Managing Acute Hamstring Injuries in Athletes

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Managing Acute Hamstring Injuries in Athletes

Behandelen van acute hamstringblessures bij sporters

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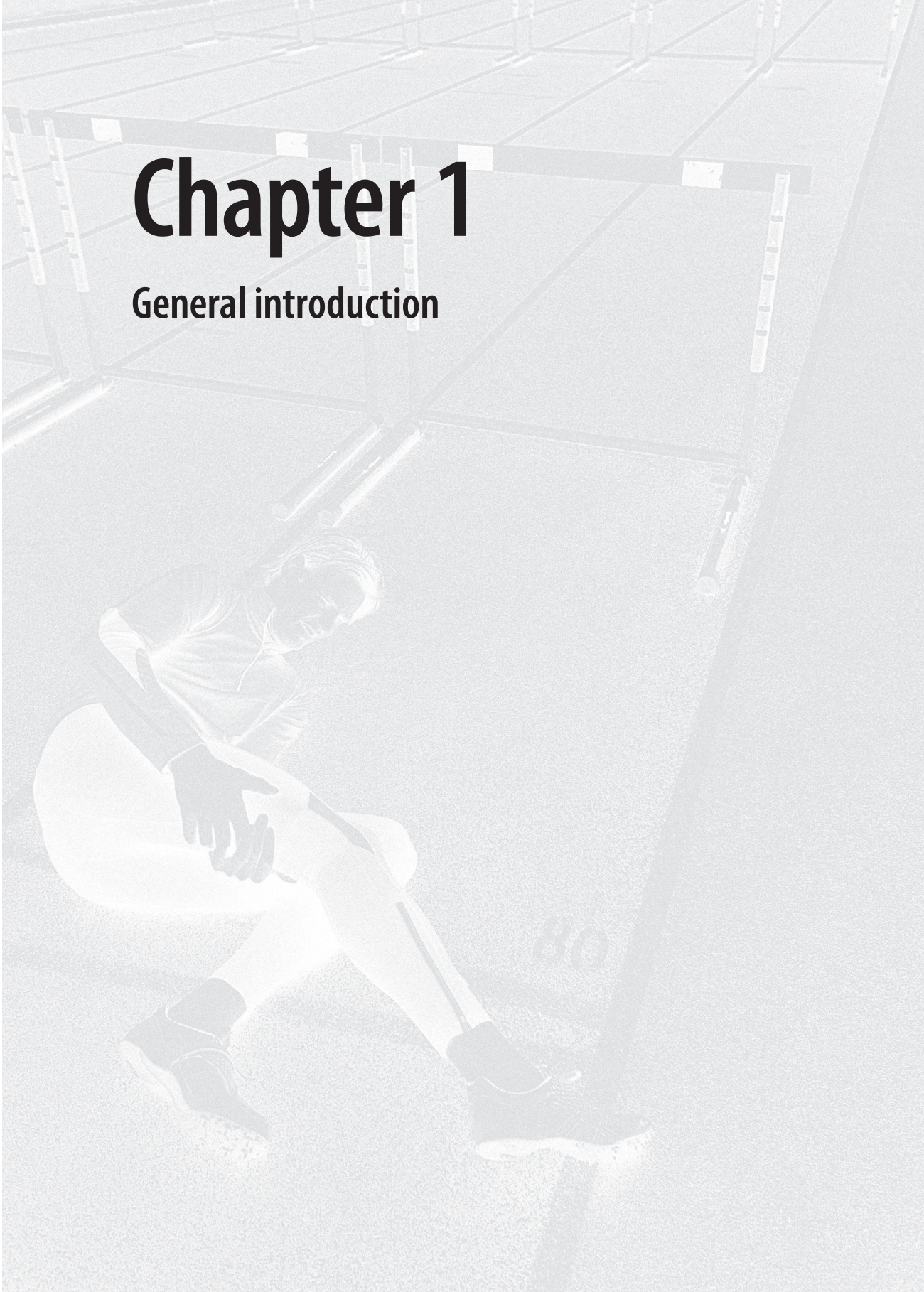
Chapter 1

General introduction



Epidemiology, practical and financial consequences

Muscle injuries are common and account for one third of all time-loss athletic injuries. The hamstrings are the most frequently injured muscles in sports that involve high-speed running, such as football, Australian football, and track and field athletics[7,60,61,84,172]. In European elite football hamstring injury is the most common diagnosis: 12% of all injuries are hamstring injuries[60,61,84]. An average 25 player squad can expect five hamstring injuries per season[61].

Hamstring injuries impair both the player and club performance, as athletes often cannot train and compete for several weeks or even months. Even after return to play athletes have an increased risk of recurrent injury, which has been reported to be 16% within two months in football and up to 34% per season in Australian football[61,169]. The financial loss due to missed games is substantial in elite sports, with an estimated annual salary burden in the Dutch top professional football league of approximately €1.5 million. In a top European football league, such as the English premier league, this salary burden from hamstrings injuris reaches over €20 million per season.

Although accurate data on the extent of hamstring injuries in amateur athletes is missing, a considerable number of these injuries can also be expected in these athletes. For example, in the Netherlands more than 2 out of 17 million people participate regularly in competitive sports such as football, field hockey and track and field athletics, in which hamstring injuries are common[246].

Anatomy, function and injury mechanism

The hamstring muscle group consists of the biceps femoris long head (BFlh) and short head (BFsh), the semitendinosus (ST) and the semimembranosus (SM). The BFlh, ST and SM originate proximally from the ischial tuberosity, where the BFlh and the ST share a common tendon (conjoined tendon). Distally the ST and SM insert at the antero-medial side of the tibia at the pes anserinus. Both heads of the biceps femoris insert at the proximal fibula. The hamstring complex (BFlh/ST/SM) is a bi-articular muscle group that mainly acts as a hip extensor and knee flexor. The BFsh is a mono-articular muscle that only crosses the knee joint as a knee flexor and is rarely injured.

In high speed running the bi-articular hamstring muscles are mainly active during the second half of the swing phase, while they are also lengthening during extension of the knee[46,47]. During this eccentric contraction they absorb energy and contribute to the deceleration of the swinging leg. The occurrence of hamstring injuries during high-speed running is generally assumed to occur during this terminal swing phase as a result of excessive eccentric loading. This is supported by some evidence from biomechanical studies showing that peak stretch and loading is at its highest during this terminal swing phase[47,102,103]. The BFlh undergoes more stretch than the other hamstring muscles and

absorbs the most energy of the swinging leg, which may explain why the majority of the high-speed running related injuries occur in the BFlh[15,46,103].

Although less common, hamstring injuries also occur during activities other than high-speed running, such as dancing, stretching and kicking, suggesting other mechanisms of injury[13,17,23]. These injury situations commonly involve a position of combined hip flexion and knee extension resulting in lengthening of the hamstring muscles. They often involve the SM muscle and have been found to have a longer recovery time compared with the high-speed running injuries[13,17].

Diagnosis and prognosis

The clinical diagnosis of an acute hamstring injury is straightforward and consists of a history of an acute onset of posterior thigh pain, on physical examination the triad of localised pain on 1) palpation, 2) stretching and 3) contraction of the hamstring muscle[15,21]. Flexibility and strength measurements are commonly used to obtain information on injury severity, but their reliability have not been established in subjects with acute hamstring injuries. Especially in the elite athlete, additional ultrasound or magnetic resonance imaging (MRI) is increasingly used to confirm the diagnosis and to obtain additional prognostic information[63].

Estimating the prognosis remains one of the major challenges in dealing with acute hamstring injuries. Previous research has suggested that a number of clinical and imaging findings are associated with the time needed to return to play[15,17,52,63,77,203,216,231,238]. Due to the large variation in days to return to play on group level, it remains challenging to provide an accurate prognosis for the individual athlete[15,17,52,63,77,203,216,231,238].

