper IV (n=176), there was for the MRI-positive injuries moderate agreement between the severity gradings. Substantial variance in RTS within and overlap between the MRI categories was demonstrated. Mean differences showed overall main effect for severity gradings, but varied for anatomical sites for Chan and BAMIC. The total variance in RTS explained varied from 7.6% - 11.9% for severity gradings and BAMIC anatomical site. In the 19 athletes included with a reinjury (Paper V), 79% of these reinjuries occurred in the same location within the muscle as the index injury. More than 50% of the reinjuries occurred within 25 days after RTS from the index injury and 50% occurred within 50 days after the index injury. All reinjuries with more severe radiological grading occurred in the same location as the index injury.

Conclusions

Based on the findings, MRI can be performed on any day during the first week following acute hamstring muscle injury with equivalent findings. Regarding prognosis, there were wide individual variations in RTS. The additional predictive value of MRI for time to RTS was negligible compared to baseline patient history taking and clinical examinations alone, and the MRI systems poorly explained the large variance in RTS for MRI-positive injuries. Thus, our findings suggest that baseline clinical or MRI examinations cannot be used to predict RTS just after an acute hamstring injury, and provides no rationale for routine MRI. If used, the specific MRI system should be reported, to avoid miscommunication or misinterpretation in daily clinical practice. The majority of the reinjuries occurred in the same location as the index injury, relatively early after RTS and with a radiologically greater extent. Specific exercise programs focusing on reinjury prevention initiated after RTS from the index injury are therefore highly recommended.

Introduction

Muscle injuries are very common in sports and constitute approximately 20% of all injuries sustained by athletes, depending on the type of sport (1). In major sports, like football (soccer), more than 1/3 of all injuries occurring are reported as muscle injuries (2–5), of which the majority (81-92%) are located to the 'big four' lower extremity muscles: the hamstrings, quadriceps, adductors and gastrocnemius (2,3). Also among track and field athletes and other football and rugby codes, thigh muscle injuries represent the most common diagnosis (6–14). After a muscle injury, the risk of sustaining a recurrent injury is high (2,15), increasing the total time off from training and competition. Also, the consequences for the individual athlete of a (muscle) injury might not only be related to pain and physical impairments, there may also be psychological impact (16). Interestingly, fear of reinjury is a common negative psychological response that might influence the rehabilitation and the return to sport process (17,18), although no data exist specifically on muscle injuries. In elite sports, a muscle injury resulting in time loss and reduced performance may also influence the team's performance and chances of success (19–21), and decisions regarding return to sport (RTS) and athlete availability can have significant financial or strategic consequences for the athlete and the team (22). There is therefore, particularly at the professional level, great interest in optimizing the diagnostic, prognostic, therapeutic and rehabilitation processes after muscle injuries in order to minimize absence from sport and reduce recurrence rates (22,23).

The following sections form the theoretical background for this thesis, highlighting the gaps of knowledge and the rationale for the specific aims presented.

Muscle injuries

Definitions

An acute muscle injury resulting from sport activity is characterized as a traumatic injury with a clearly defined cause or sudden onset, where the force applied to the tissue generates stresses and/or strains that are greater than the tissue can withstand (24–26). The macro-trauma of the tissue is generally caused by either internal forces as distension ruptures (strains/tears) or by external forces from direct trauma, such as contusions (24,25). An overuse injury is thought to be caused by repetitive micro-trauma of the tissue, presenting with a more gradual onset of pain (27,28), usually with underlying pathology and/or precipitated by a period of inappropriate load (28). In the large UEFA UCL injury studies among European professional football players, an acute injury is defined as; '*Injury with sudden onset and known cause*', and a muscle injury is defined as; '*traumatic distraction or overuse injury to the muscle leading to a player being unable to fully participate in training or match play*' (2,25,27); however, direct contusions are excluded from their registration and not accounted for in these reports from these studies. Generally, it is easy to classify an injury as acute or overuse based on its onset characteristics. Yet, in some cases it may be less obvious, particularly when the symptoms present with a sudden onset, but the injury may actually be the result of a long-term process (29). There is currently no uniform consensus on the definitions and classifications of muscle injuries and various terms and definitions have been described and are debated in the literature (23,25,27,30,31). Thus, establishing standardization and guidelines for the assessment and management of muscle injuries remains challenging. In Figure 1, a schematic general overview of the different muscle injury types is presented. However, it should be noted that this is not a definite model, and there are always nuances (for example myositis ossificans can also occur following a strain injury).

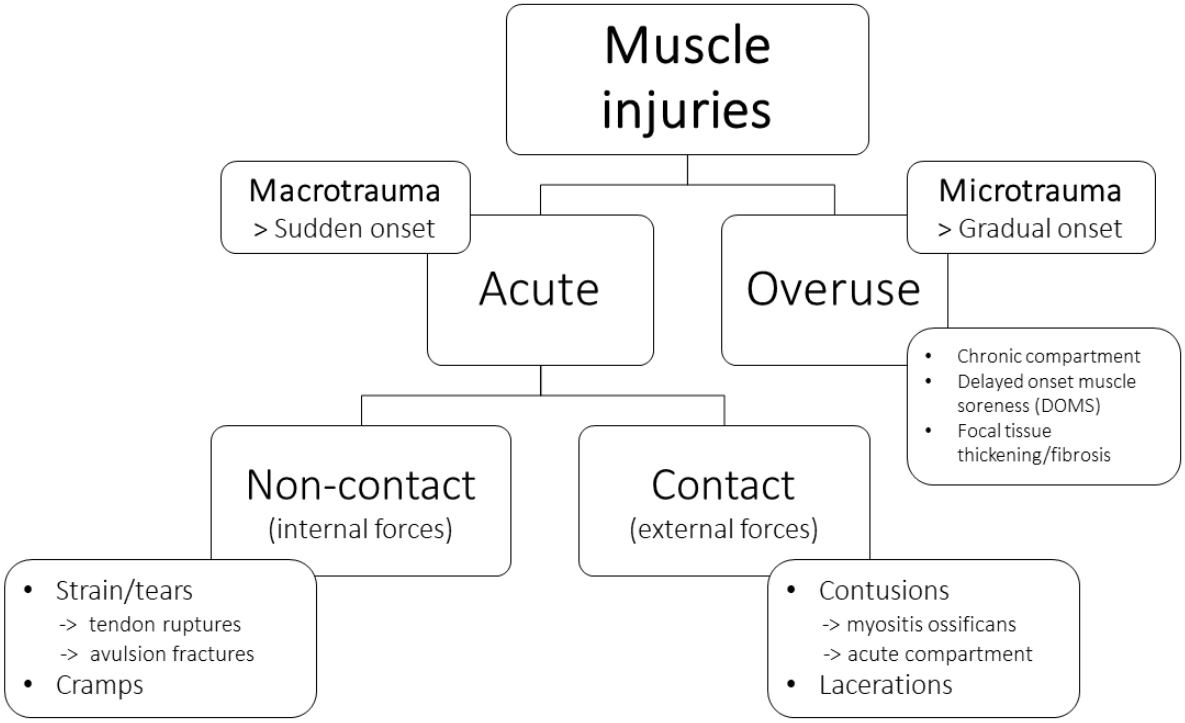


Figure 1: Schematic overview of the different types of muscle injuries. (The arrows -> represent possible consequences or sequelae related to the type of injury).

Muscle strain injuries

Acute non-contact muscle injuries caused by excessive internal tensile forces are usually defined as muscle strain injuries or muscle tears/ruptures, typically referred to as 'pulled muscle' (32–34). They commonly occur within muscles exposed to high active and passive tension, where active tension is generated by muscle contractile forces and passive tension is caused by excessive stretch on the connective tissue components (26,35,36). Based on biomechanical studies using animal models (37,38), muscle strain injuries are thought to occur during either passive stretching or during a major single eccentric muscle contractions when the muscles are lengthened while producing forces, and excessive tensile and/ or shear forces within the muscles cause muscle fibres and their surrounding connective tissue to fail (26,34,38–41). In sports, most strain injuries occur in the thigh (the hamstrings, the quadriceps, the adductor muscles), or the calf (2,4,21), as they often contract eccentrically and contain a high proportion of type-II (fast twitch) muscle-fibers, which is associated with greater active force production (35,41). The passive tension is also often high, since these muscles span two joints and are physiologically most active and

required to contract when they are stretched at both joints (32,35,42). The definitions and use of the different terms for this muscle injury type are still debated with no uniform consensus (23,31). *Strain* is referred to by Hägglund et al. (25) as '*acute distraction injury of muscle and tendons'*, reflecting primarily the biomechanical mechanism of the injury. On the other hand, Mueller-Wohlfahrt et al. (23) prefers the term '*tear*' (or '*rupture*'), which reflects more the structural characteristics of the injury. Further in this thesis, *strain* is used as the preferred term.

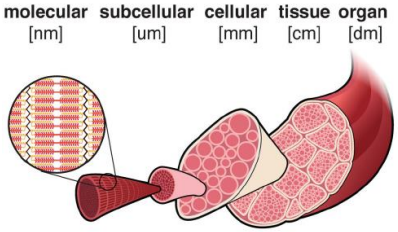
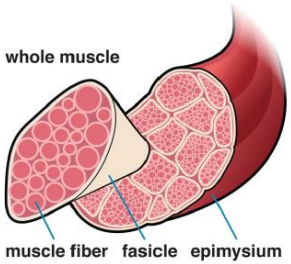
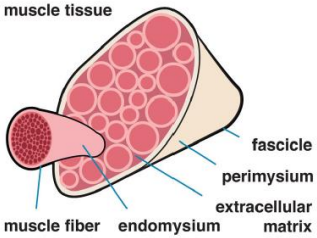
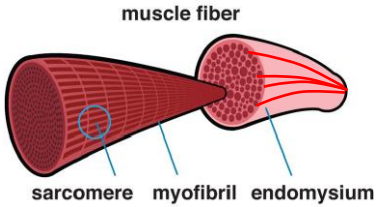
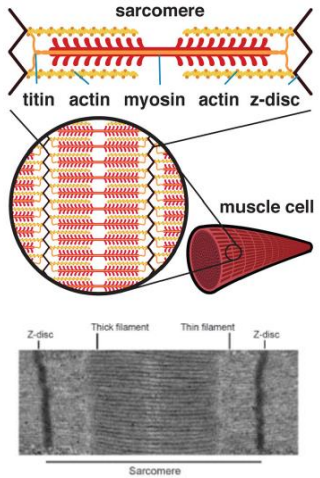
Principles of muscle healing

The diagnosis, prognosis and management of an acute muscle injury are based on the basic principles of muscle healing. However, few clinical studies exist and the current treatment principles are mostly based on experimental studies or empirical evidence only (32,33).

Muscle structure (normal)

Skeletal muscle represents the largest tissue mass in the body (43), and is a composite structure consisting of muscle fibers (fused myotubes that are differentiated muscle cells, also called myocytes), organised networks of nerves and blood vessels, and an extracellular connective-tissue matrix (ECM) (32,43–45). Muscle adaptation to mechanical stimuli spans from the molecular to the organ scale (44) (Table 1). The muscle fibers with their innervating nerves are responsible for the contractile function of the muscle, whereas the ECM provides the framework that binds the individual muscle cells together during muscle contraction and embraces the capillaries and nerves within the muscle structure (32). Thus, the ECM plays an important role in muscle fiber force transmission (43,45–47), as it sums up the contraction of the individual muscle fibers into a joint effort, converting the contraction of the individual muscle fibers into efficient joint force production (32). Additionally, the ECM also plays a vital role in maintenance and repair (43,45,46,48), as it regulates various cellular processes, such as cell growth, proliferation, differentiation, migration and adhesion (45). While the muscle fiber itself has been the main focus in the study of muscle damage and repair, relatively little is known about the ECM surrounding the fibers (48). The ECM is a complex and dynamic network of collagens, non-collagenous glycoproteins, proteoglycans and elastin (45) and bounds the individual muscle fibers together by 3 levels of sheaths; the epimysium (surrounding the muscle), perimysium (surrounding muscle fascicles), and endomysium (surrounding muscle fibers) (44,46) (Table 1). Each muscle fiber is attached at both ends to the connective tissue of a tendon or a tendon-like fascia at the musculotendinous junctions (32,49).

Table 1: Schematic overview of a skeletal muscle structure (adapted from Wisdom et al 2015 (44)[1] and Greising et al 2012 (50)[2]).

Length scales of skeletal muscle adaptation	Organ	Tissue	Cellular	Molecular and sub-cellular
				
Muscle adaptation to mechanical stimuli spans from the molecular to the organ scale, bridging eight orders of magnitude in length.	A bundle of fascicles is contained within the epimysium (the outermost connective tissue layer) to form the whole muscle.	Muscle fibers, embedded in a collagenous extracellular matrix (ECM) form a fascicle. Muscle fibers are surrounded by the endomysium, fascicles are surrounded by the perimysium, and the whole muscle is surrounded by epimysium	Sarcomeres arranged in series form myofibrils, which, arranged in parallel, make up the muscle cell or muscle fiber. Muscle fibers are surrounded by endomysium.	The sarcomere is defined as the region between two Z-discs. The Z-disc is connected to myosin via titin. To generate force, myosin filament heads ratchet along actin filaments. The myosin heavy chain isoform influences the intrinsic velocity of active force generation. The titin filament primarily affects the passive fiber force

[1]Reprinted / adapted by permission from Springer Nature [Publisher] in: Wisdom KM, Delp SL, Kuhl E. Use it or lose it: multiscale skeletal muscle adaptation to mechanical stimuli. Biomech Model Mechanobiol. 2015 Apr;14(2):195–215. [2]Reprinted with permission from John Wiley and Sons [Publisher] in: Greising SM, Gransee HM, Mantilla CB, Sieck GC. Systems biology of skeletal muscle: fiber type as an organizing principle. Wiley Interdiscip Rev Syst Biol Med. 2012 Oct;4(5):457–73.

The musculotendinous junction

The musculotendinous junctions (MTJs) are specialized, mechanical junctions at which contractile forces are transmitted from the muscle fiber to the ECM at the end of the muscle fibers (51,52) (Figure 2A). This means that the MTJ is the region of the muscle that transmits the force generated by the muscle fibres to the tendon that subsequently transmits the force to the bone (53). At the MTJ, tendinous collagen fibrils are inserted into deep recesses formed by muscle cell processes (finger-like processes), allowing the tension generated by intracellular contractile proteins of muscle fibers to be transmitted to the collagen fibrils (54). This complex architecture reduces the tensile stress exerted on the tendon during muscle contraction, however the MTJ is still considered to be the weakest point of the muscle-tendon unit (53–55). Anatomically, a MTJ describes the portion of a tendon (either proximal or distal) into which muscle fibers insert (56) and spans a relatively large distance, as opposed from the 'mini-MTJs' at the cellular level, which measure only a few microns. Muscle strain injuries that occur due to eccentric contractions are reported to commonly occur at or near the MTJ (37,51,57–60). But, on a microscopic level, the site at which failure occurs at the MTJ is still unclear, and might be influenced by the activation state of the muscle, the loaded muscle or animal species used in the different studies (37,51,55) (Figure 2B).

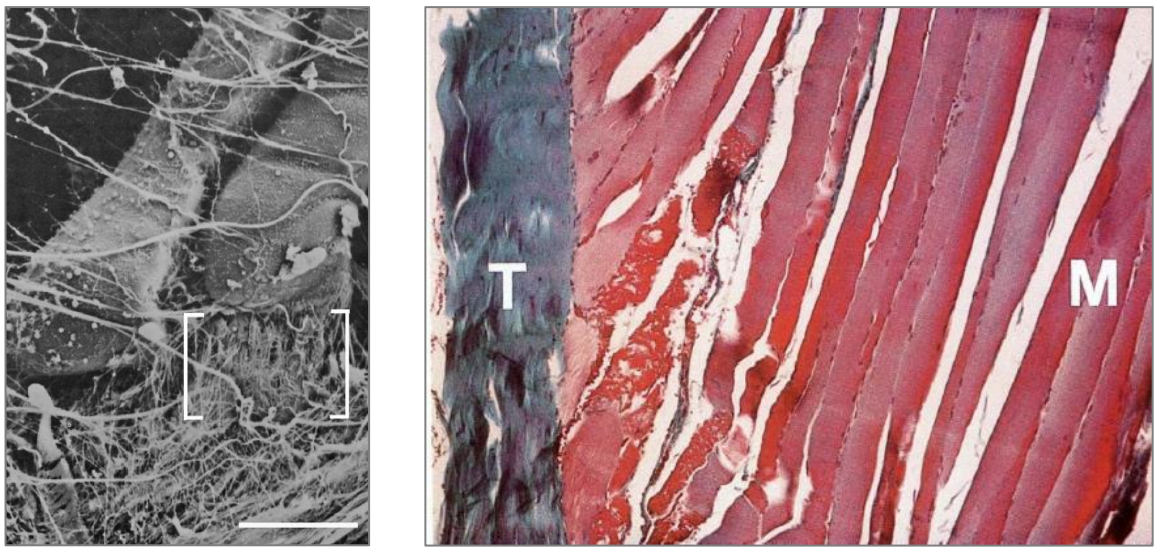


Figure 2: The MTJ. A) Scanning electron micrograph of two skeletal muscle fibers terminating at their myotendinous junctions (MTJs), where they are mechanically coupled to tendon collagen fibers. Bundles of collagen fibers pass from the tendon in the bottom third of the micrograph to bind to the ends of the muscle fibers at the MTJ (between brackets). During muscle strain injuries, lesions occur at or near the MTJ depending on the state of activation of the fiber and the muscle experiencing the strain injury. Bar = 100 µm. B) Histological appearance showing a longitudinal section of a TA muscle immediately following strain injury. There is limited rupture of the most distal fibers near the musculotendinous junction (red), along with haemorrhage. The dark, vertical band on the left of is tendon. T, tendon; M, intact muscle fibers. The figures are reprinted with permissions from the original references (55,61) and from John Wiley and Sons [Publisher] in: Tidball JG. Mechanisms of muscle injury, repair, and regeneration. Compr Physiol. 2011 Oct;1(4):2029–62.

In a three-dimensional study of the human MTJ recently published (52), the mentioned finger-like processes were shown to be ridge-like protrusions of collagen-rich tendon inserting into furrow-like indentations of the muscle, implicating a greater surface area between muscle and tendon through which force is transmitted. An increased surface area is considered to reduce the stress on the tissue, as well as increasing the load capacity at the MTJ (52), which may be related to injury susceptibility.

The healing process after an acute muscle injury

Injured skeletal muscle heals by a repair and remodelling process, in contrast to fractured bone, which heals by a regenerative process (32,62). Most of the musculoskeletal tissues when being repaired will heal with a scar which replaces the original tissue, whereas during the regeneration of a bone, the healing tissue is nearly identical to the pre-existing tissue (32,62).

The healing process of an injured skeletal muscle is reported to follow a fairly constant pattern irrespective of the underlying cause/mechanism (contusion, strain or laceration) (32,33,43,62–66); the muscle fibers and their connective tissue sheaths are disrupted and a gap appears between the stumps when muscle fibres retract. The ruptured gap is filled with hematoma, proliferation granulation tissue, and later, by a connective (scar) tissue (63). This healing response is initiated rapidly following the injury and can be divided into a sequential cycle of coordinated and interrelated and overlapping healing phases: the destruction phase, including muscle degeneration and inflammation, the repair phase including regeneration of the muscle fibres (which should not be confused with the regeneration process of a bone), and the remodelling phase, including formation of connective scar tissue and maturation of the newly regenerated muscle fibers (32,33,43,62–64). The evidence regarding this process is primarily based on animal studies (mainly following lacerations) and there is still a lack of clinical studies, which is important to keep in mind when evaluating the literature. However, although controversies exist, several research groups provide a fairly synchronised overview of the specific characteristics of the different healing phases (32,33,63,64,66). An example of this healing process is shown in Figure 3.

Destruction and inflammation

In the destruction phase, the muscle fiber is ruptured and the injured ends undergo a necrosis. However, the necrosis is rapidly stopped by a "fire door" resulting from rapid resealing of the torn sarcolemma, usually within a couple of hours, allowing the rest of the ruptured muscle

fibers to survive, and their injured ends undergo only local necrosis (32,62,63). The ruptured muscle fibers contract and the gap between the ruptured muscle stumps is filled with a hematoma. The injury induces an important inflammatory cell reaction. After injury degeneration, neutrophils (leukocytes, i.e. white blood cells) are the first inflammatory cells infiltrating the lesion. The neutrophils secrete a large number of proinflammatory molecules, such as specific cytokines (TNF-α, IL-6), chemokines (CCL17, CCL2) and growth factors (FGF, HGF, IGF-I, VEGF; TGF-β1), in order to attract other inflammatory cells, such as monocytes and macrophages (32,51,63,64,67,68). Activated macrophages with a pro-inflammatory profile first remove debris caused by the injury, and express specific cytokines that play key roles in regulating the proliferation, migration and differentiation of satellite cells. After several days, there is a subsequent invasion of anti-inflammatory macrophages, which promotes tissue repair and diminishes inflammation. Thus, the macrophages play key roles in the healing process and promoting muscle regeneration following the acute injury (51,64,67).

Regeneration and remodelling

The repair phase is characterised by two simultaneous processes: regeneration of muscle fibers and the formation of connective (scar) tissue. The regeneration process of muscle fibers begins with pathogenesis of the necrotized tissue by blood derived monocytes (33). Then, the activation cycle of satellite cells, which play a vital role in the muscle regeneration process, begins. First, the satellite cells are activated from a resting state by different stimuli and proliferate into myoblasts that differentiate in order to repair the damaged muscle fibers (64). 'Committed' satellite cells begin to differentiate into myoblasts, followed by undifferentiated satellite stem cells that begin to proliferate after 24 hours and thereafter contribute to the formation of myoblasts (32,33,64). At the same time, these satellite stem cells ensure that the depot of new satellite cells for possible future needs of regeneration is maintained, through a parallel asymmetric cell division (51). The myoblasts arising from the committed and satellite stem cells then fuse together to form myotubes (usually within a couple of days) and finally mature into muscle fibers (33,62). However, the ends of these repaired muscle fibers do not usually reunite, but instead attach to the ECM of the interposed scar via newly formed 'mini-MTJs' (62,69). Thus, each ruptured muscle fiber remains divided into two independent fibres bound together by the interposed scar. The formation of the ECM is initiated by the presence of blood-derived fibrin and fibronectin at the injury site, which cross-link to form early granulation tissue (an initial ECM), acting as a scaffold and anchor site and provide the wound tissue an initial strength to withstand the

contraction forces applied to it (32,64,69). Then, activated fibroblasts, in response to pro-fibrotic cytokines such as TGF-β1 (released by the anti-inflammatory macrophages), rapidly invade the injury site (64,69,70). The fibroblasts are responsible for producing ECM components (such as collagen type I and type III) and remodelling factors, which again increase the tensile strength of the primary scar tissue (32,63,69). The regenerated muscle fibers initially connect to the ECM at the lateral sides while they extend out of the basement membrane and penetrate the scar tissue between the stumps of the ruptured muscle fibers. Subsequently, mini-MTJs are formed at the ends of the new muscle fibers, and the scar tissue between the muscle fiber stumps is reorganized and reduces in size (32,33,64,69). Simultaneously, the injury site is also *revascularized*. In strain injuries, not only the muscle fibers rupture, but also their basal lamina as well as the myosial sheaths and blood vessels running in the endo- or perimysium (32,64). Rupture of blood vessels induces tissue hypoxia at the injury site (32) and the restoration of the blood supply/capillary ingrowths in the injured skeletal muscle is reported to be one of the first signs of muscle regeneration and essential to successful muscle healing and functional muscle recovery (64). Without formation of new capillaries that occurs quickly after injury, the muscle regeneration is reported to be incomplete and significant fibrosis can occur (64,65).

Innervation

Muscle repair is complete when injured muscle fibers are fully regenerated and become innervated. The synaptic contact between a motor neuron and its target muscle fiber often takes place at the neuromuscular junction, which is centralised within the muscle fiber (71). These neuromuscular junctions are essential for the maturation and restoration of the functional capacity of the regenerating muscles. Within 2–3 weeks after muscle damage, the presence of newly formed neuromuscular junctions is observed in regenerative muscle (72,73).