Treatment

Currently the treatment of acute hamstring injuries is predominantly based on several randomised controlled trials that compared different exercise programmes[20,141,208,212]. Although there is general consensus among experts that a progressive rehabilitation program should form the cornerstone of the treatment of acute hamstring injuries, additional treatment methods to hasten recovery have gained increasing interest in sports medicine and athletic communities. Numerous medical treatment modalities, such as non-steroidal anti-inflammatory drugs, anti-fibrotic agents and intramuscular injections with corticosteroids, Actovegin or autologous blood products have been introduced[6,27,91,132,171]. Although these intramuscular injections are widely used, up to 2014 there were only case series[91,131,132] and one low quality comparative study[241] that reported the clinical outcome after application in acute muscle injuries.

Return to play decision making and re-injuries

It is a major challenge to decide whether an athlete can safely return to play, as there are no validated criteria to guide return to play decision making. In clinical practice an athlete is generally regarded as being ready once full range of motion, full strength and functional sport specific activities (e.g. sprinting, jumping, cutting) can be performed asymptomatically[104,152]. This means that athletes expose their hamstrings to high loads to determine if they are ready. With this approach, re-injury rates remain high. There is a need for validated assessment tools to differentiate between those athletes ready and those who should not return to play. MRI has been suggested to assist return to play decisions, but has not yet been validated[120].

High re-injuries rates remain a major problem following acute hamstring injuries. Re-injuries are often more severe than the initial injury and are associated with a longer absence from play[35,61]. A systematic review in 2011 showed that there is only limited evidence that a larger volume size of initial trauma, a Grade 1 hamstring injury and a previous ipsilateral ACL reconstruction are risk factors for re-injury risk[234]. Scar tissue formation is a frequently suggested predisposing factor for re-injury[75,103,111,116,210,211], but there are no clinical studies that have examined this[234].

Aim and outline of this thesis

The research described in this thesis evaluated the management of acute hamstring injuries including prognosis, treatment and return to play decision making.

We firstly investigated whether some commonly used clinical tests to assess hamstring flexibility and strength are reliable in subjects with acute hamstring injuries. For this purpose we determined the intertester reliability of hamstring flexibility measurements with the active and passive knee extension test (**chapter 2**). In **chapter 3** we determined the interrater reliability and the prognostic value of hamstring handheld dynamometry strength measurements.

Subsequently we were interested in which parameters could be used to provide a prognosis for the time to return to play. **Chapter 4** presents a systematic review on the prognostic value of MRI findings for time to return to play in acute hamstring injury. In **Chapter 5** we assessed the prognostic value of clinical and MRI parameters for the time to return to play in a prospective follow-up study.

It is common practice to examine injured muscles using palpation to assess mechanical properties like stiffness and tone, although it is difficult to quantify these in a reliable manner using manual palpation alone. Recent advances in technology allow muscle mechanical properties to be measured using muscle myometers. **Chapter 6** investigates the time course of changes in muscle mechanical properties after acute hamstring injury.

There is no consensus on the treatment of acute hamstring injuries, with a large number of different interventions currently used in clinical practise. **Chapter 7** presents

a systematic review on the effectiveness of therapeutic interventions in acute hamstring injuries.

Although injection therapies are widely used for muscle injuries, there is a paucity of evidence for their efficacy and safety. Clinical and histopathological studies showed the potential myotoxic effects of intramuscular injections. In **chapter 8** we systematically reviewed the literature on these possible myotoxic effects of commonly used injected intramuscularly preparations for muscle injuries.

Platelet-rich plasma (PRP) is probably the most popular injection therapy for musculoskeletal disorders in recent years. The rapidly growing global commercial PRP market reflects this. Despite claims of beneficial effects, data from randomized trials on its efficacy is lacking. In **chapter 9** we describe a double-blind placebo-controlled randomised trial to assess whether PRP was efficacious in the treatment of acute hamstring injury.

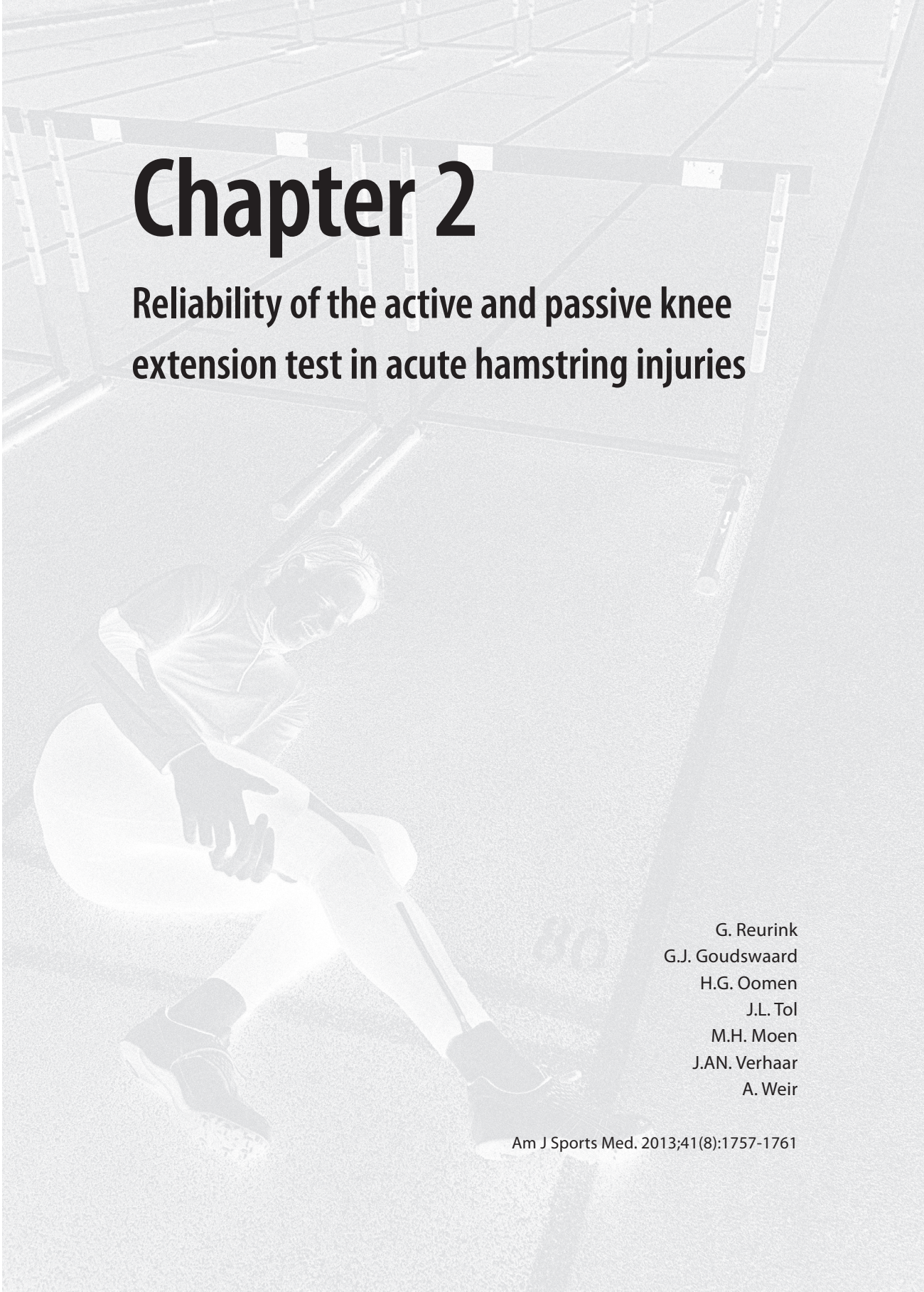
High re-injury rates after return to play remain a major problem following acute hamstring injuries. In **chapter 10** we examined the association of clinical and imaging findings with hamstring re-injuries in a prospective study with one year follow-up.

The return to play decision is challenging and generally based on expert opinion. The use of MRI has been suggested to be valuable for monitoring recovery after injury and assist return to play decisions, but has not been validated yet. In **chapter 11** we describe MRI findings of clinically recovered hamstring injuries in athletes who were cleared for return to play. As a continuation of this study we performed a one year follow-up study to examine the association between MRI detected fibrosis at return to play and hamstring re-injury (**chapter 12**).

Finally in **chapter 13** the most important findings of these studies, their limitations and implications for clinical practise and future research are discussed.

Chapter 2

Reliability of the active and passive knee extension test in acute hamstring injuries



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ABSTRACT

Background – Hamstring flexibility measurements are of clinical relevance for the prognosis and monitoring recovery after hamstring injury. The active knee extension test (AKET) and passive knee extension test (PKET) are proven to be reliable in healthy subjects. Reliability has not been determined in patients with acute hamstring injuries.

Purpose – The purpose of this study is to determine intertester reliability of the AKET and the PKET in patients with acute hamstring injuries.

Study design – Cohort study (diagnosis); Level of evidence, 2.

Methods – Fifty consecutive athletes with acute hamstring injuries confirmed with magnetic resonance imaging were included in this study. For each subject two testers performed the AKET and the PKET within five days after injury. Intraclass correlation coefficients (ICCs), standard error of measurements (SEMs) and minimal detectable differences (MDDs) were determined.

Results – In the injured leg the ICC of the AKET was 0.89 and PKET 0.77, SEM of the AKET 5.3° and PKET 7.6°, MDD of the AKET 15° and PKET 21°.

Conclusions – Good intertester reliability was found for the AKET and the PKET in injured hamstrings. Thus both tests can be reliably used to assess flexibility in injured hamstrings, despite pain and discomfort during testing.

INTRODUCTION

Hamstring flexibility measurements are of clinical relevance for prognosis and monitoring recovery in acute hamstring injuries[11]. In these patients, hamstring flexibility of the injured leg is reduced compared to the uninjured leg[1, 13, 19]. Hamstring flexibility has been showed to be an important prognostic factor in hamstring injuries; there is level II evidence that clinical grading on the basis of flexibility deficit is correlated with the time to return to play[12, 19]. During rehabilitation hamstring flexibility measurements are commonly used to monitor progression of recovery and there is a number of experts that state that hamstring flexibility should be regained before return to play[9, 13, 15].

It is obvious that flexibility testing is used in hamstring injuries and conclusions are drawn on the basis of the results of these tests. Previous studies reported moderate to good reliability of flexibility testing in healthy subjects[5, 8, 20, 22]. In injured muscles however, flexibility testing is often limited by pain and discomfort, which raises concerns about the reliability of testing[9, 11, 14]. The reliability of flexibility testing has not been examined in acute hamstring injuries.

A common method to assess hamstring flexibility is the measurement of the knee extension angle during a maximal stretch of the hamstring[2, 12, 13]. Distinction is made between the active knee extension test (AKET) and the passive knee extension test (PKET). In the AKET, the patient actively extends the knee till maximal stretch of the hamstring while the ipsilateral hip is kept at a fixed angle, usually 90° or 120° flexion. The PKET is performed identically except that the knee is extended passively by the tester. These tests have the advantage that there is no significant movement of the hip, sacroiliac joint and lumbar spine during the test[6, 18].

The clinical relevance of flexibility testing is evident from previous studies[140,203]. In a prospective cohort study in 58 professional Australian Football players Schneider-Kolsky et al. found that clinical grading based on hamstring flexibility measurements was significantly correlated with the actual duration of recovery after hamstring injury[16]. Malliaropoulos et al. also showed that the range of motion deficit, measured with the active knee extension test, was significantly correlated with the rehabilitation time in a prospective cohort study in 165 elite track and field athletes[10]. The reliability of these tests in hamstring injuries has never been examined. Therefore the aim of this study was to determine intertester reliability of the AKET and the PKET in patients with acute hamstring injuries.

METHODS

Subjects

Fifty consecutive athletes with a clinical diagnosis of an acute hamstring injury confirmed with magnetic resonance imaging were included in this study. The inclusion criteria are presented in table 2.1. Magnetic resonance imaging grading of the injury was performed using a modification of Peetrons' classification[4, 16] : grade 1): increased signal intensity without muscle tissue disruption indicating increased signal intensity with no tear, grade 2): muscle tissue disruption indicating a partial tear and grade 3): total muscle or tendon rupture. At inclusion, informed consent was obtained from all patients. Approval was obtained from the Regional Medical Ethical Committee of South West Holland. Patients in this study were part of a randomized controlled trial on the effect of platelet-rich-plasma in hamstring injuries (Dutch trial register number 2771).

Table 2.1 Inclusion criteria

Age 18-50 years
Presenting within five days after onset of the injury
Clinical diagnosis acute hamstring injury, defined as:
- Acute onset of pain in posterior thigh
- Localised pain when palpating the hamstring
- Localised pain during passive stretch of the hamstring
- Increasing pain during isometric contraction of the hamstring

Confirmation hamstring injury on magnetic resonance imging, defined as: Presence of intramuscular increased signal intensity on short tau inversed recovery images or T2-weighted images

Testers

This study was performed at the sports medicine departments of a large general district hospital, a university hospital and the medical center of the national soccer association. Eight testers, with from one to sixteen years of experience as a sports medicine clinician, participated in this study. All testers were instructed similarly and practiced the testing protocol in one session with a pilot subject. In this session the testers practiced until they were familiar with the testing protocol and could perform the complete testing protocol independently. Two clinicians tested each patient independently and were blinded to each other's results. Depending on the availability of the clinicians, for every subject two testers were chosen out of the larger pool of eight clinicians.

Testing protocol

The AKET and PKET were performed within five days after occurrence of the injury. The AKET and the PKET in both the injured and the uninjured leg were performed in a ran-

dom sequence. The randomization process was performed using the program Microsoft Excel 2010 (Microsoft Cooperation, Redmond, WA, United States) on a computer. Printed assessment forms were numbered and used in order of inclusion of the subjects.

An inclinometer (Inclinometer Dr. Rippstein, Zurich, Switzerland) was positioned at the anterior tibial border halfway the inferior pole of the patella and the line between the two malleoli[8]. A second inclinometer was placed on the anterior side of the thigh, ten centimeters proximal of the superior pole of the patella[2]. The inclinometers were attached to the leg with elastic straps. Subjects were positioned supine on an examination table with the hip of the tested leg in 90° flexion. The contralateral leg remained flat on the examination table. For the AKET, the subjects were instructed to extend the knee until maximal tolerable stretch of the hamstring muscle, while the tester maintains the ipsilateral hip in 90° flexion by reading the inclinometer on the thigh (Figure 2.1)[8, 12]. For the PKET, the tester extended the knee until maximal tolerable stretch of the hamstring muscle as indicated by the tested subject, with the ipsilateral hip remaining in 90° flexion (Figure 2.2)[2]. At the endpoint of maximal tolerable stretch, the absolute knee angle measured with the inclinometer on the tibia was read out by the tester. Both testers performed the AKET and the PKET once in the injured and the uninjured leg in the same order.

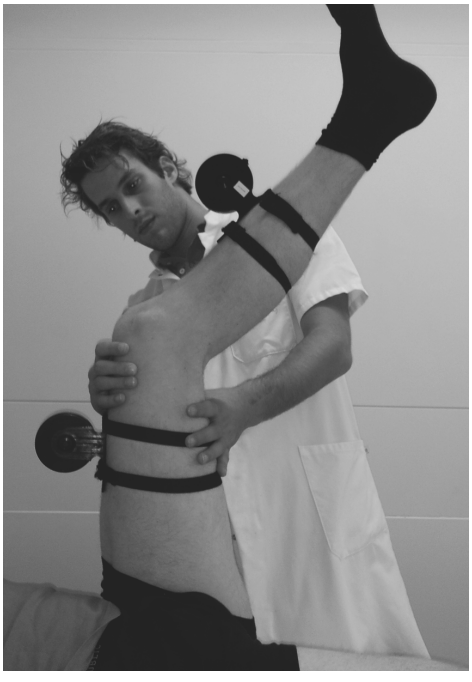

Figure 2.1a. The active knee extension test (AKET)

Figure 2.1b. The passive knee extension test (PKET)

Sample size calculation and statistical analysis

The appropriate sample size was estimated based on the approach of Girandeau and Mary[7, 10]. This calculation incorporates the number of replicates, the expected intraclass correlation coefficient (ICC), the confidence interval and the width of the confidence interval. Two test replicates were performed on each subject by two different testers. The confidence interval was set at 95% and the width at ± 0.1. The expected ICC of this study is based on ICCs found in previous studies for intertester reliability performed in healthy subjects[5, 8, 20, 22]. As hamstring flexibility testing is often limited by pain and discomfort in patients with acute injuries, the variance across testers was expected to be higher in this population compared to healthy subjects. Based on this, the expected ICC was set at 0.8. The appropriate sample size was estimated at 50 subjects.