Regeneration vs scar tissue formation

The regeneration of the injured muscle fibers and nerves and the formation of a connective scar tissue between the stumps are two simultaneous processes which are both supportive, but also competitive with each other. The scar is needed to keep the stumps together and provides the connective tissue to re-establish the firm attachment of muscle fiber ends. A great majority of the injuries to the skeletal muscle heal without formation of a functionally disabling fibrous scar; however, the proliferation of fibroblasts may sometimes be excessive, resulting in the formation of a dense scar tissue within the injured muscle (32), which may impede regeneration of the muscle fibers and reinnervation of the stumps (69).

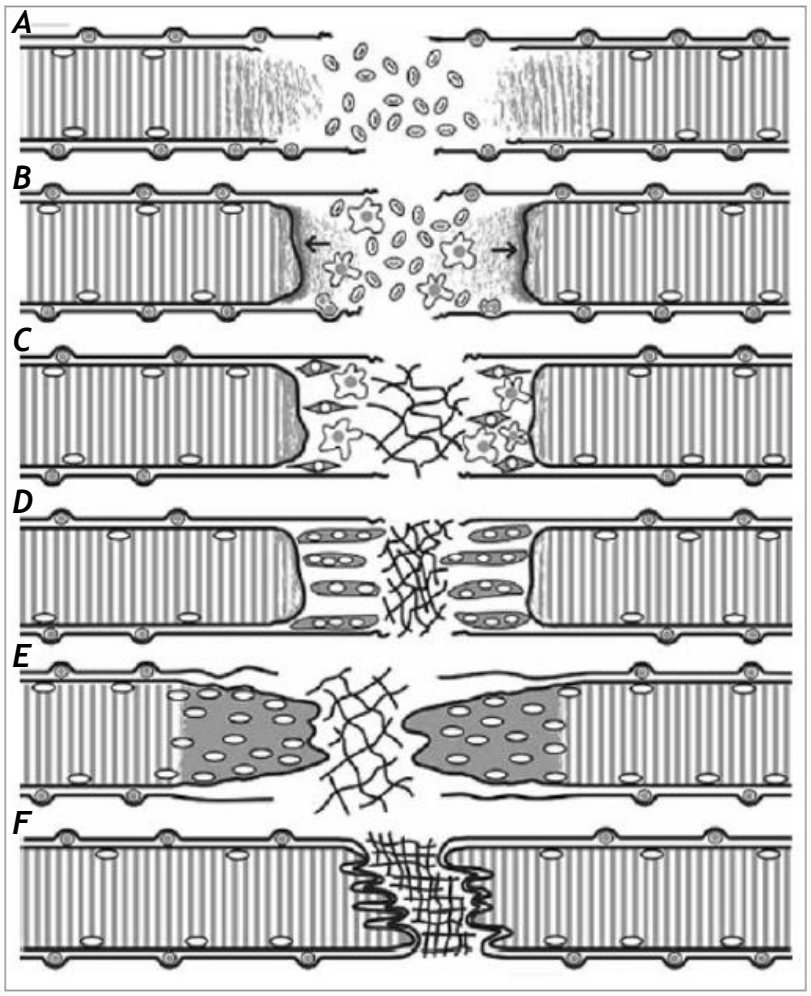


Figure 3: Illustration showing the regeneration of a shearing injury. (A) Torn muscle fiber and basal lamina. (B) Contraction band and demarcation membrane seal the torn fiber ends. Satellite cells begins to proliferate and inflammation reaction begins. (C). Satellite cells differentiate into myoblasts and fibroblasts begin to produce collagens and form scar tissue. (D) Myoblasts fuse into myotubes. (E) Myotubes fuse with the surviving part of the torn fibers and start to form new MTJs. (F) Fully regenerated fiber with organised scar tissue and MTJs attached to it. (reprinted with permission from Järvinen et al 2013 (33) in: Järvinen TA, Järvinen M, Kalimo H. Regeneration of injured skeletal muscle after the injury. Muscles Ligaments Tendons J. 2013 Oct;3(4):337–45.)

Acute hamstring injuries

Epidemiology

Injury definition

As mentioned above, the terms and definitions regarding muscle injuries are debated (23,31). The term *acute hamstring injury* in this thesis refers to an acute hamstring muscle strain injury occurred during sports activity with a sudden onset where the athlete can recall the inciting event.

Injury incidence and prevalence – how large is the problem?

Of all non-contact muscle injuries, acute hamstring injury is the most prevalent in sports involving high-intensity running, repeated sprints, accelerations and decelerations. Although differences in injury registration methods make it difficult to directly compare hamstring injury rates and incidences between all sports and levels, there is a growing number of larger epidemiological studies among the different football, and rugby codes, as well as in track and field. In football (soccer), hamstring injuries represent between 6% to 29% of all injuries sustained (2–4,74–81). Data from the large UEFA UCL studies among male professional football players report that 12 % of all injuries (82) and more than one third (31-37%) (2,3) of all muscle injuries are located in the hamstrings. Thus, on average, a team with a squad of 25 players can therefore expect 4-6 players to sustaining a hamstring injury each season, with a mean of 14.3 days off (range 1-128) (2). Analyses from our research group at Aspetar show a similar burden in the Qatar professional football league (QSL) (4). During the past four seasons, an incidence of hamstring strains of 0.92/1000 h of exposure was reported (personal communication, Cristiano Eirale, 2013). This means that, with the average of 6.8 hamstring strains per club per season, the amount of lost playing time per club per season due to this specific injury in QSL was more than 123 days. Critically, the incidence of acute hamstring injuries and re-injuries seems to remain high (80). Recent time-trend analysis from European professional football reports an annual average 2.3% year on year increase in the total hamstring injury rate over a 13-year period (80). Importantly, the injury burden, which is the cross-product of severity (duration of time loss) and incidence (83), has increased by 4% (80), representing one of the injuries with the highest injury burden in the UEFA Champions League. Other football and rugby codes, such as Australian rules football (9), rugby union (10,30) and American

Football (11,12), report comparable numbers and trends. Injury surveillance over 2 decades in the Australian football league documents that the most common and prevalent injury over a 21-year period was a hamstring strain, with an incidence of 6.0 new hamstring strains per club per season, causing 20.4 missed matches per club per season (9). In athletics (track and field), acute hamstring injury is the most common injury occurring in competitions and tournaments among both young and adult athletes, in particular within the running and sprinting disciplines (7,8,84), representing 17.1% of all injuries sustained in international athletics championships between 2007 and 2015 (7). Due to the extreme requirements on range of motion, acute hamstring injuries are also frequently seen among dancers (85–87). Moreover, there is generally a high reinjury rate, ranging from 12% to 63%, in the same playing season up to 2 years after the initial injury (15).

The hamstring muscle complex: anatomy and function

The hamstring muscle complex is composed of three muscles in the posterior thigh region, including the biceps femoris, the semitendinosus and the semimembranosus (88–91) (Figure 4).

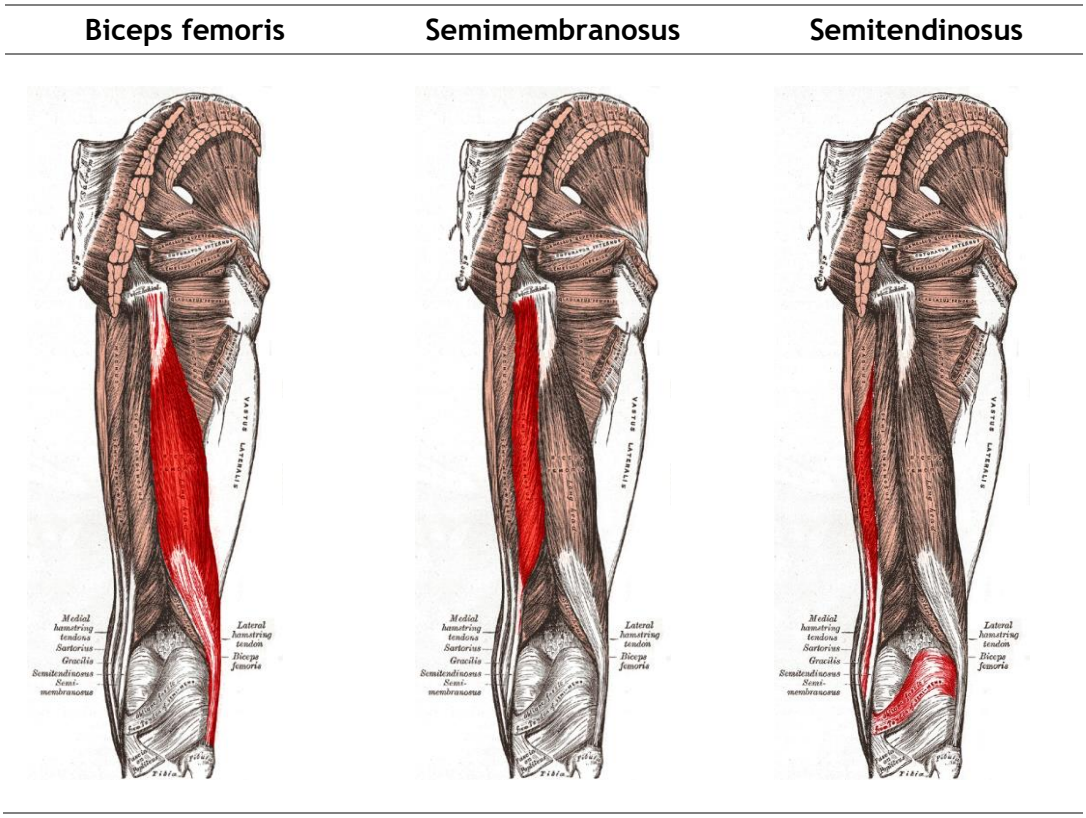


Figure 4: Anatomy of the hamstring muscles (By Mikael Häggström (92), used with permission).

The biceps femoris has two heads with separate origins; the long head arising from the medial facet of the upper region of the ischial tuberosity, and the short head arising from the lateral lip of the linea aspera and the lateral supracondylar ridge of the femur. The proximal and distal tendons, with the corresponding MTJs, span the entire length of the biceps femoris muscle. Interestingly, the proximal and distal tendons overlap (57,91), which means that the middle sections of these muscles have attachments to both the proximal and distal tendon (91). Injuries involving the intramuscular tendon have been suggested to have a worse prognosis (93,94). This question is investigated further in *Paper IV*. Distally, both the long and the short heads of the biceps femoris form a distal common tendon and insert on the styloid process and the head of the fibula, the lateral collateral ligament and the lateral tibial condyle (89,91). Proximally, the hamstring muscles form a complex entity close to their area of origin (90) (Figures 5 a-b and Figure 6).

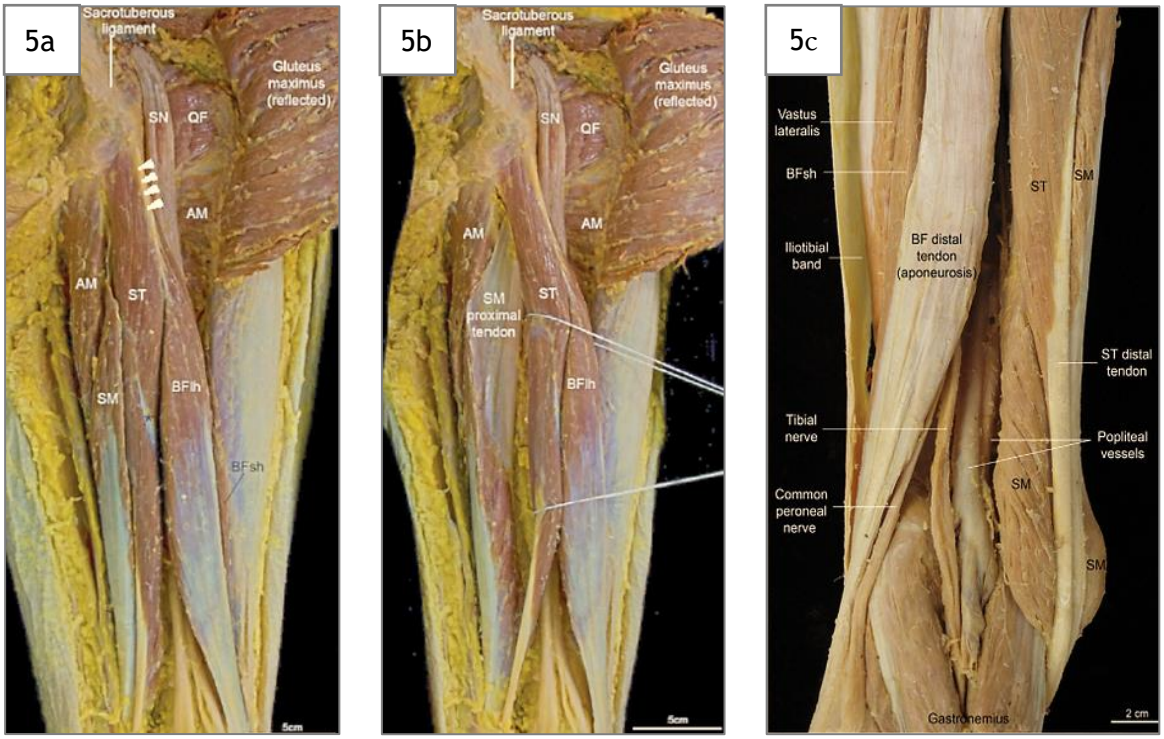


Figure 5: Dissection images of the proximal (a and b) and distal (c) hamstring complex. Note the proximal tendon of BFlh (arrowheads), the tendinous inscription of ST (*) and the long aponeurotic distal tendons of BFlh and SM (5a). In 5b, ST and SM have been reflected to expose the expansive proximal tendon of SM. (All images show right limb, posterior view). BFlh, biceps femoris long head; BFsh, biceps femoris short head; SM, semimembranosus; ST, semitendinosus; AM, adductor magnus; SN, sciatic nerve, QF, quadratus femoris. (From: Woodley SJ, Storey RN. Review of hamstring anatomy. Aspetar Sports Medicine Journal 2013; TT Hamstring Injuries:432-437. Reproduced with permission).

The proximal free tendon length of the biceps femoris is reported to be approximately 5-6 cm down to its first origin fascicles (57,90,91). From a common origin at the ischial tuberosity, the semitendinosus together with the biceps femoris long head form a common proximal tendon (often called the conjoint tendon). The free tendon of semitendinosus is minimal (mean length 0.2 cm) and muscle fibres of the semitendinosus are often seen attaching directly onto the ischial tuberosity (57,91), meaning that the semitendinosus contributes to the majority of the fascicles extending proximally (the first 9-12 cm) down from the ischial tuberosity (90). The fascicles of the semitendinosus and biceps femoris muscles attach to the common tendon with a pennation angle (90). The pennation angle and the fascicle lengths (particularly of the biceps femoris) are influenced by changes in the position of the hip (95). The common tendon ultimately divides into two separate tendons approximately 9 cm from the ischial tuberosity (91). The semitendinosus also constitutes a midline raphe (inscription) of tendinous/connective tissue near the middle of the muscle belly (56,57,57,91), running in a proximal to distal direction. Whether this raphe protects the semitendinosus from being the primary muscle injured is unclear, but this has been suggested (91). Distally, the semitendinosus forms a long tendon and attaches to the medial condyle of the tibia via the superficial pes anserinus. The semimembranosus originates from the superolateral aspect of the ischial tuberosity, anterior to the common tendon, thereby its tendon runs medial and anterior to the other hamstring tendons (89). The most proximal part of the semimembranosus tendon is conjoint with the common tendon of semitendinosus and biceps femoris, but separates approximately 2-3 cm from the ischial tuberosity (90,91). The proximal tendon is an elongated structure, with connections to both the adductor muscle tendon and the long head of the biceps femoris (89). Similar to the biceps femoris, the proximal and distal tendons of semimembranosus and its MTJ span the entire length of the muscle (57), with overlapping proximal and distal tendons, which is not present in semitendinosus (90,91). The semimembranosus inserts with five tendinous arms to the posteromedial aspect of the medial condyle of tibia, the posterior oblique ligament and the posterior joint capsule and arcuate ligament (oblique popliteal ligament) (88,89). The long head of the biceps femoris, semitendinosus and semimembranosus are biarticular (i.e. span across two joints) and are innervated by the tibial portion of the sciatic nerve. The short head of the biceps femoris is monoarticular and innervated by the common peroneal nerve (56). The hamstring muscles function as extensors of the hip and flexors of the knee during the gait cycle (88), and are found to be most active during the late swing phase, where they absorb kinetic energy and protect the hip and knee joints by limiting knee extension just before heel strike (96). When the knee is

partially flexed, the biceps femoris rotates the leg externally due to its oblique direction, whereas the semitendinosus (and partly semimembranosus) rotate the leg internally. The hamstrings support the pelvis onto the head of the femur when distally fixated and also contribute to slow the forward swing of the leg and decelerate the forward translation of the tibia during heel strike, thus in conjunction with the anterior cruciate ligament function as dynamic and static stabilizers of the knee (88,97). Additionally, during the gait cycle the hamstrings and quadriceps muscles interplay as antagonists. The function of the hamstring during running is described below.

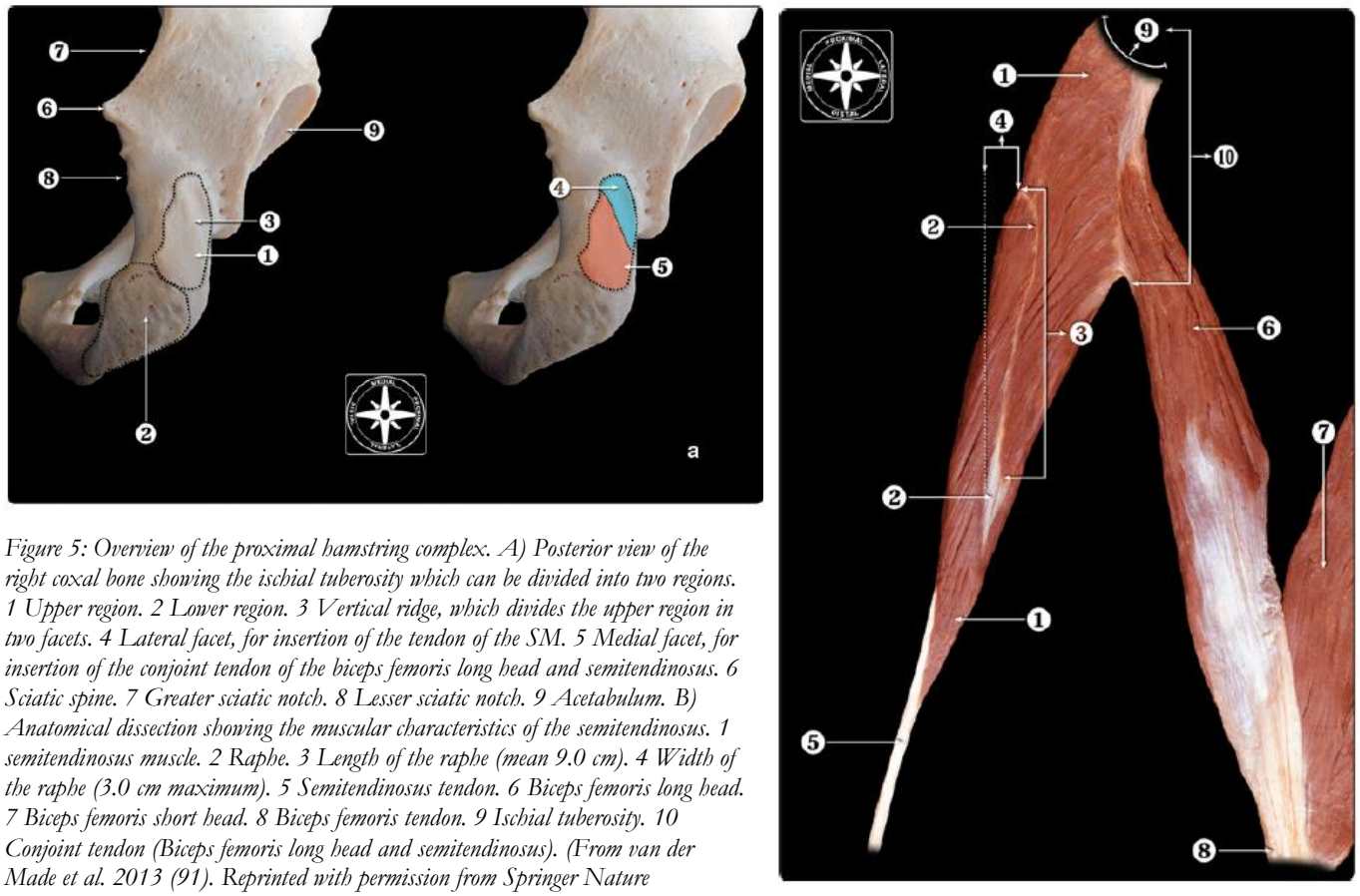


Figure 5: Overview of the proximal hamstring complex. A) Posterior view of the right coxal bone showing the ischial tuberosity which can be divided into two regions. 1 Upper region. 2 Lower region. 3 Vertical ridge, which divides the upper region in two facets. 4 Lateral facet, for insertion of the tendon of the SM. 5 Medial facet, for insertion of the conjoint tendon of the biceps femoris long head and semitendinosus. 6 Sciatic spine. 7 Greater sciatic notch. 8 Lesser sciatic notch. 9 Acetabulum. B) Anatomical dissection showing the muscular characteristics of the semitendinosus. 1 semitendinosus muscle. 2 Raphe. 3 Length of the raphe (mean 9.0 cm). 4 Width of the raphe (3.0 cm maximum). 5 Semitendinosus tendon. 6 Biceps femoris long head. 7 Biceps femoris short head. 8 Biceps femoris tendon. 9 Ischial tuberosity. 10 Conjoint tendon (Biceps femoris long head and semitendinosus). (From van der Made et al. 2013 (91). Reprinted with permission from Springer Nature [Publisher] in: van der Made AD, Wieldraaijer T, Kerkhoffs GM, Kleipool RP, Engebretsen L, et al. The hamstring muscle complex. KSSTA 2013).

Injury type and injury situation / mechanism

The evidence regarding the actual injury mechanism related to acute hamstring injuries is limited and debated. The majority of hamstring injuries are reported to occur during high-speed running when the athlete is running at maximal or close to maximal speed (30,81,98–101) in typical sports like football (81,99), rugby (10) and athletics (98,102). Another hamstring injury type is referred to as the slow-speed stretching type of injury (101), occurring during slow movements with excessive stretch and large joint excursions including hyperflexion of the hip combined with knee extension, typically seen in dancers (85,87). Other injury situations, such as kicking, high kicking, glide tackling, twisting and cuttings are also reported (30,101). Hip hyperflexion combined with knee extension is commonly seen in patients sustaining a proximal hamstring tendon avulsion injury, but an alternative injury mechanism is recently suggested in a smaller case study (n=3), involving a substantial hip abduction component (flexion-abduction injury mechanism) (103). The biceps femoris long head is reported to be the most frequently injured muscle (99,104–106). Biomechanical studies show that the hamstrings are most active from mid-swing until terminal phase of the stride cycle phase during running and sprinting (107–111), and actively lengthened during a combined hip flexion and knee extension during the terminal swing phase, absorbing energy from the decelerating limb in preparation for foot contact (36).
Muscle strain injuries during high-speed running are thought to occur during eccentric muscle contractions when the muscles are lengthened while producing forces (39,40). Other biomechanical studies (96,112–115), among these two independent case reports with video footage of hamstring injuries occurring during high-speed running (112,113,115), have hypothesized that hamstring injuries most likely occurs during this terminal swing phase of high-speed running where the peak hamstring musculotendinous stretch seems to occur, and is significantly greater for biceps femoris (probably because of a shorter knee extension moment arm) (107). However, controversies exist and the early stance phase has also been suggested as highest risk period during the gait cycle, since hamstring then is also working against potentially large opposing forces (116).

Diagnosis and prognosis

An accurate diagnosis is essential to ensure that the injured athlete receives appropriate treatment and rehabilitation, and correct information related to the prognosis (117). The diagnosis and prognosis for time to RTS after acute hamstring injuries are mainly based on a comprehensive clinical examination (32,33,36,62,118,119). In cases where the clinical appearance and severity is unclear and determining the optimal treatment can be difficult, supplementary radiological imaging is often used to confirm the diagnosis and to provide information about the radiological severity and the location of the injury, as well as to guide further treatment (120). Complete ruptures of the tendinous insertions (with or without avulsion fractures) usually have a worse prognosis and in some cases, surgery is indicated (89,121). One important goal of these initial investigations is therefore to identify those infrequent cases where surgical treatment may be needed (89).

Clinical examinations

The initial clinical examinations is recommended to begin with a comprehensive patient medical history taking followed by specific physical assessments and tests (32,33,118), commonly performed within the first days after injury (85,98,118,122–124). A quick initial clinical diagnosis is essential in order to facilitate early initiation of optimal mobilisation and rehabilitation after the injury (33,62,125)

Patient history

Patient history is considered as the foundation of the diagnosis and might in many cases alone provide an accurate diagnosis. The patient history provides an important overall picture of the injury situation and a preliminary impression of the injury severity. To get a total overview of the injury situation, the injury mechanism (for example high-speed running or more stretching related type of injury) (101,118), whether there was a sudden onset with sharp/severe pain in the posterior thigh, whether the player was forced to stop immediately and whether an audible 'pop' was heard, can aid the clinician in confirming the diagnosis and might give some indications about severity (36,119). To rule out more severe injuries, excessive pain located to the tendon insertions at the ischial tuberosity or distally and typical acute injury situations with a mechanism of extreme hip flexion with the knee extended (e.g. sagittal split or falling forwards with the upper body while the leg is fixated to the ground) combined with audible 'pop' commonly lead

the suspicion towards a total rupture of the proximal tendon(s), and further radiological investigations are indicated (121). The type of sport may lead to a suspicion of a complete rupture; for example, water skiers are at a high risk of avulsion injuries (120,126). Commonly, subjective pain at the time of injury is measured with a visual analogue scale (VAS) or a numeric rating scale.

Physical assessment

The physical assessment commonly begins with observation of gait pattern and function, followed by inspection of the injured area, palpation of the hamstring complex, active and passive flexibility and range of motion (ROM) testing of the hip and knee joint, isometric pain provocation and muscle strength testing (32,36,118,122). Pain provocation tests and deficits compared to the contralateral uninjured leg with the different tests are usually registered (118) VAS or a numeric rating scale is also used in order to quantify the athlete's subjective pain (118,127) during testing. To measure side-to-side differences/deficits in ROM and muscle strength, objective assessment tests using goniometers or inclinometers and hand-held dynamometer have been used (6,118,122,124). Hamstring flexibility of the injured leg is usually reduced compared to the uninjured leg after acute hamstring injury (36,118,122,128), and commonly examined in conjunction with other assessments to establish a diagnosis. The active and passive straight leg raise tests (SLR) and active and passive knee extension tests are most commonly referred to in the literature following hamstring injuries (118,122,124,129–131). In studies among healthy participants, these flexibility tests are found to show moderate to good reliability (130). But since these tests in an acutely injured athlete are usually limited by pain and discomfort, reliability results from healthy participants may not be directly applicable to injured athletes. Up to this date, only one study has reported on the reliability of flexibility testing in athletes with acute hamstring injuries (131), showing good intertester reliability for the active and passive knee extension tests. Pain with isometric contraction and hamstring muscle strength deficits compared to the uninjured leg is commonly present initially after an acute hamstring injury (36,118,132). Just recently, a meta-analysis reported that lower isometric strength was found <7 days postinjury (d=-1.72), but did not persist beyond 7 days after injury (132). However, there are few studies that have reported strength deficits just after the injury, as the focus in the literature mainly has been directed towards isokinetic and eccentric strength deficits at or (long time) after RTS (132). Additional tests needed to rule out other possible sources of posterior thigh pain are also commonly performed, such as sensitive structures (36,59,133).

In adolescents reporting an acute onset injury, where one in adults would suspect an acute hamstring injury, there might be an apophyseal avulsion fracture (134,135). Since the cartilaginous growth plates at the apophyses of the adolescents are more vulnerable than the musculotendinous units, they may fail, resulting in an avulsion. The pain is typically more severe during activity and decreases with rest, and clinical examination reveals local tenderness, reduced ROM and swelling (136). Radiography (X-ray) of the pelvis in at least two planes should be performed in athletes with typical clinical findings and an adequate history of trauma (134). Further, differential diagnoses should always be considered (36,89), but will not be elaborated in detail in this thesis.

Radiological imaging

The overall goals of imaging following a hamstring injury are to confirm the clinical diagnosis and provide a radiological evaluation of the extent and severity of the injury (as supplementary information to the clinical examinations) (89,104).

The preferred imaging modalities for hamstring injuries are Magnetic resonance imaging (MRI) and ultrasound, which both provide detailed information of the hamstrings complex regarding the localisation and characterisation of the injury (89). MRI is lately suggested as the preferred imaging technique over ultrasound, based on its greater sensitivity for minor injuries and the ease of use for prognosis (119). However, the prognostic value of MRI is still not established. Also, few studies have actually investigated the diagnostic and prognostic values of MRI compared to ultrasound measurements in acute hamstring injuries (137,138). Connell et al. (2004) compared MRI and ultrasound findings in Australian football players and reported MRI to be more sensitive for follow-up imaging of healing. Ultrasound was as useful as MRI in depicting acute hamstring injuries and because of lower costs, the authors suggested ultrasound as the preferred imaging technique. Another advantage is that ultrasound allows dynamic imaging while maneuvering the injured leg to elicit symptoms and may aid in clarifying the diagnosis (139). One of the major drawback with ultrasound is that it is highly operator dependent (140) and its prognostic value is also disputable (138,140). However, the operator dependency is also indisputably present in MRI, and the type and use of imaging of hamstring injuries are still debated. In this thesis, MRI is the diagnostic tool utilised and will be of main focus.

MRI

MRI provides images with high-contrast resolution of soft tissues and osseous structures in multiple planes, and has the ability to use different type of pulse sequences to exploit differences in soft tissue contrast that are not available with other modalities (141). It has therefore been considered as the gold standard for evaluation of the musculoskeletal system (142).

Basic MRI physics

MRI uses powerful magnet and radiofrequency pulses to produce detailed images. Typically for lower limb muscle injuries, the patient is positioned on a moveable table inside an MRI scanner with a defined static magnetic field strength, and sets of coils (magnetic coils, gradient coils, shim coils and radiofrequency transmitter coils (RF coils)) that generate and receive the MR signal (143,144). The strength of the magnetic field is quantified as Tesla (T), where 1 T refers to approximately 20,000 times the earth's magnetic force (145). The most common field strength used for imaging of lower limb muscle injures are 1.5T or 3.0T (146,147), which are considered high field strength. The major advantage of a higher field strength is the increase in signal-to-noise ratio, which improves spatial and/or temporal resolution and reduces scan time while preserving imaging quality. All high-field scanners are closed-magnet MRIs, which refers to the original tube shape of most MRI scanners (145).

The MR signal used to generate almost all clinical images is based on the physical phenomenon nuclear magnetic resonance, where the electromagnetic activity of atomic nuclei (protons and neutrons) is measured (143–145). Hydrogen nuclei are commonly used in MRI because of their abundance in the body (144). The nuclei of hydrogen atoms consist of a single proton, which possess a positive charge, and are constantly spinning around their own axes generating their own magnetic field (the magnetic moment) (143,144) and is associated with fat and water molecules (148). When a patient is placed in an external static magnetic field, the small magnetic fields of the protons align themselves parallel or antiparallel with the external magnetic field, and begin to spin at a frequency that is proportional to the strength of the external magnetic field (Larmor frequency) (143,145). In the MRI scanner, linear variations of the magnetic field strength in a selected region (gradient) is applied in addition to the large external magnetic field, causing protons at different locations in the body to rotate with slightly different frequencies, and the MRI system is able to detect which tissue the signal is coming from (144). A radiofrequency energy pulse with the same frequency as the protons spinning in the imaging location/tissue of interest is sent from the radiofrequency coil by *resonance*; protons spinning at

frequencies different from the radiofrequency pulse do not capture this energy (143,144). The energy from the radiofrequency pulse 'disturbs' the selected protons so that they fall out of alignment with the external magnet field, causing a wobbly movement. When the radiofrequency pulse is stopped, the selected protons relax back to their original alignment with the external magnetic field and release energy in the form of a radio signal (echo), which is captured by the RF receiver coil and processed to give information about the protons in the patient's tissues. The coils are driven by the pulsed electric currents in the strong magnetic field and receive a repetitive strong force, which is heard as a loud sound during the MRI scan (143). Normally, in addition to the integral radiofrequency coil, surface coil (-s) covering the injured area is used to increase the signal to noise ratio. This process of 'disturbing' the selected protons and then collecting the energy released as radio signals when the protons relax is the basis of MRI. The relaxation occurs either as a longitudinal relaxation (T1 relaxation time) or a transverse relaxation (T2 relaxation time), and each tissue has a characteristic T1 and T2 time. Several factors can influence the intensity of the MRI signal and thus the image visualized, and specific sequences and settings are chosen by the operator for the specific purpose (143).

Factors influencing MRI signal

Contrast between tissues allows adjacent structures to be differentiated from another and is determined by signal intensities (varying from bright to dark) (143), and mainly related to differences in T1, T2 and proton density (number of hydrogen nuclei) (144). Two key parameters determine the MRI contrast; repetition time (TR), which is the time between the start of two following radiofrequency pulses applied to the same slice, and echo time (TE), which is the time between the initial radiofrequency pulse and the peak of the echo signal (145). T1-weighted images represent image contrast due to differences in T1 relaxation times and is created by using short TR and low TE. T2-weighted images represent image contrast due to differences in T2 relaxation times and is created by using long TR and long TE (144,145). T1-weighted images are best in depicting the anatomy, where fat has lower relaxation times and higher MRI signals and appears as bright, in contrast to fluid (water) and muscles, which has higher relaxation times and intermediate to low MRI signals (appearing as darker grey). T2-weighted images better depict pathological processes, since fluid (water) appears bright on these images (144,145). Proton density-weighted (PD-w) images are an intermediate between T1-weighted and T2-weighted images, with longer TR and shorter TE, and produces contrast mainly by minimizing the impact of T1 and T2 differences. PD-w images depict both anatomy and

pathology, where the visualization is predominantly influenced by the proton density of the tissue (144), which increases the signal-to-noise ratio, but may reduce the sensitivity in differentiating fluid. When examining acute muscle injuries, fat suppression techniques are usually applied in T2-weighted or PD-w images, which make fat appearing darker and clearly differentiate between water content tissues near fatty tissues on these images. Fat suppression can also be applied using separate a short tau inversion recovery (STIR) sequences (145,149).

MRI after hamstring muscle injuries

The ultrastructural changes as a result of a muscle injury, where torn myofibrillar Z bands cause protein degradation with release of protein-bound ions leading to oedema, is visualised if beyond the resolution of MRI (89,120). The extent of injury and associated architectural distortion is commonly evaluated using multiplanar acquisitions (axial, sagittal and coronal images) oriented along the long and short axes of the involved musculotendinous unit (139,150). The axial plane is useful to assess muscle contours and to delineate the musculotendinous junction and its exact anatomical relation with focal lesions (151), while coronal and sagittal planes are used to assess the longitudinal extent of injury (139) and might be useful to determining whether a loss of tension in the intramuscular tendon is presence, presenting as a 'waviness' appearance (93). Normal skeletal muscles show intermediate to low signal intensity on both T1-weighted, T2-weighted, PD-w or STIR images (139,144). Alterations in water content in the affected musculotendinous units are common to all forms of traumatic injuries (104,139,150). Fluid-sensitive sequences (i.e. fat-suppressed T2-weighted or PD-w), and STIR sequences are suitable for detecting oedematous changes (hyperintensity with a 'feathery' appearance) in the musculotendinous unit, and to delineate and locate intramuscular or perifascial fluid collections or haematomas as increased signal intensity (139). Such sequences can depict abnormal hyperintensities at the site of symptomatic old tear. T1-weighted sequences are used to visualise atrophy and fatty infiltration and to differentiate between haemorrhage/haematoma and oedema, but they are less sensitive (104,139,150).

MRI artifacts

MRI produces several specific artifacts, which are important to be aware of for a correct diagnosis. Voluntary and involuntary motion by the patient is presumably the most common artifact, causing ghosts and blurring on MR images, as the phase gradient cannot anticipate and encode signals from moving structures (145,152). Motion artifacts are caused by voluntary

motions, involuntary motions and physiologic motions, and to avoid motion artifacts, careful explanation of the importance of lying still during the scan is important (145).

Timing of MRI after injury

There is currently no consensus on the optimal MRI timing for diagnosis after hamstring strains and the ideal day for imaging is debated (59,106,119). A recent literature review and expert opinion (119) recommended imaging at 1-2 days post-trauma. However, this recommendation was based on an in vivo rabbit study (55), where controlled strain was applied to the tibialis anterior muscle, showing that the amount of oedema was histologically maximal after 24 h and decreased after 48 h. A similar time frame (24-48 h) is also requested in a large UEFA UCL (106) whereas Speer et al. (59) recommend MR imaging between 1 and 3 days post-injury as an ideal time, based on the occurrence of oedema (which is one of the predominant histological findings in muscle strains). However, evidence to support these expert-based recommendations for the optimal timing to detect presence and extent of oedema and fiber disruption is lacking. Other experimental studies have suggested that signs of acute muscle strain injuries are best detected on MRI between 24 h and 5 days (153,154) but data are limited to small samples sizes, different muscle groups investigated and no continuous daily MRI throughout the first week after injury. Reported correlations between different measurements of the extent of oedema and RTS are based on MRI measurements from single MRI scans performed between 2 to 10 days after injury (85,98,99,105,122,138,155) (see Table 4). Hence, the time course of changes in the extent of oedema after hamstring injuries is still unknown and the optimal moment for detecting fiber disruption is unclear. In *Paper I*, we therefore investigate this further.

Grading and classifications systems

Although there has been several clinical and radiological grading and classification systems proposed for muscle injuries, there is currently no uniform approach or consensus to the categorization and grading of hamstring muscle injuries. An overview of some of the most common clinical and radiological grading and classification systems suggested are summarized in Tables 2 and 3. One of the more widely used muscle injury grading systems based upon clinical signs was devised by O'Donoghue in his book about treatment of injuries to athletes, first published in 1962 (23,156). This system utilises a classification founded on injury severity related to the amount of tissue damage and associated functional loss, categorising muscle injuries into three grades. The Munich consensus statement classification system (23) was then developed for

muscle injuries in 2012, highlighting that previous grading systems are limited by the lack of sub-classifications within grades or types, and consequently, injuries with a different etiology, treatment pathway and different prognostic relevance are categorized in one group. This comprehensive classification was based on clinical signs, location and imaging, and discriminates between 'functional' and 'structural' muscle injuries (see Table 3). It has been tested for validity (157), but not yet been established specifically for acute hamstring injuries, and the differentiation between 'functional' and 'structural' injuries has been criticized (31,158).
Regarding radiological grading and classifications systems, muscle injuries are traditionally categorized with simple grading systems based on the severity/extent of the injury ranging from 0-3 representing minor, moderate and complete injuries (106,137,159,160), and widely used among clinicians and researchers (119). The four grade modified Peetrons classification is an ultrasound-based ordinal severity grading system (159), first described for MRI findings after hamstring injuries in a large study on European professional football players showing correlations with lay-off time (106) (Table 2). However, it has been criticised for being too simplistic, without considering the anatomical location and specific tissue involvement (158,161). The anatomical location was used by Askling et al. (85,98), including six different anatomical locations of the injury. But, these anatomical locations were not combined with a grading severity system. New MRI classification systems have lately been proposed including both the extent (severity grading) as well as the anatomical site/location of the injury (158,161). For example, Chan et al. (161) described a comprehensive system to classify acute muscle injuries based on the severity of imaging assessments and the exact anatomical site using MRI or ultrasound. This study has not been used in any clinical studies, and its validity is unknown. The British Athletics Muscle Injury Classification (BAMIC) (158) was recently suggested in a publication from 2014. This classification system grades the muscle injuries based on MRI parameters of the extent of injury and classifies the injuries according to their anatomical site within the muscle (Table 3). But, the validity of these mentioned grading and classification systems and their prognostic value for RTS after muscle injuries have been scarcely explored. We therefore further explored the validity of these new grading and classification systems in *Papers III* and *IV*.

Table 2: Overview of clinical and imaging grading systems

	O'Donoghue (156) **(1962)**	**Järvinen** (32) **(2005)**	**Schneider-Kolsky** (122) **(2006)/ Malliaropolous** (6) **(2010)**	**Takebayashi*** (137) **1995**	**Peetrons** (159) **(2002)**	**Lee** (162) **(2004)**	**Ekstrand** (106) **(2012)**
0				Ultrasound: Normal findings	Lack of any ultrasonic lesion		Negative MRI – no visible pathology
I Mild	No appreciable tissue tearing, no loss of function or strength, only a low-grade inflammatory response	(Strain/contusion): - tear of only a few muscle fibers with minor swelling and discomfort - no or only minimal loss of strength and restriction of the movements	*Schneider-Kolsky:* - Pain: Nil -mild - ROM deficit: <10° *Malliaropolous:* - ROM deficit: <10°	- Clinical (mild): Neither discernible loss of strenght nor any restriction of motion - Ultrasound: hyperechoic infiltration - Ultrasound/MR size of lesion (small): <20% CSA	Minimal elongations with less than 5% of muscle involved. These lesions can be quite long in the muscle axis being usually very small on cross-sectional diameter (from 2 mm to 1 cm max.)	Normal, or focal/general areas of increase echogenicity +/- perifascial fluid	Oedema but no architectural distortion
II Moderate	Tissue damage, strength, only a low-grade inflammatory response	(Strain/contusion): greater damage of the muscle with a clear loss in function (ability to contract)	*Schneider-Kolsky:* - Pain: moderate/severe - ROM deficit: 10-25° *Malliaropolous:* - ROM deficit: 10-19°	- Clinical (moderate): any degree of oss of strenght short of complete loss of strenght and function - Ultrasound: mass (subdivided according to echogenicity to that of ontact muscle) - Ultrasound/MR size of lesion (moderate): 20-50% CSA	Partial muscle ruptures; lesions involving from 5 to 50% of the muscle volume or cross-sectional diameter. Hypo-and/or anechoic gap within the muscle fibers	Discontinuity of muscle fibers in echogenic perimyseal stria; hypervascularity around disrupted muscle fibers; intramuscular fluid collection; partial detachment of adjacent fascia or aponeurosis	Architectural disruption indicating partial muscle tear
III Severe	Complete tear of musculotendinous unit, complete loss of function	(Strain/ contusion): tear extending across the entire cross section of the muscle, resulting in a virtually complete loss of muscle function is termed.	*Schneider-Kolsky:* (with or without presence of palpable gap) - Pain: Severe - ROM deficit: >25° *Malliaropolous:* - ROM deficit: 20-29° Grade IV: - ROM deficit: >30°	Clinical: complete loss of strength and dunction Ultrasound: compound of hyperechoic infiltration and mass Ultrasound/MR size of lesion (large): >50% CSA	Muscle tears with complete retraction.	Complete myotendinous or tendon-osseous avulsion; complete discontinuity of muscle fibers and associated hematoma; 'bell clapper' sign.	Total muscle or tendon rupture.

CSA, cross sectional area; MR, magnetic resonance imaging; ROM, range of motion; US, ultrasound;

Table 3: Overview of comprehensive muscle injury classification systems

Munich consensus statement Classification (23)	**Chan acute muscle strain injury classification** (161)		**British Athletics Muscle Injury Classification (BAMIC)** (158)		
	Grading	**Anatomical site**	**Grading**	**Anatomical site**	**Combined classification**
A. Indirect muscle disorder/injury: **<u>Functional muscle disorder</u>** ***Type 1: Overexertion-related muscle disorder*** Type 1A: Fatigue-induced muscle disorder Type 1B: Delayed-onset muscle soreness (DOMS) ***Type 2: Neuromuscular muscle disorder*** Type 2A: Spine-related neuromuscular Muscle disorder Type 2B: Muscle-related neuromuscular Muscle disorder **<u>Structural muscle injury</u>** ***Type 3: Partial muscle tear*** Type 3A: Minor partial muscle tear Type 3B: Moderate partial muscle tear ***Type 4: (Sub)total tear*** Subtotal or complete muscle tear Tendinous avulsion **B. Direct muscle injury** - Contusion - Laceration	Grade 1 (strain): ≤5% fibre disruption and oedema Grade 2 (partial tear): Fibre disrution, oedema and haemorrage Grade 3 (complete tear): complete discontinuoty muscle fibres, haematoma and retraction of muscle ends	1. Proximal MTJ 2. Muscle *Proximity within the muscle:* A. Proximal B. Middle C. Distal *Location within the muscle:* a. Intramuscular b. Myofascial c. Myofascial/ Perifascial d. Myotendinous e. Combined 3. Distal MTJ	Grade 0: Negative MRI** Grade 1: "Small injuries (tears) to the muscle" Grade 2: "Moderate injuries (tear) to the muscle" Grade 3: "Extensive tears to the muscle" Grade 4: "Complete tears to either the muscle or tendon"	a. Myofascial b. Musculotendinous c. Intratendinous	**0a:** MRI normal **0b**: MRI normal or patchy HSC throughout one or more muscles. **1a**: HSC evident at the fascial border <10% extension into muscle belly. HSC of CC length <5 cm. **1b**: HSC <10% of CSA of muscle the MTJ. HSC of CC length <5 cm (may note fibre disruption of <1 cm). **2a:** HSC evident at fascial border with extension into the muscle. HSC CSA of between 10%-50% at maximal site. HSC of CC length >5 and <15 cm. Architectural fibre disruption usually noted <5 cm. **2b**: HSC evident at the MTJ. HSC CSA of between 10%-50% at maximal site. HSC of CC length >5 and <15 cm. Architectural fibre disruption usually noted <5 cm. **2c**: HSC extends into the tendon with longitudinal length of tendon involvement <5 cm. CSA of tendon involvement <50% of maximal tendon CSA. No loss of tension or discontinuity within the tendon. **3a**: HSC evident at fascial border with extension into the muscle. HSC CSA of >50% at maximal site. HSC of CC length of >15 cm. Architectural fibre disruption usually noted >5 cm **3b**: HSC CSA >50% at maximal site. HSC of CC length >15 cm. Architectural fibre disruption usually noted >5 cm **3c:** HSC extends into the tendon. Longitudinal length of tendon involvement >5 cm. CSA of tendon involvement >50% of maximal tendon CSA. May be loss of tendon tension, although no discontinuity is evident **4**: Complete discontinuity of the muscle with retraction **4c**: Complete discontinuity of the tendon with retraction

CC, craniocaudal; CSA, cross sectional area; HSC, high signal change; MTJ, musculotendinous junction; MRI, magnetic resonance imaging;

Prognosis for RTS after acute hamstring injuries

When an injury has occurred, the medical staff faces pressure to return the athlete to training and competition as soon as possible, particularly at elite level (106). However, hamstring muscle injuries are considered to be a heterogeneous group of different injury types, locations, severities and sizes, making prognosis and decisions about RTS challenging (106,119).

Several prospective and retrospective studies have reported associations between clinical and/or MRI findings and time to RTS, as summarised in Table 4. Yet, there seems to be no consensus on the prognostic value of these findings for RTS. The current literature is characterised by relative small studies with the majority using univariate analyses, for example reporting simple correlations or comparing grades on a group level, and without controlling for possible treatment confounders. Another problem is the lack of clear definitions and criteria for time to RTS, and the varied reporting of RTS, making direct comparisons between the studies more difficult. Regarding the prognostic value of grading and classification systems after acute hamstring injuries, the evidence is scarce. Ekstrand et al. (106) concluded that radiological grading was associated with lay-off times and also reported that 70% of the hamstring injuries were Grade 0 or Grade I. These injuries appeared with no signs of fiber disruption, but still they caused the majority of absence days. The clinical applicability of the BAMIC was investigated retrospectively in elite track and field athletes with acute hamstring injury, showing in a recent publication from 2015 that injuries extending into the tendon experienced delayed return to full training and were more prone to reinjury (94). The only consistently reported evidence suggests that athletes with "MRI-negative" muscle injuries (without increased signal), have a favourable outcome and quicker RTS, compared to athletes with muscle injuries evident on MRI ("MRI-positive") (99,106,122,127,163). No studies have investigated the predictive value of clinical examinations alone and the additional predictive value of MRI, using multivariate analyses and controlling for treatment confounders, which we therefore aimed to investigate in *Paper II*. Further, the predictive value of the BAMIC (158) and the Chan classification (161) has not been prospectively investigated, and was therefore assessed in *Paper IV*.