Statistical analysis was performed using SPSS (version 20.0, SPSS Inc., Chicago, IL, USA). Mean outcomes of the knee angles of all measurements were compared using a paired T-test. ICCs were calculated to determine intertester reliability. As the two testers were selected out of the larger pool of eight clinicians, ICCs were calculated using a one-way random effects analysis of variance (ANOVA) model[21]. A single score ICC was used because this type of ICC (1,1) is most suitable for generalization to individual testers[17, 21]. ICCs were calculated for the AKET and the PKET in both the injured and the uninjured leg. According to Portney and Watkins an ICC <0.50 was considered poor reliability, 0.50 to 0.75 moderate reliability and >0.75 good reliability[17]. Additionally, the standard error of measurements (SEMs) and the minimal detectable differences (MDDs) were calculated. SEM is calculated using the equation:

$$SEM = \sqrt{(MS_W)}$$[23]

(MS_W represents the within-subjects mean square term obtained from the ANOVA)
MDD is defined as:

$$MDD = 1.96 \cdot \sqrt{2} \cdot SEM$$[23]

RESULTS

Subject characteristics are shown in Table 2.2. Mean outcomes (standard deviations) of all measurements in the injured leg were 132° (± 15.9) for the AKET and 132° (± 15.8) for the PKET. In the uninjured legs, the means were 142° (± 13.2) for the AKET and 142° (± 13.4) for the PKET. The recorded knee angles were significantly lower in the injured leg compared to the uninjured leg for both the AKET ($p < 0.001$) and the PKET ($p < 0.001$).

Table 2.2 Subject characteristics

No. of subjects	50
Age, median (range), years	28 (19 – 47)
Gender: male/female, No. of subjects	46/4
Sports, No. of subjects	
Soccer	33
Field hockey	10
American football	2
Track athletics	2
Tennis	1
Futsal	1
Fitness	1
Level of Sports:	
Professional	0
Competitive	34
Recreational	16
Injured side: right/left	23/27
MRI grading:	
grade I	17
grade II	32
grade III	1
Number of days after injury, median (range)	3 (1-5)

There was no significant difference of the recorded knee angles between the AKET and the PKET in either the injured ($p = 0.318$) or the uninjured leg ($p = 0.650$).

The ICCs, SEMs and MDDs are presented in Table 2.3.

Table 2.3 Intertester reliability of the AKET and PKET*

	Injured			**Uninjured**		
	ICC (1,1) (95% CI)	SEM (°)	MDD (°)	ICC (1,1) (95% CI)	SEM (°)	MDD (°)
AKET	0.89 (0.81 – 0.94)	5.3	15	0.76 (0.61 – 0.86)	6.5	18
PKET	0.77 (0.63 – 0.86)	7.6	21	0.69 (0.52 – 0.81)	7.5	21

*AKET, active knee extension test; PKET, passive knee extension test; ICC, intraclass correlation coefficient; SEM, standard error of measurement; MDD, minimal detectable difference

DISCUSSION

This is the first study that shows that both the AKET and the PKET are reliable in acute hamstring injuries. These tests can be reliably used in hamstring injuries, despite the pain and discomfort during testing. Reliability of the AKET is superior to the PKET.

A good intertester reliability was found for the AKET (ICC 0.89) and the PKET (ICC 0.77) in the injured hamstring. According to Portney and Watkins results greater than 0.75 are indicative of good reliability[17]. The specific studied population should always be considered when interpreting reliability coefficients such as ICC[3,10,23]. It can be expected that due to variability of injury severity the differences of hamstring flexibility between subjects in injured hamstrings are higher than in uninjured hamstrings. Not surprisingly, the differences between subjects (≈ the true between subjects variability) in hamstring flexibility were higher in the injured leg than in the uninjured leg in the present study. ICC measures the proportion of the total variability that is due to true between-subject variability[23]. Hence, the magnitude of the ICC is dependent on the variability in the data; for the same test in similar conditions low between-subjects variability will depress the ICC and high between-subjects variability will elevate the ICC. Therefore, the ICC is population specific and heterogeneity of the subjects should be considered[3,10,23]. Consequently, the difference in between-subjects variability between the injured and uninjured hamstrings makes the ICCs of injured and uninjured hamstrings difficult to compare.

The SEM is an absolute index of reliability and is largely independent of the between-subjects variability[3,23] and is therefore more suitable for comparing reliability of the tests between the injured and uninjured leg. The SEM quantifies the precision of individual scores on a test[23]. MDD is derived from the SEM and is useful for the clinical utilization of a test, where it indicates what difference between two measurements within the same subject is needed to be considered a real difference[23]. As an extensive explanation of the interpretation of reliability measures in general is beyond the scope of the present study, we would like to refer the readers to the useful papers of De Vet et al.[3], Karanicolas et al.[10] and Weir[23] that provide convenient information on the interpretation and application of reliability measurements of test data.

Hamstring flexibility was reduced in injured legs and limited by pain and discomfort. A lower SEM and MDD were found for the AKET in an injured hamstring compared to an uninjured hamstring. Only a small difference in SEMs was found for the PKET, which is not considered to be clinical relevant. This suggests that maximal tolerable stretch limited by pain and discomfort in an injured hamstring is a more accurate and reliable endpoint than maximal tolerable stretch in an uninjured leg.

In uninjured hamstrings, Schulz et al.[22] found a SEM of 6.6° for the AKET, Gnat et al.[8] reported a SEM of 2.29°-3.75° for the PKET. Schultz et al.[22] tested hamstring flexibility

with the hip fixed at 120° flexion, which was maintained using a steel frame during the extension. After five trials hamstring extensibility was recorded. Reliability analyses of the PKET by Gnat et al.[8] was done using a stool to keep the hip at 90° flexion during the test and a force gauge to help the different testers to perform the PKET all with the same force. The lower SEM found in the study of Gnat et al.[8] may be due to the use of a more standardized testing protocol. In present study, a testing protocol without any tools for fixation or stabilization of the patient, or force gauges while testing hamstring flexibility was chosen. This testing protocol was chosen for the reason that the findings could more easily be generalized for daily clinical practice where there is often a lack of time to standardize the tests by using a comprehensive testing protocol.

No significant differences are found between the recorded knee angles using the AKET or the PKET in both injured and uninjured hamstrings. The reliability of the AKET and the PKET has not been studied and compared in the same population. In this study ICC, SEM and MDD of the AKET and the PKET can be compared, because both tests were performed in the same subjects. The AKET is shown to be a more reliable test than the PKET, especially in injured hamstrings. It seems that the patient could better indicate the point of maximal tolerable stretch while actively extending the knee compared to passively extension of the knee by the tester. The outcome of the PKET is probably more dependent on influences due to the tester. This effect seems to be more pronounced when maximal stretch is limited by pain and discomfort in an injured hamstring.

The present study has some limitations. No intratester was determined, due to methodological restrictions: blinding of the tester for the outcome of the first test and re-testing on the same day could not be guaranteed. We therefore refrained from determining the intratester reliability. As the aim was to examine the reliability in the acute setting it is impossible to wait another week before the same observer would re-examine the patient. Lack of sufficient blinding of the tester for the outcome of the test introduces a risk of bias in information of the tester and would result in an overestimation of the intratester reliability. Intratester reliability of the AKET and the PKET can be expected to be higher than, or at least equal to the reported intertester reliability[10, 17]. Another limitation is that the allocation of the testers was not at random. As the present study was a substudy of a multicenter randomized controlled trial, the allocation of testers depended on the clinic where the injured subjects presented and the availability of the physicians at that time. This introduces a potential source of bias. In our expectations this potential source of bias is limited, because the patients were well-instructed and the endpoint of maximal tolerable stretch of the hamstring muscle was indicated by the patient. Clinicians should bear in mind that the testing protocol for the AKET and PKET used in this study is not suitable to asses hamstring flexibility in patients that do not reach maximal tolerable stretch of the hamstring muscle at a knee angle of 180°. In this study, there was one patient that did not reach maximal tolerable stretch in the

uninjured hamstring at a knee angle of 180°. When expecting higher hamstring flexibility in a target population, the use of the AKET and the PKET with the hip fixed at 120° flexion can be considered.