Table 4: Studies published reporting associations between clinical and/or MRI findings and time to RTS reported as days or weeks.

Author (publ., year)	Study design, study population	Number of participants	Prognostic tool (time after injury)	Statistical analyses	Time to RTS (mean days) (* if median days)	Associations with RTS	Reinjury follow-up after RTS **
Askling (2013) (99)	Prospective RCT, Swedish elite football players	L-protocol n = 37 C-protocol n = 38 MRI negative group n = 11	Clinical examination and MRI (≤5 days)	Univariate: Spearman's rho/ Mann-Whitney U	L-protocol: 28 ± 15 (range 8–58) C-protocol: 51 ± 21(range 12–94) MRI negative group: 6 ± 3 (range 3-14)	+ C-protocol longer vs. L-protocol (p<0.001)	Yes **
Comin (2013) (93)	Retrospective study	n = 62	MRI (timing NR)	Univariate: Kruskal Wallis/ Mann-Whitney U	No CT disruption: 21* (IQR, 9-28) CT disruption 72* (IQR, 42-109) (3 underwent surgery)	Univariate: + CT disruption (p< 0.01)	No
Silder (2013) (155)	RCT, M/F involved in high speed running ≥ 3 days pr.week	PATS: n = 13 PRES: n = 12	MRI (≤10 days)	Univariate: Pearson correlation	PRES: 28.8 ± 11.4 (28*, IQR:20-33) PATS: 25.2days ± 6.3 (23*, IQR:21-28) (p=0.346)	+ PRES vs. PATS (p = 0.346) + Initial CC length (r = 0.41, p = 0.040)	Yes **
Ekstrand (2012) (106)	Prospective cohort, professional football players	n = 207	MRI (24-48 hours) - modified Peetrons classification	Pairwise comparisons	Grade 0 (13%): 8 ±3 Grade 1 (57%): 17 ±10 Grade 2 (27%): 22 ±11 Grade 3 (3%): 73 ±60	Univariate: + Modified Peetrons grading (p<0.001)	Re-injuries ≤2 mths registered as part of the cohort **
Klicoyne (2011) (164)	Retrospective case study, Intercollegiate athletes; football, lacrosse, rugby, track and other	n = 48	Clinical grade I-III based on clinical examinations (≤48 hours)	Univariate: log rank tests. Multivariate: Cox proportional hazard regression	Average 11.9 (5-23)	No associations	Yes (>6 mths) 3/48 (6.2%)
Malliaropoulos (2010) (6)	Cohort study, track and field athletes	n = 165	Clinical grade (AROM): I: <10° II: 10°-19° III: 20°-29° IV: <30° US (48 hours)	Univariate: Pearson correlation and one-way ANOVA Multivariate: Linear regressions	US abnormalities: 54.6% (90/165) Mean: 14.7 ± 9.6 Clinical Grade I (45.4%): 6.9 (± 2.0) Clinical Grade II (35.2%): 11.7 (± 2.4) Clinical Grade III (15.8%): 25.4 (± 6.2) Clinical Grade IV (3.6%): 55 (± 13.5)	Univariate: + All 4 AROM gradings and RTS (F3,162 = 68.579, P<0,001). + AROM deficits: r = 0.830 Linear regression: AROM deficit + CSA > 25% + presence of hematoma (p = 0.003, strength of association NR)	Yes
Warren (2010) (124)	Prospective study, Australian elite footballers	n = 59	Clinical examinations (≤3 days)	Univariate X^2 or Fischer exact) Multivariate: Backward, stepwise logistic regression analyses (Adjusted odds ratios (AORs)	26* (range 1-8 weeks) - 26 players (44%) ≤ 3 weeks - 31 players (53%) between 3-6 weeks - 2 players (3%) ≥ 6 weeks	Univariate testing: + Time to walk pain free (>1 day): RR 2.0 (95% CI 1.0-3.7), p = 0.027 Multivariate testing: + Time to walk pain free (>1 day): AOR 4.0 (95% CI 1.3-12.6), p = 0.018 + Past hamstring injury AOR 4.2 (95% CI 1.0-18.0), p = 0.050	Yes (≤3weeks after RTS) 9/59 (15%)

Askling (2008) (165)	Prognostic case series, subjects from different sports	n = 30	Clinical examinations (median days after injury: 12 (1-51) MRI (median days after injury: 13 weeks, 1-52)	Univariate: (Spearman's who)	31* weeks (range 9-104)	No associations	-
Rettig (2008) (166)	Retrospective review, NFL football players	n = 21	MRI (timing NR)	NR	Grade I: 16 ('average to recover') Grade I: 21.5 ('average to recover') Grade I: 28.5 ('average to recover')	NR	Yes
Askling (2007) (98)	Prospective case serie, Sprinters	n = 18	Clinical examinations and MRI (4 time points; 2-4, 10, 21, 41 days)	Univariate: Pearson correlations	16* weeks (range 6-50)	Initial examinations (2-4 days): + Palpation pain-distance to IT: r = 0.695, p = 0.004. + PT involvement (RTS 34.8 w) vs. no PT involvement (RTS 13w), p = 0.009. + CSA, r = 0.695 (p = 0.004) + Volume r = 0.608 (p = 0.016) + Antero-posterior extent r = 0.584 (p = 0.022) + Distance to IT, r = 0.544 (p = 0.044)	Yes **
Askling (2007) (85)	Prospective case serie. Dancers	n = 15	Clinical examinations and MRI (4 time points; at baseline 2-4 days, follow-up at 10, 21, 41)	Univariate: Pearson correlations	50* weeks (range, 30-76)	No associations	Yes **
Askling (2006) (118)	Prospective prognostic study, Sprinters and dancers	n = 33	Clinical examinations (≤2 days)	Univariate: Spearman's who	Sprinters: 16* weeks (range 6-50) Dancers: 50* weeks (range, 30-76) Reported as "actual time back"	Sign.longer time to RTS dancers vs.sprinters (no p-values reported)	Yes (≤24 mths post-injury) 3/33 (9%)
Schneider-Kolsky (2006) (122)	Cohort study	n = 58	Clinical examination and MRI (≤3 days(	Univariate: Spearman's who	21* (range 4-56)	Clin.ex: r = 0.69 (p< 0.001) MRI: r = 0.58 (p< 0.001) Clin. predictions + MRI: r = 0.36, (p< 0.006).	No
Connell (2004) (138)	Diagnostic case series, Professional Australian football players	n = 60	MRI and Ultrasound (3 timepoints: at baseline ≤3 days, and at 2 and 6 weeks follow-up))	Univariate: Spearman's who Multivariate: multiple regressions	MRI abnormalities at baseline: 42/60 (70%) All: 21* (range 4-56) Absence of MRI abnormalities: 7* (IQR 7–14) - 23 (38.3%): <2 weeks - 35 (58.3%): between 2-6 weeks - 2 (3.3%): >6 weeks	Univariate analyses MRI: + Presence vs absence of hyperintensity (p < 0.001) + Injury BF (p<0.05) (coefficient NA) + Injury outside MTJ (p<0.05) (coefficient NA) + Longitudinal length r = 0.58, p < 0.001 Multivariate analysis MRI + Injury BF (p = 0.049) & longitudinal length (p = 0.001), adjusted R^2 = 37.9%	No
Gibbs (2004) (163)	Prospective study,	n = 31	MRI (24-72 hours)	One-way ANOVA	MRI positive group (55%): 20.2 (±52.3)	+ Longitudinal length: r=0.84 (p<0.001) + CSA: r=0.78 (p<0.001)	Yes **

	Australian Football League				MRI negative group (45%): 6.6 (±8.23, range 2-12)		
Verrall. (2003) (127)	Prospective clinical study, Australian Football players	n = 83	Clinical examinations (12-18 hours) MRI (2-6 days)	Univariate: t-tests / Spearman's rho	MRI confirmed (82%): 27 MRI not confirmed (18%): 16 All athletes: 25	+ Presence vs. absence of MRI abnormality ($p<0.01$) + Maximum pain experienced with injury (VAS scale): ($r = 0.78$, $p<0.01$) + Clinician-predicted time to RTS ($r = 0.58$, $p<0.01$)	No
Slavotinek (2002) (105)	Prospective study, Australian Rules Football	n = 37	MRI (2-6 days)	Univariate: Spearman's rho/ Gamma/ Mann Whitney U	MRI abnormalities: 30/37 (81%) 27* (range 13-48)	- Absence vs presence of hyperintensity $y = -0.69$ ($p = 0.04$) $r = 0.63$ ($p = 0.001$) Volume: $r = 0.46$ ($p = 0.01$).	No

† Studies published up and until 2013. * When median days RTS is reported. ** For studies with follow-up MRIs for re-injuries, see table 6; + means increased value associated with longer time to RTS.
Note: Askling et al 2007; 2007 based on similar dataset as in Askling 2006. Schneider-Kolsky (2006) and Connell (2004) based on similar dataset.
ANOVA, Analysis of variance; BF, biceps femoris; SM, semimembranosus; ST, semitendinosus; CSA, cross sectional area; M, male; F, female; IT, ischial tuberosity; PT, proximal tendon.

Reinjuries

One of the main challenges after an acute hamstring injury is to ensure an optimal timing of RTS for the individual athlete, yet with a low or acceptable risk of reinjury. Despite an increased focus on the prevention and management of hamstring injuries recent decades, the risk of sustaining a reinjury is considerably high. The reinjury rates are reported to range from 14% to 63% within the same playing season or up to 2 years after the initial injury (2,3,15,106,155,166,167).

Yet, the current literature regarding hamstring reinjuries lacks consistency when it comes to terminology, definitions and reporting of epidemiological and prospective data. In addition, there is also a lack of detailed knowledge about the hamstring reinjury characteristics.

Terminology and definitions

Several studies and consensus statements have attempted to define and/or classify types of subsequent injuries (27,168–171). An *index injury* is referred to as the first injury occurring (during the study period) and any injury occurring after this first injury is considered a subsequent injury. *Recurrent* injuries have been defined as a subsequent injury of the same type and at the same site as an index injury (27,168). Since athletes may return to full participation before an injury has completely recovered, a framework for recording time-loss recurrent injuries (169) further suggested to subdivide *recurrent* injuries into *reinjury* or *exacerbation. Reinjury* was defined as a repeat episode of a fully recovered index injury (based on medical opinion and preferably RTS criteria), and *exacerbation* was recommended to be used if there is a worsening in the state of a non-recovered index injury. Reinjuries have also been categorized according to the timing of the occurrence after the first injury: 'early' (within 2 months after RTS), 'late' (2-12 months after RTS) and 'delayed' (more than 12 months after RTS) (27,168). According to this, in the larger UEFA UCL studies, a hamstring reinjury is defined as an 'early' reinjury (3,106). However, determining when an injury really is 'fully recovered' might be challenging, since RTS criteria vary widely among clinicians and between different studies, and some athletes may also return with pain.

Risk factors/predictors for reinjuries

Although several risk factors for hamstring reinjuries have been suggested, there are few high-quality studies and no consensus. De Visser et al. (15) included five prospective studies investigating risk factors for reinjuries in a systematic review and found limited evidence for three risk factors and one protective factor for recurrent hamstring injury. However, the number of reinjuries within the included studies was critically low. They reported that there was limited evidence that patients with a recurrent hamstring injury had an initial injury with a larger volume size measured on MRI (47.03 vs 12.42 cm^3), more often had a Grade 1 initial trauma (Grade 0: 0–30.4%; Grade 1: 60.9–100%; Grade 2: 8.7%) and more often had a previous ipsilateral anterior cruciate ligament (ACL) reconstruction (66.6% vs 17.1%) independent of graft selection. Athletes in a rehabilitation programme with agility/stabilisation exercises rather than strength/stretching exercises had a lower risk for reinjury (7.7% vs 70%). Further, no significant relationship with reinjury was found for 11 related determinants and there was conflicting evidence that a larger cross-sectional area represent a risk factor for recurrent hamstring injury (15). Although persistent fibrosis (connective scar tissue) has been suggested to predispose for reinjury (172), no clinical studies have yet identified fibrosis as a risk factor for hamstring reinjury.

Reinjury characteristics

Despite the relatively high reinjury risk, there is a lack of exact knowledge about their *severity*, *location* and *timing,* and the reinjuries reported in previous studies are predominantly diagnosed clinically. Reinjuries are reported to commonly occur early after RTS (30,106,166,173), but an increased susceptibility seems to be present for several months after the index injury (123,163,167,173,174). Although MRI confirmed hamstring reinjuries have been shown to occur most frequently in the biceps femoris (106,155,175), the exact location within the muscle has only been evaluated in two small studies (155,175) (Table 5). It has been suggested that a reinjury should be defined as an MRI- or ultrasound-confirmed trauma to the same location as the index injury (15), but studies including imaging-confirmed reinjuries are limited and the exact MRI location within the reinjured muscle compared with the index injury is poorly described, as summarised in Table 5. In *Paper V*, we therefore wanted to evaluate the location, the radiological severity and the timing of MRI confirmed reinjures compared to MRI-confirmed index injuries.

Table 5: Studies including MRI assessments of index hamstring injury and follow up for reinjury†

Author (publ., year)	Study design, study population	Number of participants	Diagnostic tool Index injury	Diagnostic tool Reinjury	Follow-up period (active or passive) *	Number of reinjuries	Reinjury characteristics
Askling (2013) (157)	RCT, Elite Swedish football players	n=75	Clinical examinations and MRI ≤5 days	Clinical examinations and MRI ≤5 days	≤12 months after RTS (passive; medical team contacted study leader)	1/75 (1.3%) (C-protocol)	BF (RTS after 12 days)
Ekstrand (2012)† (106)	Prospective cohort, Professional football players	n = 207	NR	MRI ≤5 days	≤2 months	34/207 (16%) - Grade 0: 2 (7%) - Grade 1: 20 (17%) - Grade 2: 12 (21%) - Grade 3: 0	All reinjuries with MRI abnormalities (n=30) in the BF. No sign. difference in lay-off times (18±18 vs 18±11 days, p=0.98)
Silder (2013) (155)	RCT, Athletes from different sports involving high-speed running	n=29	Clinical examinations and MRI ≤10 days	MRI (timing: NR) (Clinical signs) **	12 months (active; at 2 weeks and 3, 6, 9 and 12 months)	4/29 (13.8%) (3 assessed with MRI)	"Occurred in generally same location as the initial injury, and injury severity did not appear worse"
Askling (2007) (98)	Prospective case series, Sprinters	n=18	Clinical examinations ≤2 days and MRI ≤4 days	NR	≤24 months after injury (Passive + active at 3, 12, and 24 months after index injury)	3/18 (16.7%)	8, 9, and 20 months after initial injury.
Askling (2007) (85)	Prospective case series, Dancers n = 15	n=15	Clinical examinations ≤2 days and MRI ≤4 days	NR	≤24 months after injury (Passive + active at 3, 12, and 24 months after index injury)	0/15	-
Koulouris (2007) (175)	Cohort study; Australian Football League	n=41	Clinical examinations and MRI ≤3 days	MRI ≤3 days (if sustained in competition season)	"Recurrent hamstring strain in the same playing season"	10/41 (24%) Strain <60 mm: 1/14 (7%) Strain >60 mm: 9/27 (33%)	Muscle injured: - 9 BF/1 SM Anatomical location: - 5 MTJ/5 myofascial Length: median 115 mm (35-160) (sign. longer than index, p=0.07). CSA (%): median 10 mm (5-60). RTS: mean 34.4 days (±11.8)
Verrall (2006) (123)	Prospective cohort study, Australian Football league	n=30***	Clinical examinations (12-18 hours) MRI ≤2-6 days	NR	Same season and subsequent playing season	12/30 (40%) same season +7 in subsequent season	40% within same season. 7 had a reinjury subsequent season.
Gibbs (2004) (163)	Prospective study, Australian Football League	n=31	Clinical examinations before MRI between 24-72 hours	NR	NR	6/17 MRI positive (35.3%) 0/14 MRI neg	Within the same season

†Ekstrand (2012) included despite no MRI information of index injury. *Active: investigator regularly following up through phone calls, e-mails etc.; Passive: athlete or medical staff responsible for reporting reinjury. ** Reinjury considered based on specific injury mechanism, pain with resisted knee flexion, tenderness to palpation along the muscle/tendon unit, and decreased ability to do sporting activities (perceived strength and power), but not included and reported in results. ***30/162 athletes met criteria for confirmed hamstring injury and were included in analyses. C-protocol, conventional protocol; BF, biceps femoris; CSA, cross sectional area; MTJ, musculotendinous junction; MRI, magnetic resonance imaging; NR, not reported; RTS, return to sport; SM, semimembranosus

Aims of the thesis

The overall aim of this thesis was to investigate aspects related to diagnosis and prognosis of acute hamstring injuries in male athletes, based on baseline clinical examinations and MRI. In particular, we wanted to explore and answer three key research questions: What is the optimal timing of MRI after an acute hamstring injury? What is the prognostic value of baseline clinical examinations and MRI for time to RTS? And where and when do the re-injuries occur after RTS?

These three questions led to the following specific aims addressed in the five papers of this thesis:

1. To describe the day-to-day changes in the extent of oedema following acute hamstring injuries and to investigate the optimal timing for detection of fiber disruption (*Paper I*).
2. To investigate the predictive value of patient history taking and clinical examination at baseline alone and the additional predictive value of MRI findings for time to RTS (*Paper II*).
3. To assess and compare the inter- and intrarater reliability of the modified Peetrons grading system, the Chan classification and the BAMIC (*Paper III*).
4. To determine the agreement between the modified Peetrons, the Chan classification and the BAMIC, and to prospectively investigate each of their associations with time to RTS (*Paper IV*).
5. To investigate the location, radiological severity, and timing of reinjuries on MRI compared to the index injury (*Paper V*).

Methods

Study location and study setting

The projects which form the basis for the papers included in this thesis were executed at one single study centre, Aspetar Orthopaedic and Sports Medicine Hospital, which is a specialised hospital located in Doha, Qatar. Aspetar provides medical care for sports-related injuries through the delivery of sports medicine, physiotherapy, medical imaging, sports science, orthopaedic surgery and rehabilitation. The hospital provides medical services for football and sport clubs and Olympic federations through the state of Qatar. The Qatar National Sports Medicine Program Aspetar (NSMP), which Aspetar established in 2009, facilitates sports medicine care for all registered athletes in sporting clubs and federations within Qatar and the Aspire Academy. Aspetar is referred to as the study centre throughout this thesis.

Study designs and study period

Athletes with acute onset posterior thigh pain (potential acute hamstring injury) have continuously since 2009 been invited to participate in prospective studies at the study centre through a standardised recruitment procedure described in detail below. The athletes included in this thesis were recruited in two separate study projects (Study 1 and Study 2) between January 2011 and December 2015.

Paper I is based on a descriptive prospective study (Study 1), with athletes included between January 2014 and December 2015. *Papers II-V* are based on a prospective cohort study (Study 2), with pooled data from athletes included in a previous RCT investigating the effect of platelet-rich plasma (ClinicalTrials.gov Identifier: NCT01812564) (176) or an ongoing prospective case series. Athletes in Study 2 were included in the study period between January 2011 and June 2014. During the work with *Paper II*, a new MRI classification was published (158). This encouraged us to dig deeper into the prognostic value of different MRI grading and classification systems. Thus, we first had to assess the reliability of the MRI scorings for these MRI systems. *Paper III* is therefore a methodology study based on 40 athletes selected from Study 2, whereas *Papers II* and *IV* are prospective case series. *Paper V* is a descriptive study, based on the athletes included in Study 2 that sustained a reinjury.

Participants

Recruitment procedure

Athletes with a potential acute hamstring injury were recruited consecutively in the Outpatient Department (OPD) at the study centre. The athletes were mainly brought to the OPD through their respective NSMP team doctor and/or physiotherapist. They underwent a standardised assessment procedure including clinical examinations by one of the sports medicine physicians as well as an MRI examination. The hamstring project coordinator/principal investigator was called immediately and assisted with the clinical examinations and was responsible for the further eligibility procedures and coordinating the study participants.

Level and type of sports

All athletes in Qatar registered as an athlete within one of the national sports federations have access to free medical care at Aspetar, and are classified as either 'professional' or 'competitive' athletes. In Study 1, both unregistered athletes ('recreational') and registered athletes ('professional' or 'competitive') were included, whereas in Study 2, only registered athletes were included, the majority being classified as 'professional'. We included all types of sporting codes performed within the clubs and federations in Qatar. The majority of the athletes played football (soccer), which is the most popular sport played, followed by handball, basketball and futsal.

Inclusion and exclusion criteria

Male athletes aged 18-50 with acute posterior thigh pain when training or competing were assessed for eligibility. In all studies, participants were excluded if they had contraindications to MRI (pacemaker, intracranial aneurysm, severe claustrophobia, foreign metallic objects). The eligibility criteria for Study I and the initial eligibility criteria common to the participants included in Study 2 are listed in Table 6. Additional specific eligibility criteria for each of *Papers II-V* are described below.

Table 6: Eligibility criteria for Study 1 and the initial eligibility criteria common for participants included in Papers II-V in Study 2.

Study 1	Study 2	
Inclusion criteria	**Inclusion criteria**	
▸ Clinical diagnosis of acute hamstring injury ≤1 day ▸ MRI ≤1 day since injury ▸ MRI-confirmed hamstring lesion ▸ Available for 6 consecutive MRI examinations	**Prospective case series** ▸ Clinical diagnosis and MRI performed ≤5 days after injury ▸ Available for follow-up	**RCT** ▸ Presenting and MRI ≤ 5 days from injury ▸ MRI confirmed grade 1 or 2 hamstring lesion ▸ Able to perform five sessions of physiotherapy a week at our clinic ▸ Available for follow-up
Exclusion criteria	**Exclusion criteria**	
▸ Previous hamstring injury (acute or chronic) same leg ≤5 years ▸ Chronic low back pain	**Prospective case series** ▸ Reinjury ≤2 months after RTS ▸ Chronic hamstring complaints >2 months ▸ Grade 3 hamstring tear ▸ Already included with prior injury	**RCT** ▸ Reinjury ≤2 months after RTS or chronic hamstring injury >2 months ▸ Other concurrent injury inhibiting rehabilitation ▸ Unwilling to comply with follow-up ▸ Needle phobia ▸ Overlying skin infection ▸ Diabetes, immune-compromised state ▸ Medication with increasing bleeding risk ▸ Medical contraindication to injection

Additional specific eligibility criteria:

In *Paper IV*, we included only athletes with complete sets of predefined MRI sequences. In *Paper V,* we included all athletes who experienced acute onset posterior thigh pain in the same leg as the index injury within ≤365 days since RTS after index injury, confirmed as a hamstring reinjury on MRI. If the MRI was performed >10 days after onset of suspected reinjury, they were excluded from the study.

Baseline assessments

Clinical examinations

The initial clinical examinations included patient history and physical assessment tests performed by the treating physician within 1 day (Study 1) or 5 days (Study 2) after injury. Throughout the study period, 19 physicians, all with a minimum 5 years of sports medicine experience, performed the baseline assessments.

Patient history

By interviewing the athlete, we obtained information about type of sport, maximal pain experienced at the onset of injury (using VAS, where 0 reflected no pain and 10 reflected maximal pain), type of injury mechanism, occurrence during training or competition, if they were forced to stop playing or training within 5 min after the onset of injury, any previous history of hamstring injury or previous low back pain.

Physical assessments

The physical assessment included hamstring ROM testing, active slump test, tenderness/pain with palpation and manual muscle resistance testing (provocation tests). Some of these physical assessment tests have also previously been used in other relevant studies, and are described in Table 7.

Table 7: Test descriptions of the initial physical assessments tests.

Physical assessment	Test descriptions
Trunk flexion (122,124)	From a standing position, the athlete performed a progressive trunk flexion with knees extended towards the level of maximal flexion. Presence or absence of recognisable pain at the injury site was registered.
Active slump test (59,133)	The athlete was seated with hands behind his back while maintaining a neutral spine position, then asked to tuck the chin towards the chest and to slump, bringing the shoulders towards the hips with full cervical, thoracic and lumbar flexion. Then, the athlete was asked to perform a full active dorsiflexion of the foot of the injured leg and thereby actively extend the knee until a stretch or pain was felt in the hamstring muscle due to the original pain. Then the athlete was asked to extend the neck to a neutral position and describe the change in sensation that occurred in the hamstring muscle. The test was considered positive if the athlete's original hamstring pain was decreased and then reproduced with cervical flexion.
Palpation (85,98)	Length and width of the region of tenderness (palpation pain) was examined with the athlete prone. The origin of the hamstring muscles on the ischial tuberosity was identified and the complete posterior thigh starting from the hamstring origin at the ischial tuberosity was palpated, moving continuously inferiorly to the hamstring muscle insertions. The longitudinal cranial-to-caudal length and the medial-to-lateral width (cm) of the tender/painful area was measured using a ruler.
Passive straight leg raise (118,122)	The athlete was lying in a supine position and the physician raised the athlete's leg with extended knee until the first point of reported stretch or pain at the site of injury and absence or presence of pain was noted.
Active knee extension test (6,122,128,131)	The athlete was lying in a supine position with 90° hip flexion of the tested leg, while the other leg remained flat on the examination table. The physician instructed the athlete to gradually extend his knee to the point of resistance to further extension, or the onset of pain at the site of the injury, and registered presence or absence of pain.
Active knee flexion	The athlete was lying supine and asked to actively perform repeated knee flexions. Pain was registered as yes or no.
Resisted knee flexion w/ 90° hip and knee flexion	The athlete was lying supine with 90° hip and knee flexion of the tested leg and the physician's hand against the posterior heel. The physician asked the athlete to actively contract the hamstring muscles while performing isometric knee flexion with maximum force. Pain was registered as yes or no.
Resisted hip extension w/30° hip and knee flexion	The athlete was lying supine with 30° hip and knee flexion of the tested leg and the physician's hand against the posterior heel. The physician asked the athlete to actively contract the hamstring muscles and while performing a hip extension and isometric knee flexion with maximum force. Pain was registered as yes or no.

MRI imaging

MRI protocols

All MRI examinations were performed with the patient in the supine position. Images of the hamstring muscle were obtained from the ischial tuberosity to the knee using a 1.5 Tesla (T) magnet system (Magnetom Expert, Siemens, Erlangen, Germany) with a phased-array surface coil and additionally two-body matrix coils, which were strapped over the injured thigh and centred over the painful area. We attached a vitamin E capsule to the posterior thigh corresponding to the point of maximal tenderness on palpation to function as a marker and confirmed with the athlete. To avoid voluntary motion artefacts, the athletes were explained the importance of lying still during the examination. Coronal and axial fast-spin echo proton density-weighted images were obtained first and subsequently coronal and axial fast-spin echo proton density fat-saturated images (PD-w FS) were obtained. A detailed overview of the MRI sequences used for Study 1 and Study 2, respectively, is presented in Table 8.

Table 8: MRI parameters (Study 1 / Study 2)

Parameters	Coronal FSE PD-w	Axial FSE PD-w	Coronal FSE PD-w FS	Axial FSE PD-w FS
Repetition time (ms)	2800 / 3000	2800 / 3000	4670 / 3000	3310 / 34490
Echo time (ms)	30 / 30	28 / 30	27 / 32	28 / 27
Slice thickness (mm)	5 / 3.5	4 / 3.5	4 / 3.5	4 / 3.5
Matrix size	307x384 / 333x512	307x384 / 333x512	256x320 / 326x512	256x320 / 333x512
Field of view (mm)	300 / 220-240	240/220-240	300 / 240	240 / 320
Echo train length	9 / 9	6/6	7 / 6	8 / 6

FSE, fast-spin echo; PD-w, proton density-weighted; PD-w-FS, proton density-weighted fat saturation.

MRI assessments

In both studies, we considered the muscle injured if the MRI demonstrated increased signal intensity on fluid sensitive sequences (PD-w FS), defined as abnormal intramuscular increased signal compared with the unaffected adjacent muscle tissues. We first identified the involved muscle (-s) that were injured (biceps femoris long head, biceps femoris short head, semimembranosus, semitendinosus) and scored the overall severity injury grading (grade 0–III) using modified Peetrons (106,159); grade 0: no abnormalities, grade I: oedema (increased signal

intensity) without architectural distortion, grade II: oedema (increased signal intensity) with architectural disruption, grade III: complete tear. Specific MRI assessment details are described below.

Paper I

When the initial MRI was positive for an acute hamstring injury (increased signal intensity), consecutive MRI examinations were obtained every day throughout the subsequent week using an identical protocol. We performed the MRI as close to a 24-hour interval as possible. One experienced radiologist (EA) assessed and scored the MRIs, and determined the localisation and extent of the injury using a standardised scoring form based on the literature (93,98,105,106,138,159). In a previous study, we reported good to excellent intratester reliability with the same radiologist (177). Quantitative assessments of the maximal extent of the oedema included three-dimensional measurements (mm) of the craniocaudal length, mediolateral width and anteroposterior depth of increased signal intensity on the fluid-sensitive sequences (PD-w FS) in the slice where the maximal extent of oedema was present, as well as the distance from the most cranial pole of the injury to the ischial tuberosity. The extent of the tear (presence of fluid collection/focal area of well-defined high signal intensity indicating fibre disruption) was measured in the same three dimensions (mm) as described above. The anatomical location within the muscle was scored (proximal tendon, proximal musculotendinous junction, proximal muscle belly, distal muscle belly, distal musculotendinous junction, distal tendon) (98,178), and within the same third (proximal, middle, distal) of this anatomical location. Conjoint tendon injury was scored if the common tendon of the biceps femoris long head and semitendinosus was injured (91). Finally, we scored the overall severity injury grading (modified Peetrons). If more than one muscle was injured or more than one lesion within the muscle was observed, the muscle (or lesion) with the greatest extent of signal abnormality was defined as the 'primary' lesion and included in the analysis. The seven consecutive MRIs of each case were scored in sequence, from day 1 through day 7.

Paper II

The same radiologist as in *Paper I* (EA) assessed and scored the MRIs, and determined the localisation and extent of the injury using a standardised scoring form (93,98,105,106,138,159). He was blinded to the clinical status of the injury and the RTS outcome. Quantitative assessments of the maximal extent of the oedema were assessed as described in *Paper I*.

Disruption of the central tendon as described by Comin et al. (93) was also noted. The involved cross-sectional area of oedema was calculated as a percentage of the total muscle cross-sectional area in the transversal plane. We approximated the volume of the total oedema using the formula for a prolate ellipsoid ([π/6] × anteroposterior × mediolateral × craniocaudal extent) (98,105). If more than one muscle was injured, the muscle with the greater extent of signal abnormality was defined as the 'primary' injury.

Papers III-IV

For *Paper III*, the principal investigator selected 40 cases based on the clinical MRI reports, to reflect a wide range of injury locations and severities. The principal investigator was not involved in reviewing or scoring of the images. Two musculoskeletal radiologists (AG and FR), each with >15 years of experience in MRI analyses, reviewed the MRIs independently, blinded to patient clinical status. First, the radiologists were familiarised with the MRI standardised scoring form, which included the three different MRI systems investigated (see below), and performed a calibration exercise. In this calibration session, they reached consensus on 10 randomly selected patients who were not part of the dataset, and agreed on each of the specific scores. Two months later, they independently scored the 40 MRIs in random order using the standardised scoring form to assess interrater agreement. MRIs were evaluated using the three scoring systems, but the readings were separated by two weeks for each of the three scoring systems to avoid recognition bias. An additional two months later, one radiologist (AG) re-scored the 40 MRIs a second time, in a different random order, to assess intrarater reliability.

For *Paper IV*, one of the radiologists (AG) independently reviewed all the remaining MRIs from the athletes that were not part of the reliability analyses in *Paper III* using the same procedure as in *Paper III*.

Standardised MRI scoring form Paper III and IV

The standardised MRI scoring form included the three MRI systems investigated, the modified Peetrons (106), BAMIC (158) and Chan classification (161), which is presented in detail in *Paper III* and *Paper IV*. Quantitative assessments of the maximal extent of the oedema were performed as described in Paper *I*. In cases with multiple lesions, the primary lesion was defined as the lesion with the greatest craniocaudal extent of oedema and included in the analyses. The secondary lesion was controlled for in the multivariate analyses. The Chan classification (161) identifies three MRI-positive grades (1-3), but injuries with no signs of pathology are not

classified. As a modification, we therefore scored MRI negative lesions as grade 0. We also scored proximal and distal tendon injuries, in addition to proximal and distal musculotendinous junction and muscular injuries, as suggested, resulting in 5 anatomical site categories. The anatomical site 2 (within the muscle) could be scored with several alternatives (A-C for proximity and a-e for location). In total, 48 combinations could be scored in addition to sub-combinations. The severity grading for the BAMIC (158) involves measurements of the extent of high signal changes and distinguishes between grade 0a (MRI normal) and grade 0b (MRI normal or patchy high signal change throughout one or more muscles). However, the radiologists were not able to distinguish between 0a and 0b, where both might show no signs of injury on MRI, without clinical information. We therefore combined 0a and 0b into one category (0a/b). Since the grading categories might overlap due to the different measurements of high signal changes, if any characteristics of a higher-grade injury were present, the injury was scored with the highest grade, as suggested (158).

Paper V

The MRIs of the index injuries were reviewed and scored as described for *Paper II* and the anatomical location of the injury was scored (similarly as in *Paper I* (98,142)). MRI examinations of the reinjuries were reviewed and scored by the same radiologist (EA) using the same scoring form as for the index injury, while blinded for the index injury scorings. In addition, the location of the reinjury and the presence of intramuscular scar tissue (fibrosis) were scored. To determine the location of the reinjury, axial and coronal views of the index injury and reinjury were directly compared on PD-w FS images and scored as 1) same muscle and same location within the muscle, 2) same muscle, but other location within the muscle, and 3) different muscle. The reinjury was considered as being in the same location if the main signal abnormality was observed in the same region as before (i.e. within the same anatomic location and within the same third) of this anatomic location). The location of the injury was scored as the conjoint tendon if it affected the common tendon of the biceps femoris and semitendinosus (91). The final decision was made by the radiologist through direct comparisons of the axial and coronal views. The severity of the reinjury was graded similarly as the index injury (modified Peetrons). We defined an intramuscular scar as an area of abnormally low signal intensity in the intramuscular tissue compared with surrounding muscle tissue on all sequences (PD-w and PD-w FS) (139,150,179). The presence or absence of an intramuscular scar was determined as the presence or absence of low signal intensity on the PD-w images. Athletes receiving any injection therapy (PPP or PRP)

had a follow-up MRI scan approximately 3 weeks after the index injury. These follow-up images were subsequently compared with the reinjury MRI scan to assess whether there was an increase in the extent of oedema, which was interpreted as a result of the reinjury rather than residual signs of the injection.

Treatment and rehabilitation

The athletes included in Study 2 did their rehabilitation at the study centre or in their respective clubs or federations. If they were included in the previous RCT (176), they were randomised into three groups: one group received a PRP injection, one group received an injection of platelet-poor plasma (PPP) and one group received no injection. All three groups followed a six-stage criteria-based physiotherapy programme including three final stages of sports-specific functional field testing supervised by an experienced sports rehabilitator, where the final session was aimed to mimic fatigue and competitiveness as during full unrestricted training at the required training volume and intensity. This rehabilitation program has been described in a separate paper (180). The RCT showed no benefit of PRP compared to no injection and a delayed time to RTS for PPP compared with PRP (176). The athletes included in the prospective case series received either rehabilitation at the study centre, as described above, or custom-made rehabilitation at the study centre or in their club or federation. Four athletes in the prospective case series received a single PRP injection.

The participants included in Study 1 either did no standardised rehabilitation or followed a structured rehabilitation the study center. Parallel with Study 1, we initiated a new randomised controlled trial (RCT) aiming at investigating the effect of two different rehabilitation protocols for RTS after acute hamstring injuries (ClinicalTrials.gov Identifier: NCT02104258), which is still ongoing. The athletes in *Paper I* were therefore also invited to participate in this RCT, where the rehabilitation protocols are based on the six-stage criteria-based physiotherapy programme rehabilitation as described above (180). If they met the eligibility criteria and agreed to participate in this RCT, the rehabilitation appointments were scheduled directly following each MRI examination, leaving ~23 hours between potential loading and the next MRI examination. Participants not included in the ongoing RCT did not receive any standardised treatment or rehabilitation. Throughout the first week, none of the participants were allowed to take any medications (non-steroidal anti-inflammatory drugs, NSAIDs) or receive any local treatment or physical modalities (including soft tissue treatment/massage, taping, needling techniques at the

injury site). They were also strongly discouraged to load their injured leg with exercises provoking pain or perform any high-speed running or heavy eccentric exercises.

Prospective follow up for RTS

In Study 2, the athletes were followed prospectively for RTS. Time to RTS was defined as: *the number of days from initial injury until the athlete was cleared by one of the physicians at the study centre or the treating physician or physiotherapist at the club or federation, to resume full unrestricted training.* The RTS decision makers were not blinded to the baseline assessments or the MRI findings. For athletes receiving rehabilitation at the study centre, the RTS evaluation took place after the patient completed the final stage of the sports-specific functional field testing and isokinetic strength testing (180). The treating physician took a structured history and performed clinical assessments including palpation, ROM and resistance testing. Based on the clinical evaluation, the strength tests, the reports from the treating physiotherapist and the sports rehabilitator and, in addition, sports risk modifiers and decision modifiers (181), the physician made a final decision on whether the athlete should be cleared for RTS, or should resume rehabilitation and perform new measurements prior to the ultimate clearance for RTS. For athletes receiving rehabilitation in the club or federation, we registered time to RTS once the athlete returned to full, unrestricted training. The number of days until RTS registered was provided by the club medical staff at weekly phone calls or via email. The criteria for RTS were decided by the team/federation physiotherapist or physician.

Follow up for reinjuries (Paper V)

We defined reinjury as acute posterior thigh pain occurring during training or competition in the same leg as the index injury within 1 year after RTS from the index injury (27,169,169,170), confirmed by clinical evaluation and MRI. We calculated the time (number of days) until reinjury in 2 ways: as the time from the index injury until reinjury and as the time from RTS after the index injury until reinjury.

Follow-up

In the RCT, players were monitored monthly by telephone for reinjury (active follow-up). All athletes included were advised to contact the treating physician if there were a clinical suspicion of reinjury. If this was confirmed by a clinical examination, an MRI examination was scheduled

within 5 days after the onset of the suspected reinjury. In the prospective case series, athletes were advised to contact the study center if there were a clinical suspicion of reinjury (passive follow-up). From September 2013, they were monitored by phone at 2 months, 6 months, and 1 year after RTS from the initial injury (active follow-up). If a reinjury was suspected, the athlete was scheduled for MRI within 5 days after onset of the suspected reinjury.

Remuneration

All athletes completing the study in *Paper I* received a computer tablet as compensation.

Statistical analyses

In all papers, we analysed the data using SPSS software (V.21.0; SPSS, Chicago, Illinois, USA), except for in *Paper III*, where we used Stata Statistical Software, Release 11 (College Station, TX: StataCorp LP). For all statistical tests, we set the significance level (two-tailed alpha level) to 0.05, if otherwise are not stated.

Paper I

To assess the effect of time on the changes in the extent of oedema (dependent variables), we conducted a one-way repeated measure analysis of variance (ANOVA) using time as within-sbject factor (independent variable). Similar ANOVA analyses were conducted to assess the effect of time on the extent of tear. In these analyses, we excluded one case with 2 days of imaging missing. We performed a log transformation when data were not normally distributed and if our data violated the assumption of sphericity, a Greenhouse-Geisser correction was applied. In absence of comparable studies, we were unable to perform a power calculation and arbitrarily decided that $n \geq 8$ would be adequate for descriptive analyses.

Paper II

To analyse the association between the potential predictive baseline variables and time to RTS, we constructed a general linear model. In the first step, we analysed the relationship between each of the potential predictive variables and time to RTS in a univariate model. Variables with $p<0.2$ in the univariate model were included in the multiple regressions analysis. In the multiple regression analyses, we used a backward stepwise technique keeping treatment variables fixed to

control for confounding. We created two multiple regression models that included the patient history and clinical examination variables. In the first model, we did not include MRI variables. In the second model, we included the MRI variables. Regression coefficients are presented as unstandardised β-coefficients with 95% CIs.

Paper III

The MRI findings were treated as ordinal variables for the severity gradings and for the BAMIC anatomical site a–c and the final overall BAMIC (0–4c). To determine the intra- and interrater reliability, we computed linear weighted Cohen's kappa (κ) statistics on an ordinal scale. For the remaining categorical MRI findings treated as nominal variables, we computed unweighted Cohen's κ statistics. To assess the intra- and interrater reliability for each of the subcategories within the final Chan classification and the BAMIC, the MRI findings were evaluated as dichotomous outcomes (yes/no) for each of the sub-categories. For the Chan classification, the anatomical site 2 (within the muscle) could be scored with several alternatives (A–C for proximity and a–e for location). For all values, we subsequently calculated the overall agreement (%), as the percentage of agreement in the positive observations divided by the total number of observations (182). Additionally, we calculated from the crosstabulations for the dichotomous variables the prevalence (P), which reflects the number of positive scorings, and the bias index (BI), which reflects the extent to which the raters disagree on the proportion of positive (or negative) cases (182). For the weighted κ values, we calculated weighted κ percentage agreement and the actual overall percentage agreement. We expressed agreement with κ-values between 0 and 1, where the strength of agreement were $\kappa < 0.00$ was considered 'poor', 'slight' 0.00–0.20, 'fair' 0.21–0.40, 'moderate' 0.41–0.60, 'substantial' 0.61–0.80 and 'almost perfect' if 0.81–1.0 (183).

Paper IV

Primary lesions were included in the analyses, whereas secondary lesions were controlled for in the multivariate analyses. Agreement between the MRI systems was assessed through cross-tabulations. For severity grades, we assessed the agreement for primary injuries (n=176) and MRI positive primary injuries (n=140) computing Cohen's κ (183) and overall percentage agreement (%), if the category numbers were equal. When category numbers differed, Spearman's Rho correlation coefficient was calculated. To compare mean differences (without adjusting for confounders) between each of the categories within the MRI systems for time to RTS, one-way between subjects ANOVA was conducted if assumptions were met (184) and non-parametric

analyses (Kruskal-Wallis) if assumptions were not met. To analyse the associations between each of the MRI systems (independent variables) and time to RTS (dependent variable), we constructed for each MRI system a general linear model (GLM) and we kept predefined confounder variables fixed. The GLM models were created only if assumptions for multivariate analyses were met (185). Where data was not normally distributed, log transformation RTS was conducted. MRI negative injuries were not scored for anatomical sites, thereby not included in these analyses. The total overall model effect is reported as adjusted R square values and regression coefficients as unstandardised β-coefficients with 95% CIs. Post-hoc analyses with pairwise comparisons (Sidak adjustment for multiple comparisons) were performed to assess estimated mean differences.

Paper V

The severity of the reinjury compared with the index injury was categorized based on the radiological grading, in which a less severe injury was graded lower and a more severe injury was graded higher than the index injury. Changes in injury characteristics between the index injury and reinjury for continuous data were analysed using the Wilcoxon signed-rank test for nonparametric data. Time after index injury and time after RTS after index injury were presented as the cumulative proportion (%) with reinjury.

Ethics

The studies were initially approved by the ethics committees of Aspetar Orthopaedic and Sports Medicine Hospital and the Shafallah Medical Genetics Centre. They were annually renewed by the Anti-Doping Lab Qatar (ADLQ) Institutional Review Board Committee (Study 1) or by the the Shafallah (Study 2). Written informed consent was obtained from the participants in English or Arabic, as preferred (Appendix I).

Results and discussion

An overview of the study flow and athletes finally included in *Papers I-V* is presented in Figure 7.

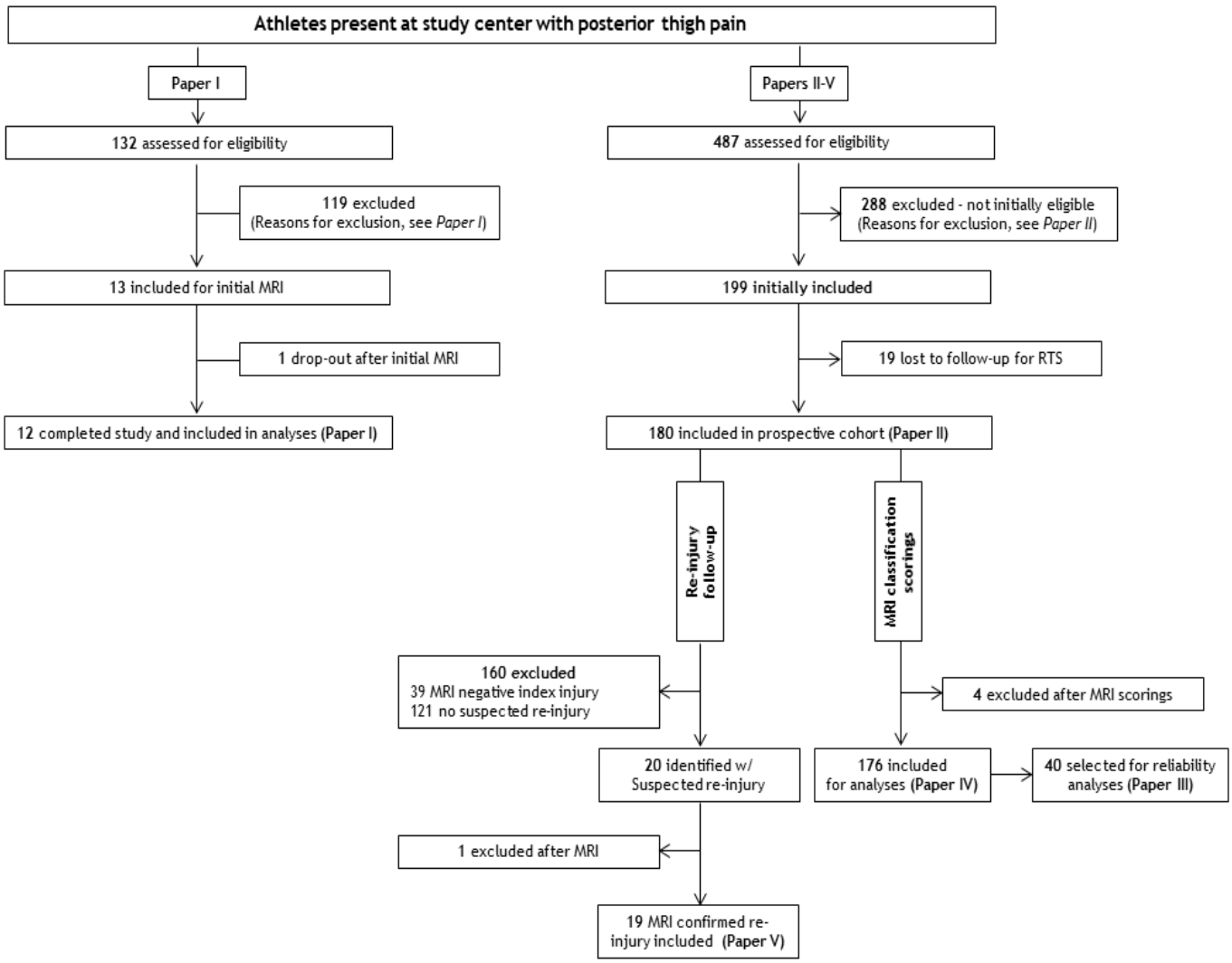


Figure 7: Study flow showing the recruitment process of athletes included in Papers I-V.

MRI appearance does not change within the first week (Paper I)

Out of 13 athletes initially included, 12 completed the study and were included in the final analyses; 11 had all 7 MRI scans performed, whereas one athlete missed two MRI appointments and had 5 MRI scans performed.

No significant changes in the extent of the oedema

Notably, for the extent of the oedema, the intraindividual day-to-day changes of the MRI features (i.e. *within* participants) were considerably smaller than the interindividual variability (i.e. *between* participants), as shown in Figure 8. When assessing the main effect for time (n=11), we did not find any significant differences between the 7 days for any of the oedema measurements: distance to tuber (p=0.16); craniocaudal length (p=0.18); mediolateral width (p=0.12); anteroposterior depth (p=0.81).