CONCLUSION

The AKET and the PKET are reliable in acute hamstring injury. Both tests can be reliably used to assess flexibility in injured hamstrings, despite pain and discomfort during testing.

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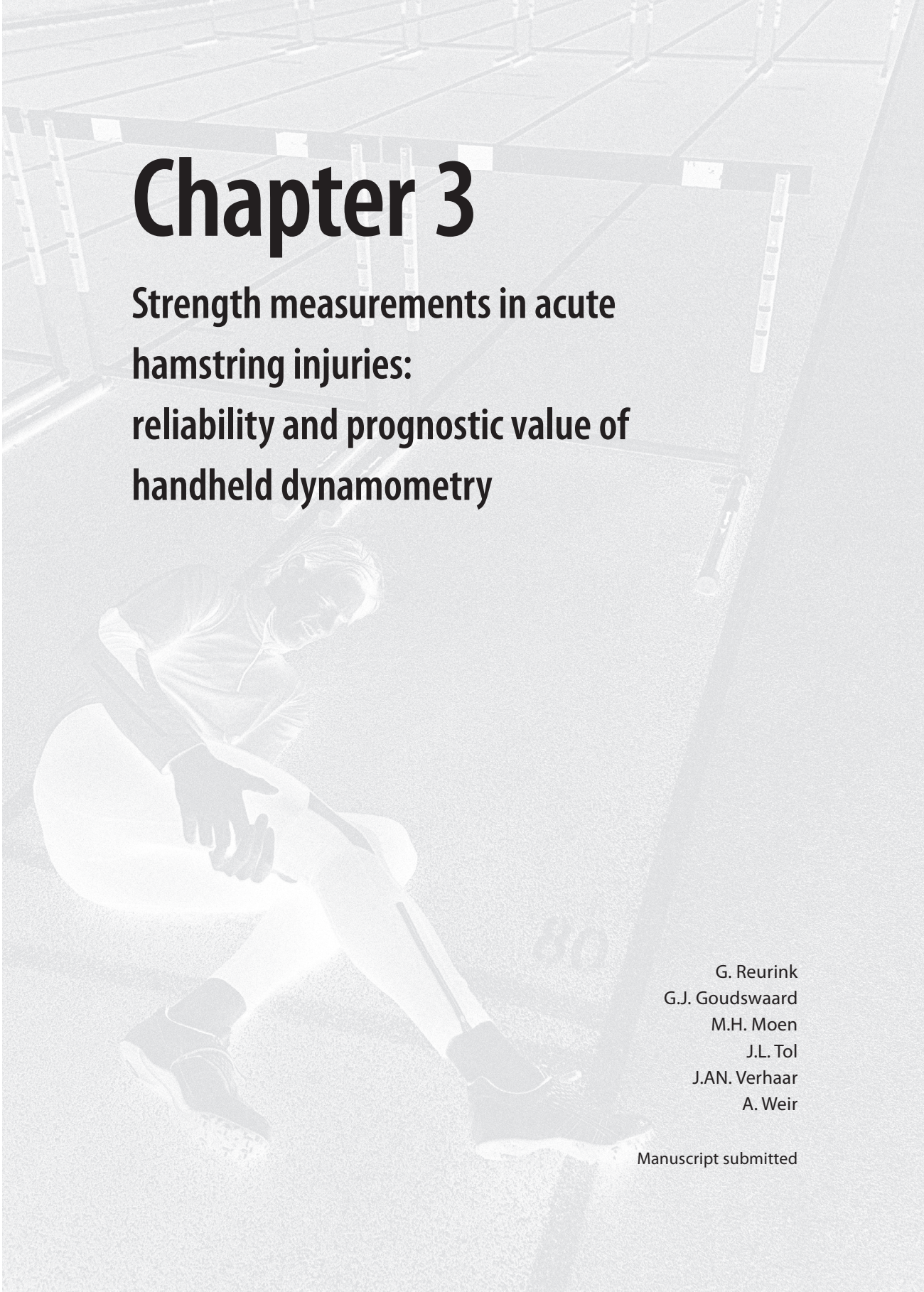
Chapter 3

Strength measurements in acute hamstring injuries: reliability and prognostic value of handheld dynamometry



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ABSTRACT

Background – Although hamstring strength measurements are widely advocated for assessing prognosis and monitoring recovery after hamstring injury, their clinical relevance has not been established yet. Handheld dynamometry (HHD) is a commonly used method of measuring muscle strength. The reliability of HHD has not been determined in athletes with acute hamstring injuries.

Purpose – To determine the interrater reliability and the prognostic value of hamstring HHD strength measurement in acute hamstring injuries.

Study design – Cohort study (diagnosis)

Methods – We measured knee flexion strength with HHD in 60 athletes at two visits: at baseline within five days of hamstring injury and at follow-up five to seven days after the baseline measurement. We assessed isometric hamstrings strength in 15°and 90° of knee flexion. We recorded the time needed to return to play (RTP). Reliability analysis testing was performed by two testers independently at the follow-up visit.

Results – The ICCs of the strength measurements in injured hamstring were between 0.75 and 0.83. There was a statistical significant but weak correlation for the baseline strength deficit at 15° of knee flexion and time to RTP (Spearman's r =0.27, p=0.048). None of the other strength variables were significantly correlated with time to RTP.

Conclusion – Hamstring strength can be reliably measured with HHD in athletes with acute hamstring injuries. The prognostic value of strength measurements is limited, as there is only a weak association between the time to RTP and hamstrings strength deficit after acute injury. Seven percent of the variance in time to RTP is explained by this strength deficit.

BACKGROUND

In acute hamstring injury, strength measurements are widely advocated for assessing injury severity, prognosis and recovery monitoring[103,120,152]. The evidence for the prognostic value of strength deficits is limited to one prospective follow-up study in 18 sprinters and 15 professional dancers. In that study no association was found between hamstring strength deficits and the time to return to play (RTP), but the sample size was insufficient to draw strong conclusions[21]. It remains therefore unknown whether hamstring strength measurements have clinical relevance in acute hamstring injuries.

Handheld dynamometry (HHD) is commonly used to measure muscle strength[128,152]. Previous HHD reliability studies were performed in healthy subjects and reported conflicting results, ranging from poor to excellent reliability[136,137,118]. In muscle injuries the reliability of HHD has not yet been studied. Potentially it might be negatively influenced by pain and discomfort. Obviously, if HHD is to be used in acute hamstring injuries, it is essential to determine reliability in this population.

The purpose of our study was to determine the interrater reliability and the prognostic value of hamstring HHD strength measurement in acute hamstring injuries.

METHODS

Subjects

The patients in this study were part of a cohort of a double blind randomized controlled trial on the effect of platelet rich plasma in hamstring injuries: Dutch trial register number 2771[187]. This multicenter randomized controlled trial started in February 2011 and was performed at the sports medicine departments of a large general district hospital, a university hospital and the medical Centre of the national football association. In this study subjects were randomized into an intervention group or a control group. The intervention group received two injections of 3 ml platelet-rich plasma (Autologous Conditioned Plasma, Biocore, ArthrexInc, Karlsfeld, Germany) and the control group received two injections of 3 ml saline at the site of the injury. The first injection was performed within five days of the injury and the second injection five to seven days later. The injections were performed using a sterile ultrasound guided technique into the region of maximal muscle injury, as determined by magnetic resonance imaging (MRI). Three separate depots of 1 ml were injected[91]. All subjects completed a standardized physiotherapy program, including range of motion exercises, progressive strength exercises, core stability training and agility exercises. The functional criteria-based rehabilitation program was supervised by a sports physiotherapist, who was blinded for the outcome of the HHD strength measurements. There were no differences between the

Table 3.1 Eligibility criteria

Inclusion criteria
• Age 18 to 50 years
• Clinical diagnosis acute hamstring injury
• Presenting and MRI within five days from injury
• MRI confirmed grade I or II hamstring lesion
Exclusion criteria
• Contraindication to MRI
• Chronic hamstring injury
• Chronic low back pain
• Cause of injury is an extrinsic trauma
• Not capable of performing rehabilitation
• No intention to return to full sports activity
• Unwilling to receive the intramuscular injections
• Injection therapy received for this injury before

intervention and the control group on the primary outcome measure time to RTP[187]. The inclusion criteria for the present study are presented in table 3.1. At inclusion, written informed consent was obtained from all patients. Ethical approval was obtained from the Regional Ethics Committee of South West Holland.