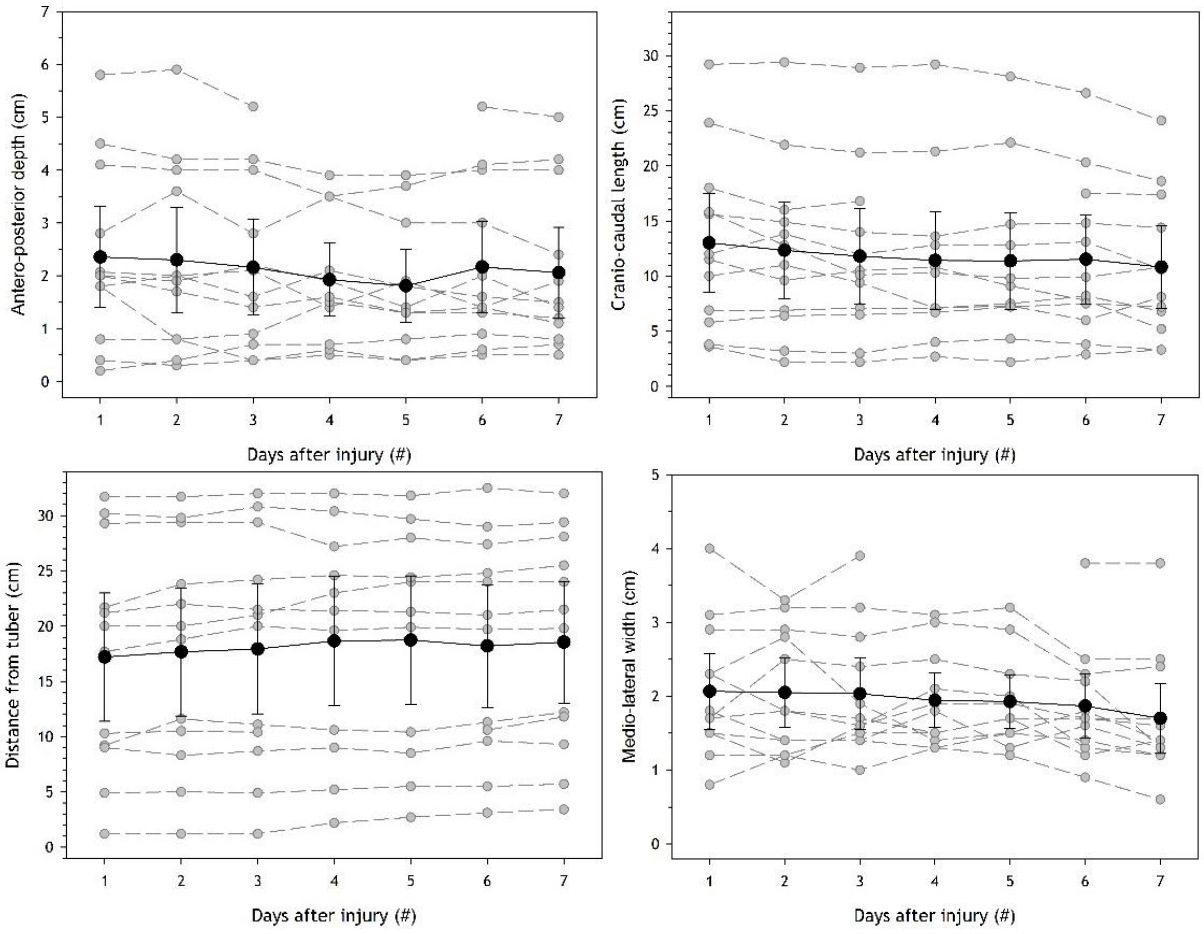


Figure 8: Day-to-day changes in the extent of the oedema measures from day 1 to 7 (n=12). The grey circles and dotted lines represent individual cases, the black circles and solid lines represent the group mean values with the corresponding 95% CI.

Does the muscle healing process correspond to the extent of oedema on MRI?

Muscle healing after a muscle strain injury follows a complex process including degeneration and inflammation (occurring within the first days postinjury), regeneration and a proliferative phase during which development connective (scar) tissue occurs (32,33,43,63,66). The evolution of acute hamstring injury throughout this acute stage, during which degeneration and inflammation occur, has not previously been described in athletes with MRI and our findings cannot directly be compared with the previous histological literature. However, since there is an overlap between the inflammatory phase and the regenerative phase (43), oedema is still expected to be present at this stage, which corresponds to our findings.

An interesting question which still remains unanswered, is *when* and *how fast* does the increased signal intensity decreases after the first week following injury? In two other studies, Askling et al. (85,98) found significant changes in MRI parameters between initial MRI at day 4 and the first MRI follow-up at day 10 in sprinters (98) and ballet dancers (85). As we did not find any significant changes within the first 7 days, the decrease in the extent of oedema seems to occur somewhere between 7 and 10 days from the initial injury. However, due to small samples sizes, we cannot draw any definite conclusions. Moreover, increased signal intensity has been reported to be present long after the injured athletes have clinically recovered and returned to sports participation (85,98,138,155,186,187). The exact time point for when a significant reduction in the extent of oedema occurs might therefore be challenging to identify. More basic research is needed in this area to fully understand the evolution of an acute hamstring injury, and its appearance on MRI.

Fibre disruption can be detected from day one after injury

The presence of fluid collection indicating fibre disruption (tear) was present in 5 of the athletes, in all cases detectable from the first day after the injury. Similar to the oedema measurements, there were small and insignificant day-to-day changes in the extent of the tear measurements. This is exemplified in Figure 9, showing the axial and coronal views of the MRIs performed the first and last day of imaging (day 1 and day 7 after injury) for one of the participants with fibre disruption.

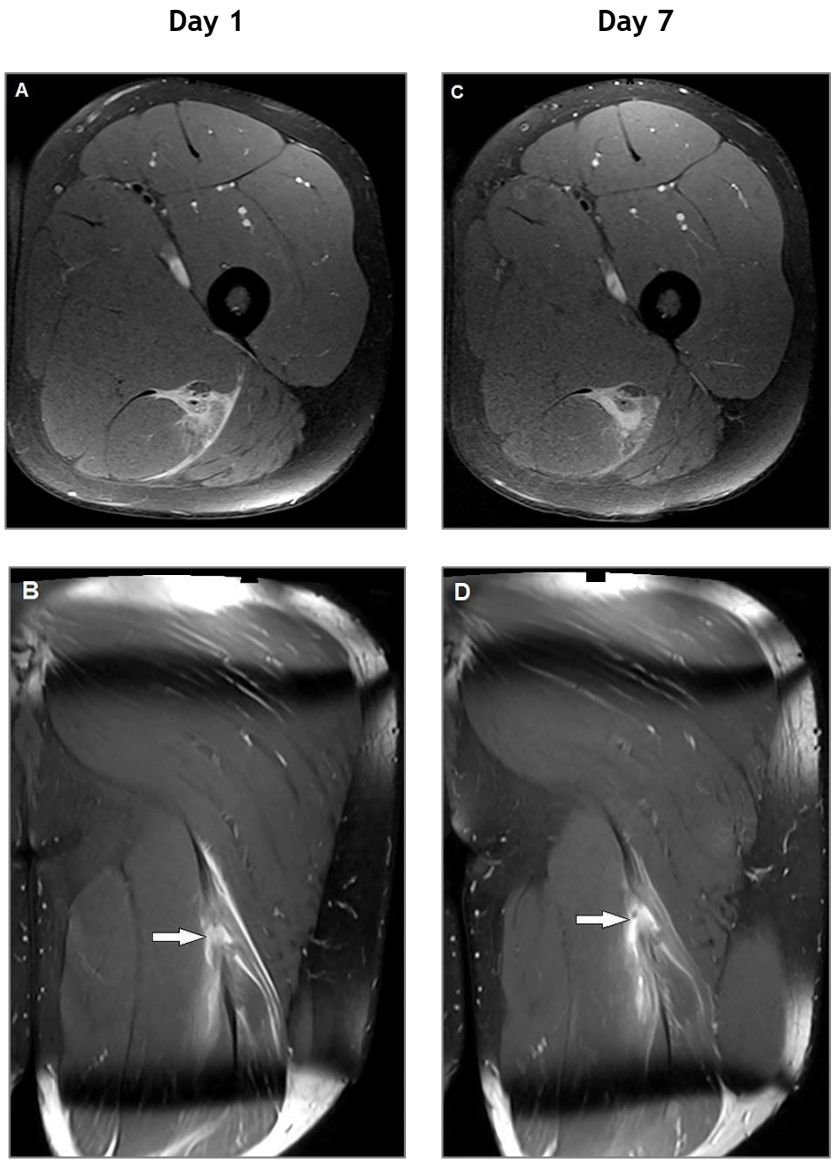


Figure 9: Axial (A) and coronal (B) proton density-weighted (fat-saturated) MRIs on day 1 after injury show oedema and fibre disruption demonstrated as a well-defined area (gap) filled with heterogeneous increased signal intensity (fluid collection) in the conjoint tendon (white arrows). On day 7, the increased signal intensity has not changed significantly and the fibre disruption is still present (C and D).

Indirect measure of fibre disruption

For fibre disruption, the extent can only be indirectly measured on MRI as the presence of fluid collection/focal area of well-defined high signal intensity. An exact description of the fibre disruption can therefore not be given without developing more advanced techniques, which might be an area for future research. Another interesting question for future investigation is: what happens within the very first hours after injury? And how soon after injury can fibre disruption

be detected? In our study, all the initial MRI examinations were obtained the first day *after* injury, leaving at least 12 hours between the acute onset of injury and the first MRI. From this study, we can therefore not provide any data on the occurrence and presence of increased signal intensity (with and without fibre disruption) within the first 12 hours post-injury.

Implications: MRI can be performed any day within the first week

Our findings suggest that MRI can be performed any day within the first week following acute hamstring injuries. This is an important message to clinicians, as it will give medical staff and athletes more flexibility in the timing of the MRI without sacrificing its accuracy. Previous recommendations, mainly based on expert opinion or small experimental studies advising MRI to be performed between day 1 and day 3 postinjury (59,106,119), are therefore not fully supported by our findings.

This is the first clinical study of its kind with daily MRIs of a homogenous muscle group (hamstrings) during the first week after injury, and therefore no prior data to which our findings can be compared directly. Despite the relative low sample size, the study is unique within the field of muscle injury research, challenging established assumptions.

MRI does not add value over and above patient history clinical examinations for predicting time to RTS (Paper II)

In this prospective study, including 180 male athletes with the majority being football players (77%), we created two regression models in order to determine the predictive value of baseline patient history and clinical examinations alone (model 1), and the additional predictive value of MRI (model 2) for time to RTS. The time to RTS ranged from 1 to 72 days, with a mean of 21 (SD±12) days for all cases, 13 (SD±8) days for the MRI-negative cases and 24 (SD±12) days for MRI-positive cases.

Limited predictive value of baseline patient history and clinical examinations

In the first model (model 1), 13 patient history and clinical examination candidate variables were included, of which four were retained in the final model showing independent associations with time to RTS (Table 9). However, the total variance in time to RTS explained by this model was only 29% (R^2=0.29; ANOVA, F=11.291, p<0.001). This is a weak association, meaning that 71%

of the variance in RTS was due to other, unknown factors. To illustrate the clinical relevance of this finding, we created a 'dummy athlete' with specific values allocated for each of the variables in the final model. For this specific athlete, the predicted time to RTS was 21.3 days with a 95% CI between 1.2 and 41.4. These large confidence intervals mean that, a physician or physiotherapist without access to imaging using the clinical variables remaining in our final model 1, could provide the following prognosis to this athlete: 'There is 95% chance that you will return between 1 and 41 days from now'. Such a wide estimate is highly essentially useless for a professional athlete.

Table 9: Model 1showing multiple regression analysis of patient history and clinical examination as predictors for TRTS after controlling for potential treatment confounders (n=180). Regression coefficients are presented as adjusted unstandardized B-coefficients with 95% confidence intervals (CI).

Predictor for time to RTS	**B-coefficient**	**95% CI**	**p-value**
Maximum pain score (VAS)	1.6	0.8 to 2.4	<0.001
Forced to stop within 5 min (yes/no[a])	5.3	1.9 to 8.8	.003
Length of palpation pain (cm)	0.7	0.3 to 1.1	.002
Painful resisted knee flexion (90°)	4.7	0.03 to 9.3	.048

[a]Reference category.

There are currently seven other studies that have investigated clinical variables as predictors for time to RTS after acute hamstring injuries using multivariate analysis (122,124,164,188–191). However, several methodological differences, such as a retrospective study design (164), dichotomous reporting of the time to RTS outcome (124,188) and pooling of several clinical tests into an overall clinical grading (122), limit the ability to compare our results to these findings. Another problem when comparing our results with the literature is the heterogeneity in the testing procedures for the different clinical findings reported.

Although four clinical variables showed independent associations with RTS, the poor predictive value of our final model 1 (29%) encouraged us to look more deeply in the evidence regarding the value of baseline clinical variables as predictors for RTS. We therefore recently systematically reviewed the literature on the prognostic value of clinical findings (patient history and physical examination) for time to RTS after acute hamstring injuries in athletes (192), and found no strong evidence that any clinical finding at baseline can provide a valuable prognosis for time to RTS after acute hamstring injuries. Further, there was moderate evidence that pain at the time of injury and predictions for RTS by the patient and the clinician are associated with time to RTS. From our results in *Paper II*, maximum pain score (VAS) at the time of injury was independently

associated with a longer time to RTS in model 1. This is supported by findings from univariate analyses in two previous publications (127,188) and from multivariate analyses in one newer publication from our study centre (191). Despite discrepancies in study methodologies and populations, asking about pain at the time of injury could potentially have some prognostic value. However, we only performed baseline assessments, it is possible that repeating these assessments regularly after the injury (e.g. weekly) could provide a greater accuracy for predicting time to RTS. Since the publication of *Paper II*, our research group has looked more into the value of using follow-up clinical examinations repeated measurements (191,193), showing that some specific daily physical measures might be valuable to inform the rehabilitation progression.

The additional predictive value of baseline MRI was negligible

In our second model (model 2), we added five MRI variables to model 1, leaving a total of 18 candidate variables. Again, four variables were retained in the final model, of which only one MRI variable (grading) (Table 10). The total variance in time to RTS explained by this model 2 was 31.8% (R^2=0.318; ANOVA, F=11.222, p<0.001), meaning that the predictive value when adding MRI to the clinical variables only increased by 2.8%. Thus, the additional predictive value of MRI was negligible beyond that possible based on patient history and clinical examinations alone.

For the example above, using our final model 2, adding an MRI grading of 2, the predicted time to RTS would be 25 days with a 95% CI between 5.4 and 44.7. In this case, the message to the athlete would be: 'There is a 95% chance that you will return between 5 and 45 days from now'. This is clearly no more helpful than the first model.

Table 10: Model 2 showing multiple regression analysis of patient history, clinical examination and MRI variables as predictors for TRTS including both MRI positive and MRI-negative injuries (n=180). Regression coefficients are presented as adjusted unstandardized B-coefficients with 95% confidence intervals (CI).

Predictor for time to RTS	B-coefficient	95% CI	p-value
Maximum pain score (VAS)	1.4	0.5 to 2.2	0.002
Forced to stop within 5 min (yes/noa)	4.9	1.5 to 8.4	0.005
Length of palpation pain (cm)	0.5	0.1 to 0.4	0.012
Overall grading			
Grade 2	8.1	3.2 to 12.9	0.001
Grade 1	3.6	-0.7 to 7.9	0.098
Grade 0	0[a]		

[a]Reference category

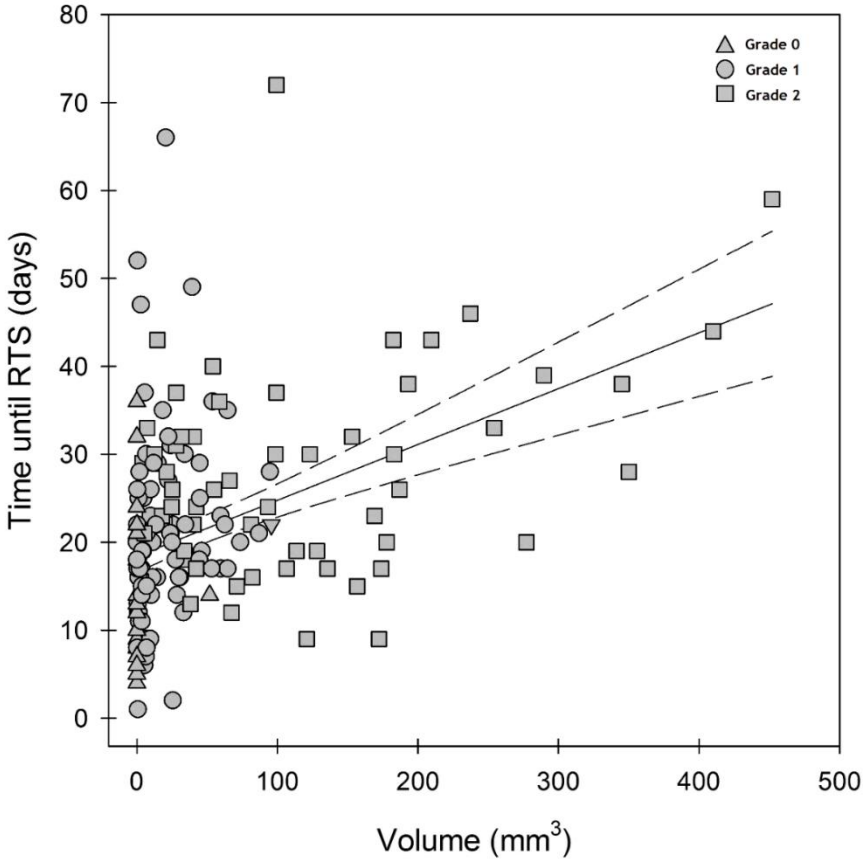


Figure 10: Scatterplot and line of best fit (solid line) with 95% CI (dotted lines) depicting the linear relationship between volume of oedema (cm3) and time to RTS (days). The square labels represent injuries scored as grade 2, the circles represent injuries scored as grade 1 and the triangles represent injuries scored as a grade 0.

Large individual variations in RTS

As illustrated in Figure 10, there was substantial variability in time to RTS *within* each of the MRI grading categories (grades 0, 1 and 2) and considerable overlap *between* grading categories. These large individual variations parallel other reports that have examined radiological grading in larger cohorts among professional football players (3,106,194). However, these MRI findings have been interpreted differently, and the predictive value of MRI debated, as discussed below. Yet, based on our findings in *Paper II*, MRI grading alone seems unhelpful for predicting time to RTS. Our results therefore provide no rationale for routine MRI after acute hamstring injuries and add further weight to the conclusions of a systematic review, which stated that recovery time cannot be predicted based on MRI findings (195).

'Substantial' to 'almost perfect' intra- and interrater reliability of three MRI classification scorings (Paper III)

We investigated the intra- and interrater reliability of three MRI classification systems in 40 selected athletes included in our prospective MRI classification study (*Paper IV*). In seven of the athletes, no injury on MRI was detected by any of the two raters. Among the remaining 33 athletes, a total of 56 lesions were scored, of these 9-12 lesions were scored as a secondary lesion (depending on the rater).

Intrarater reliability

In Table 11, both intra- and interrater reliability for the overall severity grading, overall anatomical sites and final classifications are presented. Summarised, there was 'almost perfect' intrarater agreement for the identification of the specific injured muscle, for the scoring of the injured muscle as primary and secondary lesion and for the modified Peetrons, as well as for the the overall severity grading for the Chan and the BAMIC. For the overall anatomical site scoring (1-5) in the Chan classification, the intrarater agreement was 'substantial' and for the final overall BAMIC combining the severity grading and the anatomical sites, the intrarater agreement was 'almost perfect'. The overall percentage intrarater agreement for all the ratings ranged between 81% and 100% (table 13). For the subcategories within the final Chan and the final BAMIC, there was substantial variability with κ values ranging between 0 and 1 and a low prevalence for some scorings.

Interrater reliability

Raters agreed 'almost perfectly' in the identification of the specific muscle injured, whereas 'substantial' interrater agreement was found for the scoring of whether the injured muscle was a primary or secondary lesion. There was 'almost perfect' agreement for the modified Peetrons and the overall severity grading for the Chan and the BAMIC. For the overall anatomical site scoring (1-5) in the Chan, the interrater agreement was 'substantial' and for the final overall BAMIC, the interrater agreement was 'almost perfect'. The overall percentage interrater agreement ranged between 74% and 100% for all scorings (Table 11). For the subcategories within the final Chan and the final BAMIC, there was a great variability with κ-values ranging between 0 and 1 and a low prevalence for some scorings.

Table 11: Intra- and interrater reliability of the overall severity grading, anatomical sites and final classifications based on modified Peetrons grading system, Chan classification and BAMIC in 40 athletes with clinical symptoms of acute hamstring injuries.*

	Intrarater				Interrater			
	Total valid lesions scored	**Kappa (95% CI)**	**Weighted Agreement (%)**	**Actual Agreement (%)**	**Total valid lesions scored**	**Kappa (95% CI)**	**Weighted Agreement (%)**	**Actual Agreement (%)**
Specific muscle	45	1.00 (1.00 - 1.00)	100%	100%	44	1.00 (1.00 - 1.00)	100%	-
Primary and secondary lesion	45	1.00 (1.00 - 1.00)	100%	-	44	0.93 (0.79 -1.07)	98%	-
Modified Peetrons severity grading (0-3) †	52	0.89 (0.68 - 1.10)	96%	92%	51	0.95 (0.73 - 1.16)	98%	96%
Chan classification:								
Overall severity (grade 1-3) †	52	0.85 (0.65 - 1.05)	95%	90%	51	0.85 (0.65 - 1.05)	95%	90%
Overall anatomical site 1-5	45	0.65 (0.44 - 0.86)	82%	-	44	0.77 (0.58 - 0.96)	89%	-
BAMIC:								
Overall severity (grade 0 - 4) †	52	0.80 (0.62 - 0.99)	94%	81%	51	0.77 (0.59 - 0.96)	93%	78%
Overall anatomical site (a-c) †	45	0.89 (0.63 - 1.14)	94%	89%	44	0.88 (0.63 - 1.14)	94%	87%
Overall final classification (0a/b-4c) †	52	0.80 (0.62 - 0.97)	93%	71%	51	0.81 (0.63 - 0.98)	93%	75%

* The total valid lesions for both raters of an overall total of 56 lesions scored are presented (n). Values for ordinal variables are expressed as weighted kappa (κ) and nominal and dichotomous variables are expressed as Cohen's kappa (κ). All values are presented with 95% confidence interval (CI) and overall percentage agreement (%). For the weighted κ, the actual percentage agreement (%) is also presented. † Weighted kappa. CI, confidence interval.

Implications: MRI scorings by experienced radiologists can be trusted

An 'almost perfect' reliability for the severity grading within the three MRI scoring systems is in agreement with comparable studies (177,194,196). For the modified Peetrons, Hamilton et al. (177) reported excellent intra- and interrater reliability in athletes with acute hamstring injury, and Ekstrand et al. (194) just recently reported 'almost perfect' interrater agreement in a larger cohort of injured professional football players. Similar findings are also reported for MRI grading in athletes with acute adductor muscle injuries (88). The intra- and interrater reliability was 'almost perfect' for the overall final BAMIC, as well as for the severity grading (0–4) and the anatomical site (a-c) analysed separately. This is in agreement with the study group which originally developed this classification system, recently reporting 'substantial' agreement for the overall BAMIC (196). Our findings therefore support and extend the evidence that categorical grading of the severity of (hamstring) muscle injuries is reproducible and trustworthy when scored by experienced musculoskeletal radiologists using standardised methodology.

However, within each of the subcategories for the final classifications including anatomical site categories (Chan and BAMIC), there was substantial variability for both the intra- and interrater agreements. A low prevalence of scorings within each of the subcategories might explain a substantial part of this wide range in magnitude and variability for the κ-values. Uncertainties related to diffuse definitions and risk of overlap between the injury categories originally described (158,161) might also have influenced the scorings and might be interpreted differently by other raters. A further discussion of each of these findings is beyond the scope of this dissertation. But in summary, the exact intra- and inter-rater reliability for the subcategories of the anatomical locations and the final classifications of Chan and BAMIC remains unclear.

MRI classifications, regardless of system used, cannot predict RTS (Paper IV)

We evaluated the MRIs for 176 of the athletes included in *Paper II* using the three MRI systems evaluated in *Paper III*. Thirty-six (20.5%) had no signs of injury on MRI (grade 0). Among the 140 (79.5%) with MRI-positive injury, 104 (74.3%) had one lesion and 36 (25.7%) had 2 lesions scored.

Agreement between the MRI systems

The agreement between the three MRI systems for the primary injuries are presented in Table 12 and in the Supplementary Material tables in *Paper IV*.

Table 12: Cross-tabulations showing agreement between the severity grades for the different MRI grading and classification systems (primary injuries, n=176). The distribution of injuries within the grading categories is presented (%).

		Modified Peetrons				
		Grade 0	Grade 1	Grade 2	Grade 3	*Total (%)*
Chan classification	No injury	36	0	0	0	*36 (20.5%)*
	Grade 1	0	70	36	0	*106 (60%)*
	Grade 2	0	0	32	0	*32 (18%)*
	Grade 3	0	0	0	2	*2 (1%)*
Total (%)		*36 (20.5%)*	*70 (40%)*	*68 (39%)*	*2 (1%)*	*176*

% Agreement all (n=176): 79.5%; Cohens κ: 0.68 (p<0.01)
% Agreement: MRI-positive (n=140): 74.1%; Cohens κ: 0.50 (p<0.01)

		Modified Peetrons				
		Grade 0	Grade 1	Grade 2	Grade 3	*Total (%)*
BAMIC	0 a/b	36	0	0	0	*36 (20.5%)*
	Grade 1	0	22	3	0	*25 (14%)*
	Grade 2	0	44	32	0	*76 (43%)*
	Grade 3	0	4	33	0	*37 (21%)*
	Grade 4	0	0	0	2	*2 (1%)*
Total (%)		*36 (20.5%)*	*70 (40%)*	*68 (39%)*	*2 (1%)*	*176*

Spearman's Rho correlation coefficient all (n=176): 0.80 (p<0.01)
Spearman's Rho correlation coefficient MRI-positive (n=140): 0.56 (p<0.01)

		Chan Classification				
		Grade 0	Grade 1	Grade 2	Grade 3	*Total (%)*
BAMIC	0 a/b	36	0	0	0	*36 (20.5%)*
	Grade 1	0	25	0	0	*25 (14%)*
	Grade 2	0	67	9	0	*76 (43%)*
	Grade 3	0	14	23	0	*37 (21%)*
	Grade 4	0	0	0	2	*2 (1%)*
Total (%)		*36 (20.5%)*	*106 (60%)*	*32 (18%)*	*2 (1%)*	*176*

Spearman's Rho correlation coefficient all (n=176): 0.82 (p<0.01)
Spearman's Rho correlation coefficient MRI-positive (n=140): 0.56 (p<0.01)

We observed moderate agreement between the severity grading systems for the MRI-positive injuries. This implies that reporting of MRI grading depends on which MRI system is applied; a grade 2 is not necessarily always a grade 2. To avoid misinterpretation and/or miscommunication in clinical practice and research, we recommend specifying which MRI grading system is used when reporting such MRI findings. Different 'cut-offs' for presence and extent of fibre disruption consequently influence the MRI grading; the Chan classification allows ≤5% of fibre disruption for grade 1 injuries, resulting in a greater distribution of grade 1 vs 2 injuries. For the modified Peetrons, where grade 1 injuries present with no architectural distortion, grade 1 and 2 injuries were equally distributed. Thus, no modified Peetrons grade 1 injuries were scored as a Chan classification grade 2, whereas 36 grade 1 Chan injuries were scored as a grade 2 modified Peetrons. Agreement between the Chan classification and the BAMIC is difficult to report, due to their dissimilarities in the descriptions of tissue involvement. Importantly, the Chan classification does not specifically consider the intramuscular tendon injuries alone, but could be classified as both a proximal or distal myotendinous junction injury or a myotendinous injury within the muscle. A strength with these two classifications compared to modified Peetrons is that they force a more accurate description of the injury.

Associations with RTS

Figures 13 a-c present the time to RTS and the distribution of the primary lesions (n=176) within each of the categories for the complete MRI systems (see also Supplementary Material in *Paper IV*).

Univariate analyses (mean differences)

For severity grading (n=174), there was an overall main effect of grades for each MRI system ($p<0.001$). Post-hoc comparisons for BAMIC did not show differences between grade 0a/b vs 1 ($p=0.312$) and 1 vs 2 ($p=0.054$), but differences between grade 0a/b vs 2 ($p<0.001$) and 1 vs 3 ($p<0.001$). For BAMIC anatomical sites, there was an overall main effect between the sites (ANOVA, $F[3, 170] = 15.960$, $p<0.001$). Post-hoc comparisons showed no differences between site a vs b ($p=0.974$) and a vs c ($p=0.065$), and a significant difference between b vs c ($p=0.007$). There were no differences between the Chan anatomical sites 1-5 (Kruskal-Wallis, $\chi2=6.854$, $p=0.077$) or proximity within muscle (2.A-C) ($\chi2=1.973$, $p=0.373$), but differences between anatomical sites within the muscle (2.a-e) ($\chi2=11.788$, $p=0.008$). For combined BAMIC (0a/b-3c) there was a significant difference (Kruskal-Wallis, $\chi2=28.177$, $p<0.001$).

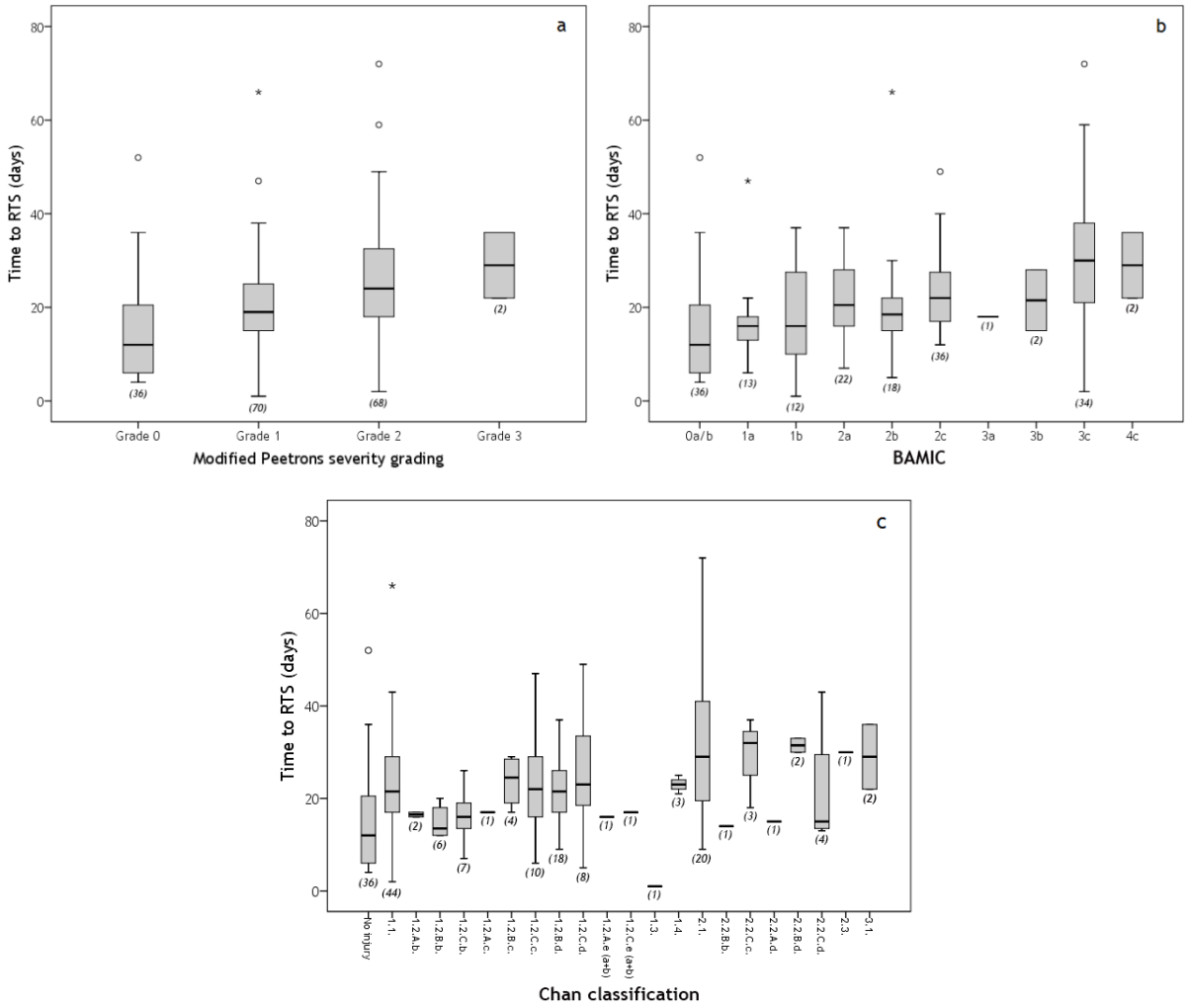


*Figure 13 a-c: Variance of the distribution of time to RTS within and between (a) the modified Peetrons (severity grading), (b) the BAMIC (combined severity grading and anatomical site) and (c) the Chan classification (combined severity grading and anatomical site), respectively (n=176). Data is presented as the median (horizontal lines), interquartile ranges (IQR) (boxes) and minimum and maximum values (whiskers). °outliers with scores >1.5 IQR; *outliers with scores >3 IQR; number of injuries within each category (n) presented in brackets below each lower whisker.*

Multivariate analyses of MRI-positive injuries

Our complete dataset for the three MRI systems did not meet the assumptions for multivariate analyses. For MRI-positive injuries (n=138), GLM models were created for the severity grading (separately) and for the BAMIC anatomical site. When controlling for confounders, the total variance in time to RTS explained by the models varied from 7.6% to 11.9%.

Associations between continuous MRI measurements and RTS have been suggested as prognostic factors (85,93,98,105,127,138,155,163), although the evidence is limited (195).

Modified Peetrons has shown correlations with RTS (3,106,194), but no differences between grade 1 and 2 injuries for RTS were found in a high-quality study (189). Grading does not seem to add any predictive value over and above clinical examinations, as shown in *Paper II*. Our findings reflect several challenges when investigating RTS prognosis based on current MRI systems. First, the low frequency of injuries within many of the categories precludes appropriate statistical analyses (i.e. multivariate analyses). For the Chan classification, less than half of the 48 possible categories were scored, many of these with only 1 lesion. Despite larger samples, it is unlikely that all the categories will ever have sufficient numbers to allow for appropriate analyses. Secondly, we observed large individual variations for time to RTS within each category for all the MRI systems. These wide ranges are similar to previous findings (3,106,194,197), illustrating one of the major limitations regarding baseline MRI findings and RTS prediction; although we report statistically significant differences in RTS between grades, which can give a broad estimate at a group level, the large range within each grade renders the MRI systems unusable for a specific athlete. For example, for an athlete sustaining a BAMIC 3c injury with mean time to RTS of 30.7 days (± 13.4 SD), we can estimate that there is 95% chance that this athlete will return within 3.9 to 57.5 days (mean 30.7 days ± 2 times SD of 13.4 days). Considering the MRI-positive injuries, the grading systems and the BAMIC anatomical site accounted for only 7.6% to 11.9% of the total variance in time to RTS, reflecting very poor associations. Although it should not be ignored that the higher-grade injuries on average took longer time to RTS, we explicitly urge looking beyond the mean values and into the consequences of the variance within and the overlap between the grading and classification categories.

Intratendinous injuries

A retrospective study with 8 2c injuries and 7 3c injuries (94) demonstrated that grade 3 and intratendinous injury were associated with longer time to full training. Due to the retrospective nature and different use of confounders and outcome definitions, a direct comparison with our findings cannot be made. Similar to Pollock et al. (94), we observed a wide range in RTS for 3c injuries, which limited the predictive value of our findings. Classification of the intratendinous injuries is based on the extent of high signal changes within the tendon. A tendon demonstrating high signal changes across all its diameter on axial views but without disruption (3c), can therefore be classified similar to a tendon demonstrating extensive partial disruption (>50%, also 3c). Several 2c and 3c injuries were therefore graded as a modified Peetrons grade 1 in our data, and this might also partly explain the large variance in RTS for the 3c injuries. The literature

regarding intramuscular tendon injuries in muscle injuries is limited (93,198–200), but they are suggested to play a role in problematic hamstring and quadriceps muscle strains (201). Theoretically, differences in healing processes between muscle and tendon could result in different healing times. Healing of a tendon is characterised by a slow metabolic rate and therefore generally slower than muscle healing (54,202). However, since the intramuscular tendons are not 'free' tendons, more data are needed to test this hypothesis. It seems like clinical examinations (i.e. hamstring flexibility and strength) cannot be used to discriminate the presence of intramuscular tendon involvement (203), and for this purpose MRI is the preferred diagnostic tool. However, we reported limited predictive value of the BAMIC (including intramuscular tendon injuries), which is partly in agreement with a new study reporting that although time to RTS for injuries with full thickness disruption of the intramuscular tendon and waviness was significantly longer (slightly >1 week) compared with injuries without intramuscular tendon involvement (204), the predictive value was limited. Thus, because of the considerable overlap in time to RTS between groups with and without intramuscular tendon involvement, its clinical significance for the individual athlete may be limited (204). The clinical importance of identifying the intramuscular tendon involvement must therefore be further explored.

Summarised, we revealed a wide overlap between and variation within the grading and classification categories. Therefore, none of the classification systems could be used to predict time to RTS in our sample of MRI-positive hamstring injuries.

Implications: To MRI or not to MRI?

In light of the findings from *Paper II* and several other studies published since we started the project in 2013 (94,189,191,194,195), there is an ongoing scientific debate within the field of hamstring injury research concerning the prognostic value of MRI (201,205,206).

The central question is: to MRI or not to MRI for predicting RTS? The findings from *Paper II* and *Paper IV* clearly support the latter, providing additional support to a systematic review first released in 2014 (195), which concluded that there is no strong evidence for that any MRI finding can predict RTS. Previous studies reporting associations between MRI findings and RTS have been based on small sample sizes and mostly univariate (correlation) analyses with a high risk of bias (195). Importantly, when conducting larger prospective studies applying multivariate analysis and controlling for confounders, we have shown that there are large individual variations in RTS, independent of the MRI findings. The variability in RTS within and between (overlap) the

grading and classification categories revealed in *Paper II* and *Paper IV* is also found in other comparable studies (3,106,194,204,207), making these results less suitable when trying to accurately predict time to RTS for the specific individual athlete. The large variance reflects the difficulty of using a baseline 'screenshot' to predict a multifactorial outcome, as RTS is. Notably, one of our main findings from *Paper II* was that MRI does not add predictive value over and above clinical examinations. Thus, clinical examinations should be the foundation of the prognostic approach.

However; this is not a call to abandon the use of MRI following acute hamstring injuries. Our findings do not support using MRI for *predicting* time to RTS, meaning that we should not use MRI to tell an athlete how long it will take before he or she can return to full sports activity or play the next game. However, MRI may have other roles. For example, if a total rupture / avulsion injury is suspected, MRI is highly recommended and useful to guide further treatment or if the clinical diagnosis is unclear. At a professional level, there may also be arguments for performing an MRI due to external pressure (from coaches, team- and club management) and possible financial consequences and/or to give the athlete 'a piece of mind'. Finally, for research purposes, MRI has an important role, providing detailed information about the injury and aids in improving the knowledge within the field. It must also be mentioned that the literature is conflicting, and more research is needed regarding, for example, the relevance of the intramuscular tendon (94,158,204,208).

Most reinjuries occur in the same location and early after RTS (Paper V)

In this descriptive study, we included 19 athletes (18 football players and 1 futsal player) with MRI confirmed re-injuries occurring within 1 year after RTS from the index injury. The median time to RTS after the index injury was 19 days (range, 5-37 days; IQR, 15 days). The median time between the index injury and reinjury was 60 days (range, 20-316; IQR, 131) and the median time between RTS after the index injury and the reinjury was 24 days (range, 4-311; IQR, 140).

Most of the re-injuries occur in the same location and are more severe

The biceps femoris muscle was the most commonly injured muscle and was involved in 95% of index injuries (n=18) and 79% of reinjuries (n=15). Of the 19 reinjuries, 79% occurred in the same muscle and same location within the muscle as the index injury, as shown in Table 13. The most common anatomic location within the muscle was the musculotendinous junction (n=13; 68.4%), followed by the conjoint tendon (n=4) and muscle belly (n=2). MRI severity grading revealed that 73.6% of reinjuries showed similar severity or were more severe than the index injury. Of the more severe reinjuries (37%), all occurred in the same location as the index injury. The reinjuries with more extensive craniocaudal length and greater extent of oedema occurred earlier after the index injury. On reimaging, 8 athletes (42.1%) had an intramuscular abnormally low signal corresponding to fibrosis, where in 7 of these, the fibrosis was located at the same site as the index injury (Figure 14).

Table 13: Radiological severity and location of the reinjury.

	Same muscle and same location	**Same muscle, other location**	**Different Muscle**
Overall Number	15 (79.0)	2 (10.5)	2 (10.5)
Muscle injured			
Biceps femoris long head	9 (47.4)	1 (5.3)	0 (0.0)
Biceps femoris long head +semitendinosus	4 (21.1)	0 (0.0)	0 (0.0)
Biceps femoris (long +short head)	1 (5.3)	0 (0.0)	0 (0.0)
Semimembranosus	1 (5.3)	1 (5.3)	1 (5.3)
Semitendinosus	0 (0.0)	0 (0.0)	1 (5.3)
Anatomical location within the muscle			
Conjoint tendon	4 (21.1)	-	-
Proximal MTJ	7 (36.8)	1 (5.3)	1 (5.3)
Distal MTJ	4 (21.1)	-	-
Distal muscle belly	-	1 (5.3)	1 (5.3)
Grading reinjury			
Grade 1	6 (31.6)	2 (10.5)	2 (10.5)
Grade 2	7 (36.8)	0 (0.0)	0 (0.0)
Grade 3	2 (10.5)	0 (0.0)	0 (0.0)
Severity reinjury vs index injury *(radiological grading)*			
Same grading	5 (26.3)	0 (0.0)	2 (10.5)
More severe	7 (36.8)	0 (0.0)	0 (0.0)
Less severe	3 (15.8)	2 (10.5)	0 (0.0)

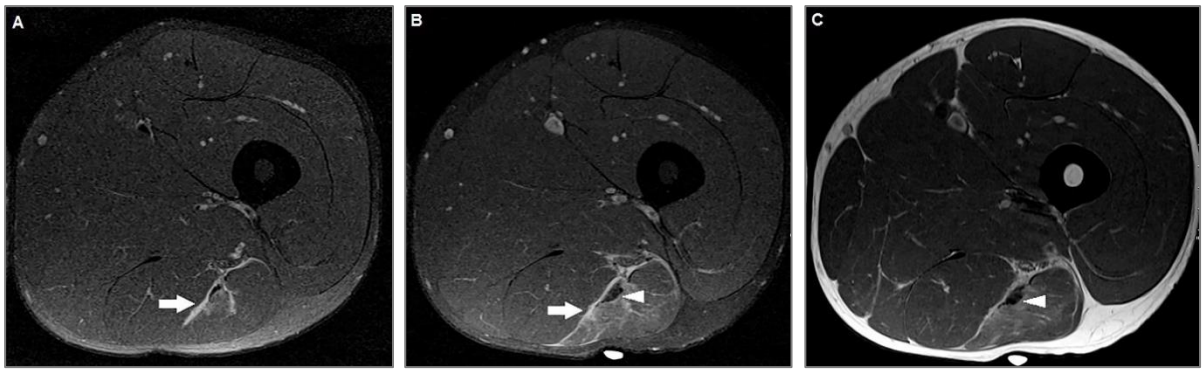


Figure 14: (A) A proton density–weighted fat-suppressed image of the index injury shows increased signal intensity at the proximal musculotendinous junction of the biceps femoris muscle (long head) (arrow). (B) A proton density–weighted fat-suppressed image of the reinjury shows increased signal intensity in the same location, with a greater extent of oedema compared with the index injury. (C) The proton density–weighted images with (B) and without (C) fat suppression show an enlarged area of low signal intensity with thickening of the tendon, indicating fibrous tissue formation (arrowhead).

To our knowledge, this study is the first to provide a detailed description of MRI characteristics, in terms of location and severity, and timing of hamstring reinjuries compared with the index injury. Two studies previously reported reinjury imaging findings in smaller samples (155,175). Although a direct comparison cannot be made, our findings are comparable with Silder et al. (155), who reported that the 3 reinjuries that were reimaged occurred in generally the same location as the initial injury (the middle MTJ of the biceps femoris), and injury severity was no worse than the initial injury. An important finding in our study was that 79% of reinjuries occurred in the same location as the index injury, which may indicate incomplete healing. In accordance with previous findings (3,99,102,106,155,175), the long head of the biceps femoris was the most commonly reinjured muscle. However, in most of the previous studies, a direct imaging-based comparison with the index injury was not described and the exact location within the muscle was not evaluated. Koulouris et al. (175) found that 90% of reinjuries occurred in the biceps femoris compared to 80% of initial injuries. In our study, for the two injuries that occurred in a different muscle, both index injuries were located in the biceps femoris, whereas the reinjuries were located in the semimembranosus and semitendinosus, respectively. Given the small number of reinjuries, no conclusions can be drawn from these findings, but it is should be noted that for the reinjuries, the semitendinosus was commonly involved in addition to the biceps femoris. An explanation may be that these reinjuries affected more than one muscle, where an index injury within the proximal musculotendinous junction also extended and affected the conjoint tendon and was more severe in terms of radiological grading. This aligns with Schuermans et al. (209), who suggested a neuromuscular alteration between the biceps femoris

and semitendinosus, making them more susceptible to (re)injury. It is frequently reported that reinjuries are associated with a longer period off from sports than index injuries (2,10,30,36,175,210). However, Ekstrand et al. (106) did not find any differences in RTS times between index hamstring injuries and reinjuries among professional football players. In our study, we found that 73.6% of reinjuries were either as severe as or more severe than the index injury in terms of radiological grading. We did not find any differences between the index injuries and reinjuries for the MRI measurements of injury extent. In contrast to Kouloris et al. (175), our study did not reveal any difference in the craniocaudal extent (of increased signal intensity) between the index injury and reinjury, although greater variance was seen in the MRI measurements for reinjuries in both studies. The most important finding, however, was that the radiologically more severe reinjuries (37%) occurred in the same location and earlier after RTS and the index injury.

Re-injuries occur early after RTS from the index injury

More than 50% of the reinjuries occurred within the first 25 days (4 weeks) after RTS from the index injury (n = 10) and 70% of reinjuries occurred within 100 days (Figure 15). As shown in Figure 16, 50% of reinjuries occurred within 50 days after the index injury. In the first 6 weeks (42 days) after the index injury, all of the reinjuries occurred in the same location as the index injury (Figure 16). An increased risk of reinjury has been reported within the first month after injury (30,173). Among English Rugby Union athletes 59% of all reinjuries occurred within 1 month (30). In European professional football players, 16% of hamstring injuries constituted reinjuries registered within 2 months after RTS (3,106,194). Our findings are comparable, with more than one-half of reinjuries (10 of 19) occurring within the first 4 weeks and 70% occurring within the first 100 days after RTS. Although most reinjuries occur early after the index injury and RTS, the risk remains high for a substantial period. An elevated risk of reinjury within the same season (123,163) as well as the subsequent season (123) has been reported in Australian Rules football players. Longer time until reinjury from RTS is also reported in elite track and field athletes (174) and recreational athletes (167). In our study, despite the skewed distribution toward early occurrence, we found a wide variation in the time between RTS and reinjury (4-311 days). In 5 of the 6 athletes sustaining a reinjury after 100 days, these also occurred in the same location as the index injury. This might reflect that the healing of the muscle is incomplete or that muscle function (eg, eccentric strength) is not fully recovered even if the athlete is symptom-free and has returned to full sports participation.