Handheld dynamometry (HHD)

Isometric knee flexion strength testing using HHD was performed at baseline, within five days of the injury, and at a follow-up visit 5-7 days later. All subjects were tested by the principal investigator (GR) at both visits. At the follow-up visit, a sports medicine physician (second investigator) independently performed the same testing protocol. Isometric knee flexion strength testing was measured at 15° and 90° of knee flexion in both the injured and the uninjured leg in a random sequence. The randomization process was performed using the program Microsoft Excel 2010 (Microsoft Cooperation, Redmond, WA, United States). Printed assessment forms were numbered and used in order of inclusion of the subjects. All testing was performed prior to the injection intervention of the RCT.

Testers

Besides the principal investigator, seven sports medicine physicians with three to sixteen years of experience participated in this study. All testers were instructed similarly and practiced the testing protocol in an injured pilot subject. The testers practiced until they were familiar with the testing protocol and could perform the complete testing protocol independently. The testers were blinded to each other's results. Depending on the availability of the clinicians for each subject the second tester was chosen out of the larger pool of eight clinicians. The testers were all male.

Testing protocol

Subjects were tested in a prone position with the knee in 15° and 90° of knee flexion[152]. The tester placed the dynamometer (MicroFET 2,Hoggan Health Industries, Inc., Draper, UT) at the heel of the subject and applied force to the heel, gradually increasing in 3-5 seconds (figure 3.1). Subjects were instructed to resist the applied force (break test)[136].At the point that the subject could not resist the force anymore (maximal isometric contraction), and the leg began to move, the test was terminated and the force was recorded. Each leg was tested 3 times in both knee flexion angles, alternating between the injured and non-injured leg. Hamstring pain during testing was rated on a 0-10 numeric rating scale. For the reliability analysis both testers performed the tests in the same order.

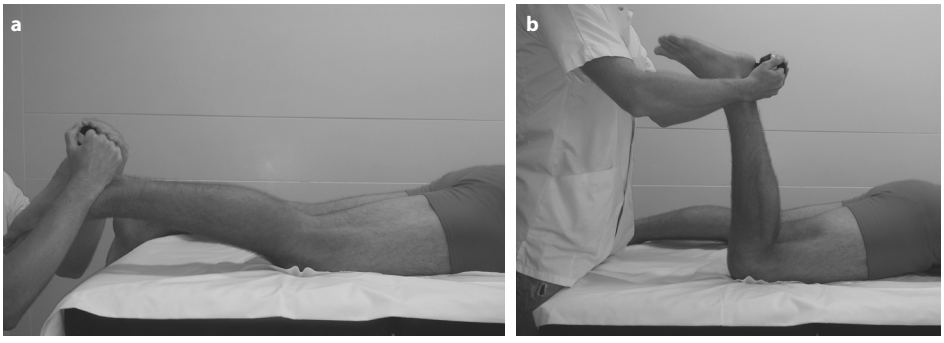

Figure 3.1. Isometric strength testing with a handheld dynamometer in: a) 15° knee flexion, and b) 90° knee flexion. Testing positions were chosen to offer testers the best possible mechanical advantage over the subjects.

Outcome measures

For the strength measures we recorded the highest force value in Newton (N), and calculated the strength deficit for the injured leg at both knee angles. Strength deficit was calculated by subtracting the knee flexion strength of the injured leg from the uninjured leg, and expressed as a percentage of the knee flexion strength of the uninjured leg. Strength deficit recovery was defined as the increase of strength from baseline to follow-up.

We recorded the time to RTP, defined as the number of days between injury and return to unrestricted sports activity in training and/or match play[73]. Clearance for RTP was given by the supervising physiotherapist once the patient completed the criteria-based rehabilitation program, including unrestricted functional sport specific testing. The supervising physiotherapist was blinded to the results of the strength measurements included in this study.

Statistical analysis

The appropriate sample size for the reliability analysis was estimated based on the approach of Girandeau and Mary[78,117]. This calculation incorporates the number of replicates, the expected intraclass correlation coefficient (ICC), the confidence interval and the width of the confidence interval. The confidence interval was set at 95% and the width at ± 0.1. Based on ICCs found in previous studies for intertester reliability performed in healthy subjects[136,137,118], the expected ICC was set at 0.8. Taking into account an expected lost to follow-up of 15%, the appropriate sample size was estimated at 60 subjects.

Statistical analysis was performed using SPSS (version 20.0, SPSS Inc., Chicago, IL, USA). ICCs were calculated to determine intertester reliability. As the two testers were selected out of the larger pool of eight clinicians, ICCs were calculated using a one-way random effects analysis of variance (ANOVA) model. A single score ICC was used because this type of ICC (1,1) is most suitable for generalization to individual testers. ICCs were calculated for the knee flexion strength in 15° and 90° knee flexion angle in both the injured and the uninjured leg and for the relative strength deficit. An ICC <0.50 was considered as poor reliability, 0.50 to 0.75 as moderate reliability and >0.75 as good reliability[182]. Additionally, the standard error of measurements (SEMs) and the minimal detectable differences (MDDs) were calculated .

As the data was not normally distributed non-parametric test were used. Differences in knee flexion strength between the injured and non-injured leg, between the knee flexion angles and between the baseline and follow-up measurements were tested using the related-samples Wilcoxon signed rank test. Spearman rank order correlations (*r*) were calculated to investigate associations between knee flexion strength measurements and the time to RTP. The significance level was set at $p<0.05$.

Association of the strength deficit recovery with time to RTP were analyzed using a linear regression model and adjusted for the baseline strength deficit.

RESULTS

We included 60 consecutive subjects in the analysis. Subject characteristics are presented in table 3.2.

From all subjects complete hamstring strength measurements were available for analysis and no one was lost to follow-up for the time to RTP analysis. An overview of the knee flexion strength measurement and pain scores is presented in table 3.3. The injured leg was force deficient compared to the uninjured leg for each variable ($p < .001$).Strength of the injured leg, strength deficits and pain scores improved at follow-up examination compared to the baseline examination ($p < 0.001$). At the baseline

Table 3.2 Patient characteristics (n =60)

Median age (interquartile range)	28 (23 - 33)
Gender Male / Female	58 / 2
Sports	
- Football	43
- Field hockey	10
- American football	3
- Athletics	2
- Tennis	1
- Fitness	1
Level of Sports	
- Professional	1
- Competitive	45
- Recreational	14

Table 3.3 Knee flexion strength measurements obtained with handheld dynamometry

Measurement	**Injured leg** – Newton	**Uninjured leg** – Newton	**Strength deficit** – %	**Pain score**
Baseline examination				
in 15° knee flexion	161 (111-233)[a]	243 (200-279)[b]	29 (8-47)[b]	5 (3-6)[b]
in 90° knee flexion	156 (121-200)[a]	188 (169-218)	14 (5-33)	3 (1-5)
Follow-up examination 5-7 days later				
in 15° knee flexion	213 (157-254)[a,b,c]	235 (201-271)[b]	12 (-2-26)[c]	1 (0-3)[c]
in 90° knee flexion	172 (144-218)[a,c]	197 (164-218)	6 (-3-19)[c]	0 (0-2)[c]

Values are median (interquartile range).
a) Significant different from uninjured leg (p<.001);
b) Significant different from measurement in 90° knee flexion (p<.001);
c) Significant different from baseline examination (p<.001).

examination the strength deficit and pain score at 15° were significantly higher than at 90° knee flexion (p < -.001), but no difference was found at follow-up examination (strength deficit, p = 0.101; pain score, p = 0.334).

Intertester reliability

The ICCs, SEMs and MDDs are presented in table 3.4.