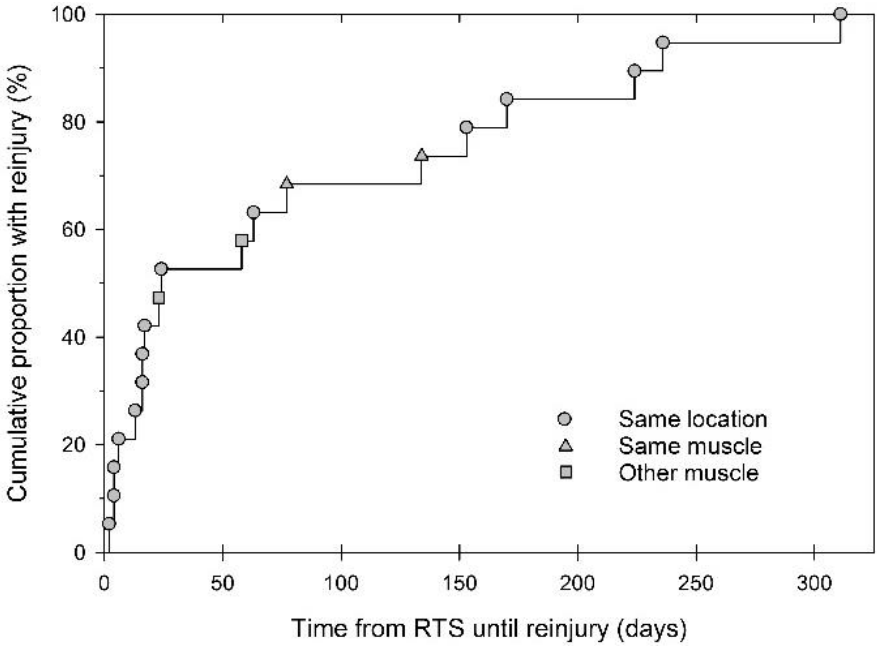


Figure 15: The cumulative proportion of the athletes with reinjuries and time between RTS after index injury and reinjury

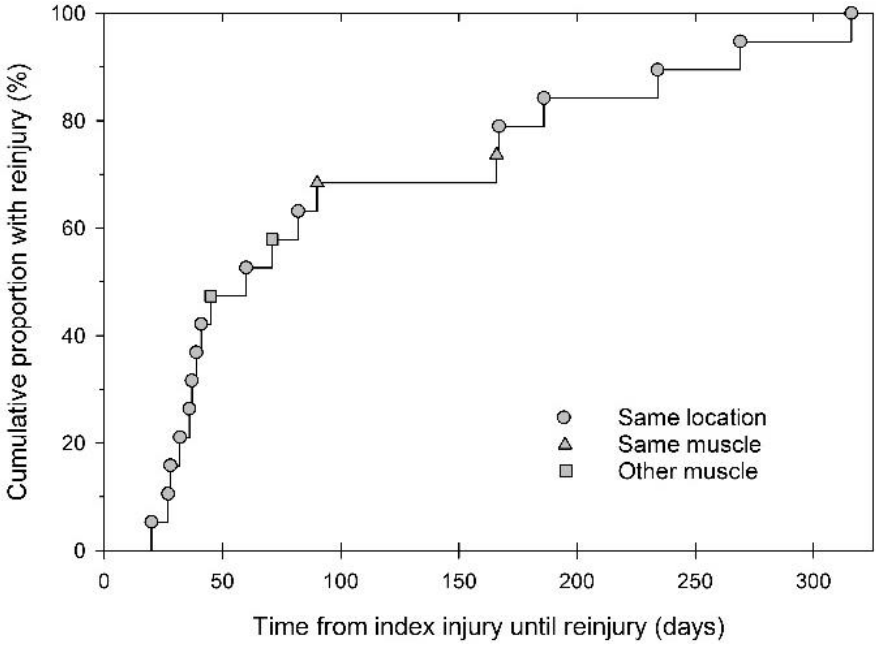


Figure 16: The cumulative proportion of the athletes with reinjuries and time between RTS after index injury and time from index injury until reinjury (b).

The time to RTS is not considered as the final end point of the RTS process (211). Thus, the athletes might not necessarily have reached their pre-injury performance level, which has been reported among professional Australian football players with hamstring injury (212). Particularly in team sports, the increased focus on high-intensity training sessions mirroring the intensity and demands of a match/game has resulted in a shift towards repeated high-intensity actions (high-speed running with increased number of accelerations and decelerations). As a consequence, athletes just returning from an injury rehabilitation period might not tolerate the demands and have a rapid increase in workload above suggested recommendations (i.e. acute:chronic workload) (213), which might lead to an increased risk of a reinjury (214).

From this descriptive study, we cannot explain why there is a high incidence of early reinjuries and why these occur in the same location as the index injury. However, the study may have implications for reinjury prevention.

Implications: Reinjury prevention should be part of the RTS process

The clinical relevance of our findings in *Paper V* lies first in how we approach the management of the index injury, not only during rehabilitation and in the RTS decision-making process, but also after RTS. Our findings indicate that the injury is not completely healed, which may explain why the majority of the athletes sustained a reinjury at the same location as the index injury and early after RTS. Also, time may be a factor that clinicians and athletes should be acutely aware of when balancing benefits and harms in the RTS process, especially at the elite level.

Firstly; the RTS process begins straight after the index injury (211), and preventing a reinjury should also preferably start at this time point, implemented as part of the rehabilitation process. Interestingly, a recent RCT study showed that patients with acute muscle injuries starting rehabilitation 2 days after injury rather than waiting for 9 days shortened the time to RTS by 3 weeks without any significant increase in the risk of reinjury (215). This may indicate that early loading of the musculotendinous tissue is important, and that immobilisation can swiftly and adversely affect muscle and tendon structure and function, and has detrimental effects on connective tissue cells (216,217). Secondly, the RTS decision-making process should be based upon a shared-decision based approach, including risk assessments and validated, objective criteria for RTS. Unfortunately, objective, validated criteria for RTS is still lacking, as discussed below in methodological considerations. Third, and importantly, protocols for optimal loading after RTS from the index injury are needed, focusing on secondary and tertiary prevention.

Individuals must continue to perform specific hamstring exercises after RTS; the rehabilitation stage (before RTS) should directly continue into a prevention stage (after RTS). High-level evidence shows that the 10-week Nordic hamstring exercise program reduces the risk of reinjury by as much as 86% (78,218). Return to optimal performance is considered the last step of the RTS process (211), but the evidence regarding what happens *after* RTS and until the athletes return to their pre-injury performance level, is totally absent. Future work is needed, considering workload and optimal load management (219) in this crucial stage after RTS from injury. Reinjury prevention should also be emphasised not only at the highest professional levels, but also at lower national and amateur level, where the recurrence rates are even higher (220).

Methodological considerations

Participants and study location/setting

The athletic population in Qatar are predominantly male. Therefore, most of the athletes presenting at the study center are male, and the majority of the sports medicine and sports science research is also performed in the male athletic population. The inclusion criterion of being a male athlete therefore reflects current practice at the hospital. It is also comparable to the UEFA UCL studies (3,82,106,194) among European male professional football players. Although ensuring homogeneity, our findings cannot be directly generalised to female athletes.

The study setting is unique, where the majority of the athletes performing at a competition and professional level in the country have easy access to the various medical services at the study centre. This provided us with quick admittance to the injuries as they occurred. The single study setting also enabled us to perform standardised and consistent examinations procedures throughout the study period. The majority of the clinicians and staff involved at the study center and in the NSMP were aware of and/or familiar with the study flow and processes. These factors increase the consistency and internal validity of the papers in this thesis. However, it has to be acknowledged that this is at the expense of generalisability.

The pool of athletes in Qatar constitute a wide range of nationalities and ethnicities, reflecting a special composition. Also, the climate and the environment in which the athletes train and compete is characterised by warm temperature and, particularly throughout the summer season, high humidity. We therefore do not know whether our findings apply to athletic populations with other compositions of ethnicities and nationalities, and/or environmental and cultural conditions.

Sample size

In *Paper I*, we were unable to perform a power calculation due to the absence of comparable studies. We arbitrarily decided that $n \geq 8$ would be adequate for descriptive analyses, but the relatively small sample size prevented us from performing more advanced statistical analysis, and might increase the risk of a type II error. Also, the sample was biased towards a relatively low grade of injury. Fibre disruption was only observed in five athletes, and although being consistent between those five, studies with larger numbers are needed to confirm our findings. However,

given the consistency of the data presented, it is unlikely that a larger sample would change our main findings substantially.

In *Paper III,* we included a sample of 40 athletes with a total of 56 lesions scored, which is equivalent with comparable studies (177,196). However, evaluation of some of the sub-categories within the Chan classification and the BAMIC, as well as the total ruptures, was limited by low frequencies which potentially influenced the κ values and the wide range of CIs for these scorings (182). Yet, even in larger comparable samples, expected frequencies of injuries within these subcategories are likely to remain low. Also, we attempted to select a representative sample with a wide range of injury severities and injury locations, but without randomisation, we cannot ascertain a complete absence of selection bias.

Study II, is one of the the largest prospective cohorts investigating prognostic factors for RTS after acute hamstring injuries to date. Three UEFA UCL studies, all based on same dataset (3,106,194), report higher numbers, but these studies did not include clinical examinations nor compared different grading and classification systems. Nevertheless, in *Paper IV*, the lack of a sufficient numbers of injuries within each of the categories limited our statistical approach. Obtaining adequate number of those specific injuries within one single study center would possibly take decades. This also applies to *Paper V*, in which we included 19 reinjuries. Despite being the largest study to date comparing the index hamstring injury with reinjury, the number is too small for any definite conclusions. Collecting data on reinjuries is even harder, since they are rarer than an index injury. In the future, working together in multi-center studies might be the solution in order to acquire bigger data sets of acute hamstring injuries with sufficient sample sizes, which recently has been encouraged (221–224).

Baseline (and follow-up) assessments

Clinical examinations

All the athletes included underwent a standardised clinical examination procedure within one (*Paper I*) or five (*Papers II-V*) days after the initial injury. We did not report intra- and interrater reliability for these examinations, which might be a limitation in *Paper II*, where the clinical examinations were assessed as prognostic factors. However, these clinical examinations have previously been referred in relevant literature on acute hamstring injuries (6,118,122–124,127). For the majority of the physical assessments tests, we registered the outcome as a positive or

negative test according to presence or absence of pain, and did not report objective measurement data. Thus, we do not believe reliability issues would have had a significant impact on our findings. For the palpation measurements, though, we do not know the magnitude of the variation between the testers and how much this could possibly have influenced the findings. Although frequently used, no other studies have investigated the intra- and interrater reliability of any palpation measures following acute hamstring injuries (192), and palpation is considered to be a subjective measure both in terms of the assessor conducting the palpation (e.g. experience and skills, how much pressure applied) and the person being palpated (subjective reporting of pain/tenderness). The utilisation of clinical tests for diagnosis of acute hamstring injuries with high quality are lacking (225). Future work might be needed to establish the reliability of different palpation measures and the diagnostic accuracy of the clinical tests commonly used for acute hamstring injuries. Another interesting aspect which might warrant further investigation is the injury situations in which the injury occurs. Since we were not able to obtain video footages of the injuries, the injury situation and mechanism was based on the athlete's reporting. Although our questionnaire was detailed in that regard, we cannot exclude recall bias. Also, we did not reveal any differences between the athletes sustaining a sprinting vs non-sprinting injury. Among the non-sprinting injuries, we observed a variety of mechanisms, which were not only 'stretching' related, but also occurred during backward kicking, landing from a jump, during cutting manoeuvres etc. Askling et al. (85,98,101,118) suggested two distinct injury types following acute hamstring injuries; sprinting and stretching type. However, based on our observations, it could be argued that acute hamstring injuries might occur as several different types (or subtypes), and that more research on the exact injury situation is needed to better understand the exact injury mechanism and the underlying causes, which might be of both diagnostic, therapeutic and preventive value.

It must also be mentioned that we only performed baseline assessments, and cannot comment on whether repeating clinical assessments regularly after the injury (e.g. daily or weekly) would result in greater accuracy for predicting time to RTS. This was outside the scope of this thesis. However, our research group is looking more into this. Jacobsen et al. (191) reported that a combination of initial clinical examinations and follow-up examinations after one week could increase the prediction for RTS, and a follow-up study was recently published showing that repeated clinical assessments may be useful to guide rehabilitation progression and aid with the RTS decision making (193). However, future validation studies are needed.

Of importance, our findings are based on structured and comprehensive clinical examinations performed early after the acute injury. We do not know whether our findings apply to athletes undergoing clinical examinations later after injury and/or without such a comprehensive examination procedure.

MRI

The MRI scanner

The MRIs were obtained using the same MRI scanner with high spatial resolution and adequate field strength (1.5 T). This is a considerable strength, which increases the internal validity of our findings. The 1.5 T is still considered the standard field strength in musculoskeletal radiology (146) and thus, we considered it to be more than satisfactory for our research purposes. Also, 1.5 T is used in the majority of the study centers performing hamstring injury research to this date, which increases the external validity of our results. On the other hand, we do not know whether using even greater field strength MRI (3.0 T) could have provided more accurate measurements or different results. In comparison to a 1.5 T MRI, a 3.0 T MRI is characterized by a higher signal-to-noise ratio due to increased MR signal with relatively less increase in background noise (146,226). This advantage could for example be used to reduce the acquisition time, or to increase the spatial resolution, which, in combination with body surface coils, can improve the visualization of small structures (226). In patients with a clinical diagnosis of acute hamstring injuries, but with negative MRIs (grade 0), the reason why these minor injuries are occult on MRI is still unclear. For example, in our *Paper II* and *Paper IV*, 20.5-22.0% of the patients were scored with a grade 0, which is in line with other studies typically reporting negative MRIs in 12-31 % of patients with clinical signs of an acute hamstring injury (3,102,122,127,157,194). It might be that the macroscopic structural damage of these injuries is beyond the resolution to be detected on a normal MRI scan (23,120). Whether a 3.0 T and/or more sensitive acquisitions, such as for example diffusion tensor imaging (DTI) or other advanced techniques, such as for example dynamic MRI (36), can better identify structural changes, remains unknown and is an area for future research. DTI parameters are for example considered to be sensitive to changes in tissue microstructure (147,227,228). Nevertheless, in *Paper III*, we found overall 'substantial' to 'almost perfect' reliability using the 1.5 T MRI, which is also in line with other studies using 1.5T (177,196,229,230). It is unlikely that our scorings and results in any of *Paper I-V* would have been influenced significantly by for example a 3.0 T magnet.

MRI-negative injuries are also suggested to be of a more 'functional' than a 'structural' character (21), but more evidence is needed in order to establish such a distinction. It has also been suggested that MRI-negative injuries are related to lumbar spine pathology (127,231), although a direct link is lacking. These MRI negative injuries might also be related to exacerbation of a gradual overuse injury with an underlying pathology, or it might be related to fatigue and excessive DOMS. However, these injuries account for a considerable number of time lost (106) and more research is needed to gain more knowledge about these hamstring injuries causing clinical pain, but not radiological changes.

The MRI protocols

The MRI protocols chosen in *Paper I* and *Paper II-V* included all acquisitions and sequences required to obtain adequate MRI images of an acute hamstring muscle injury (89,120,139,150) and attempted to reduce common artifacts, such as motion artifacts. The MRI measurements were based on two-dimensional images, which is common in similar studies. However, three-dimensional images might have provided more accurate measurements of the cross-sectional area and volume of the injury. The protocols only included imaging of the injured leg; thus a comparison with the uninjured leg, and for example evaluation of the involvement of the proximal tendon, as described and reported by Askling et al. (85,98,99,102), was not infeasible. The primary reason for this, was the time limitation within a clinical setting with pressure on the availability of the MRI scanner. Additional MRI of the uninjured leg would have been too time consuming. Increasing the FOV could alternatively be a solution, but would have reduced the quality beyond what compromise.

Follow up MRIs (Paper I)

In *Paper I,* the patients were advised not to perform any activity provoking pain or heavy eccentric loading, to avoid a possible exercise-related increase in signal intensity (142,232–234). However, they were not restricted to refrain from normal, pain-free activity and we cannot ensure that the injured leg was loaded more towards the last days of imaging as the pain probably reduced. This might have resulted in smaller reduction (or enlargement) of the extent of oedema than expected. However, the athletes that were following a structured rehabilitation programme were scheduled for rehabilitation directly after the MRI each day, leaving ~23 hours between the rehabilitation session and the next MRI appointment.

MRIs of the reinjuries (Paper V)

We considered a direct comparison between the index and reinjury MRIs as the most accurate method for assessing the exact location of the reinjury. The reproducibility of this comparison was not formally assessed, which might be a potential limitation of the study. Also, although the athletes were clinically diagnosed with a reinjury, we cannot ensure that the presence of increased signal intensity of MRI of the reinjury represented healing of the index injury or a real reinjury. The presence of intramuscular increased signal intensity on MRI might persist for a prolonged time (85,98,138,155,186,187) and may even increase after clinical recovery (98,138). The MRI findings of the reinjuries in the same location could therefore reflect an overlap of the index injury and the reinjury. However, it has to be mentioned that for the athletes in the RCT, MRIs were obtained at the time of RTS, which we compared with the MRIs of the re-injuries, to ensure that there was a reduction in signal intensity on MRI at RTS compared with the reinjury MRIs.

Unexplored factors

It is recognised that RTS is multifactorial with numerous factors related to medical health status, sports risk modifiers and decision modifiers (181,211,235), all influencing the time one individual athlete needs to return to his or hers sports activity (211). In *Paper II*, we were not able to collect data on all clinical measures that have been investigated for associations with RTS (192), and whether some of these variables would have improved our regression models remains unknown. We appreciate also that other factors related to tissue health, tissue stresses, risk tolerance modifiers and psychological factors, could influence the time to RTS (17,181,211,235). For example, fear of reinjury might negatively affect the recovery of physical impairments, reduce self-report function, and prevent a successful RTS (17,18), which has been shown among athletes with ACL injuries (17). Psychological readiness therefore seem to be an important factor (236,237), which needs to be investigated further. Other factors such as motivation, external pressure on the athlete for a quick RTS, the number of important games or competitions in the period after the injury and experience from previous injuries may potentially also play a role. Unfortunately, we were not in a position to investigate those factors, which also have not been assessed in other studies. In *Paper IV,* we did not include clinical examinations as possible prognostic variables and acknowledge that other grading and classification systems not investigated in our study (including clinical findings) are reported (23,160,238,239). Since other factors not accounted for might have a larger impact on the RTS decision than MRI findings, we admit that the risk of a type I error is present.

Outcome measures

Time to RTS

Time to RTS was the primary outcome measure in *Paper II* and Paper *IV*, and also an important indirect measure in *Paper V*, where we reported time to reinjury after RTS from initial injury. Although considerably more consistently defined and described than in many other papers reporting on RTS as an outcome measure, our reporting is not without limitations. First, the physicians who made the RTS decision in *Paper II, IV* and *V* (and thus, the time to RTS) were not blinded to the baseline characteristics. When studying the prognostic variables, the outcome measure (time to RTS) should ideally be independent of the prognostic variable of interest to prevent bias (205,240,241). One might expect that an unblinded clinician with knowledge of the baseline prognostic variables is likely to be influenced by this information and not only the clinical findings and functional test results at the time of RTS. Therefore, our findings may have overestimated the predictive value of the variables examined in *Paper II* and *Paper IV*. Second, the athletes received either standardised or customised rehabilitation, and the clearance for time to RTS was performed either by physicians who worked at the study centre or at the specific sports clubs or sporting federation headquarters. Although the guidelines for time to RTS at the study centre were well defined, the criteria for time to RTS in the clubs or federations depended on the treating club physiotherapist or physician. However, in *Paper II* and *Paper IV*, we included these factors as a possible confounder (study center vs club), which was controlled for in the multivariate analyses. Although a growing number of RCTs has tested the effect of different treatment/rehabilitation protocols after acute hamstring injuries (99,102,128,155,242–244), there is still no consensus regarding the optimal treatment or uniform guidelines for RTS clearance. The time to RTS also varies greatly depending on the rehabilitation protocol applied, both within and between these different intervention studies (99,102,128,155,242–244). Just recently, two systematic reviews have highlighted the lack of clear definitions for RTS (245), and the lack of validated objective criteria for progression through the different rehabilitation stages before RTS and for determining RTS clearance (245,246). Hence, our studies truly reflect the real-life situation and the current state of evidence and the variability in treatment received increases the generalisability of our findings. But summarised, more research is warranted in order to establish more uniform definitions and objective criteria for the process of performing informed RTS-decisions. A worldwide Delphi procedure regarding definitions, medical criteria, and decision-making for return to play after acute hamstring injuries in football players, which recently has

been published, is an important step in the right direction (237). However, it also reveals the different opinions and discrepancies among the experts within the field. Similar findings was reported from a similar Delphi study among professional football clubs in England just published (247) and larger prospective studies are needed in order to establish validated criteria. It might also be questioned whether one defined RTS timepoint is sufficient for measuring an outcome considered to be a process rather than one exact end point. Prospective studies including several time-point outcomes throughout the RTS process (such as time to sports specific, time to return to full training, time to return to match play/competition, time to return to performance and number of re-injuries) and more sophisticated multifactorial statistical analyses might be an area for future research. Yet, it has to be mentioned that research evidence is only one piece of the puzzle when making the RTS decision (248,249).

Reinjury

Although all athletes were encouraged to report any reinjury within the first year after RTS, not all were actively monitored monthly by phone. Thus, in *Paper II* and *Paper IV*, we chose to not include rate of reinjury as a secondary outcome measure, and were not able to report long-term RTS success. In relation to this, there might have been reinjuries following the index injury that we were not able to identify in *Paper V*. However, our studies do not differ from the majority of previous studies reporting rate of re-injuries, where the registration and follow-up for re-injuries is variable. In *Paper V*, we defined reinjury as the acute onset of posterior thigh pain in the same leg as index injury ≤365 days since RTS after the index injury, confirmed with MRI. Although different definitions of a hamstring reinjury are used in the literature and debated (106,170,171,250), our definition regarding the location is in accordance with previous recommendations (15,27,169). It seems likely that a reinjury in the same location as the index injury is related to the index injury. However, the degree to which a reinjury in a different location within the muscle or in a different muscle is related to the index injury remains unknown. Another limitation in *Paper V* is that we could not provide information about the days to RTS of the reinjury as a result of incomplete follow-up. Thus, the results reflect only the radiological severity of the reinjuries, and future studies should preferably report on both radiological findings and clinical outcome (time to RTS) after hamstring reinjuries to provide more accurate information about the clinical severity when comparing index injuries with reinjuries.

Conclusions

1. There were no day-to-day changes in the extent of oedema throughout the first week following acute hamstring injury. Fibre disruption was detectable from the first day after injury without change over time. Therefore, MRI can be performed on any day during the first week following an acute (hamstring) muscle injury with equivalent findings.
2. There was a wide variation in time to RTS, and the additional predictive value of MRI for time to RTS was negligible compared to baseline patient history taking and clinical examinations alone. Based on our findings, clinicians cannot provide an accurate time to RTS based on patient history and clinical examinations just after an acute hamstring injury.
3. The intra- and interrater reliability for the modified Peetrons grading system, the overall Chan acute muscle strain injury classification and the overall BAMIC were 'substantial' to 'almost perfect' when scored by experienced radiologists.
4. Regarding RTS, there was a wide overlap between and broad variation within the MRI grading and classification categories. The modified Peetrons, the Chan classification and the BAMIC poorly explained the large variance in days to RTS for MRI-positive injuries. Our findings therefore suggest that these MRI systems cannot be used alone to predict RTS after acute hamstring injuries. The MRI system used should be specified when reporting MRI findings to avoid misinterpretation and miscommunication.
5. The majority of hamstring reinjuries occurred in the same location as the index injury, relatively early after RTS and with a radiologically greater extent. Our findings suggest that although the athletes were clinically recovered after their index injury and were cleared for RTS, biological and/or functional healing of the index injury might not be fully completed, leading to a reinjury at the index injury site. Specific exercise programs focusing on reinjury prevention initiated after RTS from the index injury are therefore highly recommended.

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Papers I-V

Paper I

Paper II

Paper III

Paper IV

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Paper IV, Appendices 1-3

Paper V

Appendix

Appendix I

Ethical approvals