Association with time needed to return to play

The median time to RTP was 39 days (interquartile range, 31 to 51). Spearman's *r* between the strength measurement variables and the time to RTP are presented in table

3.5. There was a significant correlation of 0.27 for the strength deficit in 15° knee flexion measured at the baseline examination (p = 0.048), explaining 7% of the total variance in time to RTP (r^2). None of the other correlations showed statistical significance. There was no significant association between strength deficit recovery in both 15° (p = 0.419) and 90° knee flexion (p = 0.767), adjusted for the baseline strength deficit.

Table 3.4 Intertester reliability of knee flexion strength measurements with handheld dynamometry

	Injured leg			**Uninjured leg**			**Relative strength deficit**		
	ICC (95%CI)	SEM (N)	MDD (N)	ICC (95%CI)	SEM (N)	MDD (N)	ICC (95% CI)	SEM (%)	MDD (%)
HHD15	0.83 (0.73-0.90)	29	81	0.74 (0.61-0.84)	31	86	0.75 (0.62-0.84)	9	26
HHD90	0.76 (0.62-0.85)	26	71	0.71 (0.56-0.82)	23	63	0.80 (0.69-0.88)	7	20

HHD15, handheld dynamometry in 15° knee flexion; HHD90, handheld dynamometry in 90° knee flexion; ICC, intraclass correlation coefficient; SEM, standard error of measurement; MDD, minimal detectable difference; N, Newton

Table 3.5 Association between knee flexion strength measurement variables and time needed to return to play

Variable	**Spearman's *r***	**p-value**
Baseline examination		
Strength deficit		
in 15° knee flexion	0.27	0.048
in 90° knee flexion	0.12	0.371
Pain score during testing		
in 15° knee flexion	0.18	0.186
in 90° knee flexion	0.04	0.788
Follow-up examination 5-7 days later		
Strength deficit		
in 15° knee flexion	0.23	0.097
in 90° knee flexion	0.18	0.199
Pain score during testing		
in 15° knee flexion	0.10	0.490
in 90° knee flexion	0.06	0.664

DISCUSSION

Our study showed moderate to good reliability of HHD in subjects with acute hamstring injuries. A weak association was found between strength deficit measured within 5 days of injury in 15° knee flexion and time to RTP. Pain scores, strength deficits at 90° knee flexion, strength deficits at the follow-up visit 5-7 days later and strength deficit recovery between the baseline and follow-up visit were not associated with the time to RTP.

Although hamstring strength testing was limited by pain in injured legs and strength was reduced compared to the uninjured legs, only small differences in SEMs were found compared to the uninjured leg. This indicates that there is no clinical relevant difference in the accuracy of HHD in injured compared to uninjured hamstrings.

In the present study we assessed knee flexion strength at both longer hamstring length (15° knee flexion) and shorter hamstring length (90° knee flexion). As weakness at longer muscle lengths is thought to be associated with injury risk and the most commonly injured hamstring muscle, the biceps femoris long head, is activated at longer lengths, it has been proposed that hamstring strength should be assessed at long lengths[152]. The results of our study support this hypothesis as we found larger strength deficits, higher pain scores, and stronger associations with time to RTP for the strength measurements at the longer muscle length. Only the strength deficit in 15° knee flexion at the baseline examination was significantly associated with time to RTP. We therefore recommend assessing strength deficit in 15° knee flexion within 5 days after the hamstring injury.

We found a weak association between the hamstring strength deficit and the time to RTP. Its value as a single prognostic tool for the individual athlete in clinical practice is therefore limited, as only 7% of the variance of time to RTP is explained by the strength deficit. As hamstring injuries are a complex multifactorial condition[24,151], combining multiple prognostic factors is required before we be able to provide accurate injury duration predictions for the individual athlete. Our study shows that the strength deficit is a variable that can contribute to the prognostic work-up after hamstring injuries, although it only explains 7% of the variance in time to RTP.

Askling et al. measured isometric knee flexion strength at near full knee extension using a fixed dynamometer, and found no correlations between strength deficits and the time to RTP[21]. The absence of a significant correlation with the time to RTP does not actually conflict with the present study, as their sample size was too small to detect weak associations.

The methodological strengths of our study include minimization of bias by blinding of the physiotherapist who gave RTP clearance, strength testing performed by one physician for the prognostic value for time to RTP analysis and the relatively large sample size. The recruitment in three different clinical settings (academic clinic, general clinic and specialized high-level athlete clinic) and the use of a large pool of clinicians for the

reliability analysis contribute to the generalizability of the results. The studied testing protocol is feasible for use in daily clinical practice, as it is simple and quick.

This study has some limitations. Firstly, no intratester reliability was determined, due to methodological restrictions: blinding of the tester for the outcome of the first test and re-testing on the same day could not be guaranteed as it was not possible to arrange multiple subjects on one day. Lack of sufficient blinding of the tester for the outcome of the test introduces a risk of bias in information of the tester and would result in an overestimation of the intratester reliability. As the clinical condition and strength in hamstring injuries changes in the first days after injury, comparing the baseline and follow-up examination would not provide valid reliability measures. We therefore refrained from determining the intratester reliability. Intratester reliability can be expected to be higher than, or at least equal to the reported intertester reliability[117,182].

Secondly, as reliability analysis was performed at the follow-up measure only, the reliability of testing at the baseline visit within 5 days after injury remains unknown. Strength deficits and pain scores were larger at baseline examination than at follow-up examination 5-7 days later, which may alter the reliability of strength testing. There is however a larger variation in the measurements made at the baseline visit of the injured leg. When the variation in the measured subjects increases, this would be expected to result in better ICC values.

Thirdly, allocation of the testers for the reliability analysis was not at random, as all subjects were tested once by the principal investigator and the allocation of the second tester depended on the clinic where the injured athlete presented. This introduces a potential source of bias.

CONCLUSION

Knee flexion strength can be measured reliably with HHD in athletes with acute hamstring injuries. The prognostic value of strength measurements is limited, as there is only a weak association between the time to RTP and hamstrings strength deficit assessed at 15° of knee flexion within five days of injury. Seven percent of the variance in time to RTP is explained by this strength deficit.

ACKNOWLEDGEMENTS

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Chapter 4

Magnetic resonance imaging in acute hamstring injury: can we provide a return to play prognosis? A systematic review

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ABSTRACT

Background – Sports physicians are increasingly requested to perform magnetic resonance imaging (MRI) of acute hamstring muscle injuries and to provide a prognosis of the time to return to play (RTP) on the basis of their findings.

Objectives – To systematically review the literature on the prognostic value of MRI findings for time to RTP in acute hamstring muscle injuries.

Data sources – The databases of PubMed, EMBASE, CINAHL, Web of Science and Cochrane Library were searched in June 2013.

Study eligibility criteria – Studies evaluating MRI as a prognostic tool for determining time to RTP in athletes with acute hamstring injuries were eligible for inclusion.

Data analysis – Two authors independently screened the search results and assessed risk of bias using criteria for quality appraisal of prognosis studies. A best evidence synthesis was used to identify the level of evidence.

Results – Of the twelve studies included, one had a low risk of bias and 11 a high risk of bias. There is moderate evidence that injuries without hyperintensity on fluid sensitive sequences are associated with a shorter time to RTP and that injuries involving the proximal free tendon are associated with a longer time to RTP. Limited evidence was found for an association of central tendon disruption, injury not affecting the musculotendinous junction and a total rupture with a longer time to RTP. The other MRI findings studied showed either no association or there was conflicting evidence.

Conclusion – There is currently no strong evidence for any MRI finding that give a prognosis on the time to RTP after an acute hamstring injury, due to considerable risks of bias in the studies on this topic.

BACKGROUND

Hamstring injuries are the most prevalent time-loss injuries in major sports like American and Australian football, soccer and track and field athletics[7,61,69,169,206]. After injury, the main question of the athlete, coaching staff and press is: when can he or she return to play?

Magnetic resonance imaging (MRI) is more readily available than ever before and plays an increasing role in diagnosing and predicting prognosis in hamstring muscle injuries, especially in the elite athlete[120,124]. Sports physicians and radiologists are increasingly asked to assess MRIs of these injuries and to help provide a prognosis in the time to return to play (RTP) on the basis of their findings.

In the last two decades a number of studies have been published on the prognostic value of MRI in acute hamstring injuries that reported multiple findings as indicators for the time to RTP, but the large variation of the time to return to play from 1 day[61] all the way up to 104 weeks[18] makes estimating the prognosis a challenge.

The purpose of this paper was to systematically review the literature on the prognostic value of MRI findings for time to RTP in acute hamstring injuries.

Table 4.1 Search strategy*

Search strategy	records
PubMed ((hamstring*[tiab])) AND ("magnetic resonance imaging"[mh] OR diagnostic imaging[mh:noexp] OR (magnetic resonance imaging[tiab] OR mri[tiab] OR radiodiagnos*[tiab] OR imaging[tiab])) AND ("Wounds and Injuries"[mh] OR (injur*[tiab] OR tear*[tiab] OR strain*[tiab] OR rupture*[tiab] OR trauma*[tiab])) NOT (animals[mh] NOT humans[mh])	246
Embase (hamstring/exp OR (hamstring*):ab,ti) AND ('nuclear magnetic resonance imaging'/exp OR radiodiagnosis/de OR 'diagnostic imaging'/de OR ('magnetic resonance imaging' OR mri OR radiodiagnos* OR imaging):ab,ti) AND (injury/exp OR (injur* OR tear* OR strain* OR rupture* OR trauma*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)	415
Cochrane central ((hamstring*):ab,ti) AND (('magnetic resonance imaging' OR mri OR radiodiagnos* OR imaging):ab,ti) AND ((injur* OR tear* OR strain* OR rupture* OR trauma*):ab,ti)	7
Web of Science TS=(((hamstring*)) AND ((magnetic resonance imaging OR mri OR radiodiagnos* OR imaging)) AND ((injur* OR tear* OR strain* OR rupture* OR trauma*)) NOT ((animal* OR mouse OR mice OR rat? OR nonhuman OR dog? OR rabbit? OR chicken? OR swine? OR cat? OR rodent?) NOT (human* OR patient*)))	224
CINAHL TX ((hamstring*)) AND (MH magnetic resonance imaging+ OR MH diagnostic imaging+ OR TX (magnetic resonance imaging OR mri OR radiodiagnos* OR imaging)) AND (Wounds and Injuries+ OR TX (injur* OR tear* OR strain* OR rupture* OR trauma*)) NOT (MH animals+ NOT MH Humans)	177

*Search performed in June 2013

METHODS

All reviewers involved in the literature search, study selection, data extraction and risk of bias assessment were medical doctors with at least two years of experience as a clinical researcher in sports medicine.

Literature Search

The databases of PubMed, EMBASE, CINAHL, Web of Science and Cochrane Library were searched without any time limits in June 2013. An overview of the complete electronic search is shown in table 4.1. Additional citation tracking was performed by manual screening of the reference lists of the eligible studies.

Study Selection

Two reviewers independently assessed all records identified by the search strategy. Studies were eligible if they met the following criteria: subjects had a clinical diagnosis of an acute hamstring injury; MRI examination of the acute injury was performed; MRI findings as a prognostic tool for time to RTP were studied, injury time or time to return to pre-injury level were studied; the study had to be an original report; full text of the article had to be available; the article was written in English, Dutch or German. The two reviewers read all relevant full text articles to assess whether they met the eligibility criteria. If there was a difference in opinion on eligibility, a consensus was reached by the two reviewers. If no consensus was reached, the independent opinion of a third reviewer was decisive.

Data extraction

One reviewer recorded the population, details of the MRI protocol, MRI findings, time to RTP and the outcome of the analysis of association between MRI findings and time to RTP using standardised data extraction forms. Authors of the eligible studies were contacted if additional information was required.

Risk of bias assessment

Two reviewers independently assessed the potential risk of bias of the studies included, using the criteria of the consensus statement of Hayden et al.[101]. This risk of bias assessment tool assesses six potential bias domains, each consisting of specific items for opportunity of bias (Table 4.2). If there was a difference in opinion on an item, a consensus was reached by the two reviewers. If no consensus was reached, the independent opinion of a third reviewer was decisive.

As shown in table 4.2 each of the six potential bias domains consist of 3 to 5 specific items. When ≥ 75% of these items within a domain were fulfilled, we considered the bias low in that domain. To have overall low risk of bias, a study should have low bias on:

i) at least five out of the six domains.

and

ii) the outcome measurement time to RTP (domain 4)

Best evidence synthesis

Due to the heterogeneity of the MRI findings, outcome measures and methodological quality, we refrained from statistical pooling of the data. We used a best evidence synthesis, consisting of a five levels of evidence based qualitative analysis:[229]

1. Strong evidence: provided by two or more studies with low risk of bias and by generally consistent findings in all studies (≥ 75% of the studies reported consistent findings).
2. Moderate evidence: provided by one study with low risk of bias and/or two or more studies with high risk of bias and by generally consistent findings in all studies (≥ 75% of the studies reported consistent findings).
3. Limited evidence: provided by only one study with high risk of bias.
4. Conflicting evidence: inconsistent findings in multiple studies (<75% of the studies reported consistent findings).
5. No evidence: when no studies could be found

RESULTS

Literature search

Figure 4.1 shows the study selection flow diagram. Twelve studies met the inclusion criteria[15,17,20,51,52,203,63,77,11,213,216,231] (Figure 4.1).

Description of included studies

Table 4.3 presents the characteristics of the studies included.[15,17,20,51,52,203,63,77,11,213,216,231] Two reports[52,203] used the same data set and are therefore considered as one study (confirmed by the corresponding author). Table 4.4 presents an overview of the MRI protocols used in the studies included.

Risk of bias assessment

The scores on the potential risk of bias domains of the studies included are shown in Table 4.5. One study had a low risk of bias[213] and 11 studies had a high risk of bias[15,17,20,51,52,203,63,77,11,216,231].

Table 4.2 Risk of bias assessment tool

Potential bias domain	Items for assessment of potential opportunity for bias	Yes	No/ Not reported
Study participation			
The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the results. ☐ **Yes** ☐ **No**	The source population is adequately described for the key characteristics type and level of sport.	☐	☐
	Inclusion and exclusion criteria are adequately described.	☐	☐
	There is adequate participation in the study by eligible individuals.	☐	☐
	The baseline study sample is adequately described for key characteristics: sex, age, type and level of sport.	☐	☐
Study attrition			
Loss to follow-up is not associated with key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias. ☐ **Yes** ☐ **No**	Losses to follow-up are reported.	☐	☐
	Reasons for loss to follow-up are described.	☐	☐
	Loss to follow-up is less than 20%.	☐	☐
	To assess when lost to follow-up is more than 20%: There are no important differences between key characteristics and the prognostic MRI measures in participants who completed the study and those who did not.	☐	☐
Prognostic factor measurement			
The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias. ☐ **Yes** ☐ **No**	The prognostic MRI measures are adequately defined or described.	☐	☐
	The prognostic MRI measures and methods are adequately valid and reliable to limit misclassification bias (may refer to relevant outside sources of information on measurement properties).	☐	☐
	The prognostic MRI measures are blinded for the outcome measure time to RTP or injury time.	☐	☐
	More than 80% of the study sample has complete data for the prognostic MRI measures.	☐	☐
Outcome measurement			
The outcome of interest is adequately measured in study participants to sufficiently limit potential bias. ☐ **Yes** ☐ **No**	The outcome measure time to RTP or injury time is adequately defined or described.	☐	☐
	Criteria for RTP clearance or recovery of the injury are clearly described and are the same for all study participants.	☐	☐
	The clinicians/therapists involved in the rehabilitation and/or RTP decision and the subjects are blinded to the prognostic MRI measure.	☐	☐

Table 4.2 Risk of bias assessment tool (continued)

Potential bias domain	Items for assessment of potential opportunity for bias	Yes	No/ Not reported
Confounding measurement and account			
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. ☐ **Yes** ☐ **No**	Important potential confounders: - Type of sport or injury mechanism - Index injury being a re-injury (assessed at least for the 2 previous months) - Rehabilitation protocol		
	The important potential confounders measured are adequately defined or described.	☐	☐
	All important potential confounders are measured and accounted for in the study design or analysis.	☐	☐
Analysis			
The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results. ☐ **Yes** ☐ **No**	There is a description of the association of the prognostic MRI measure and the outcome measure time to RTP or injury time, including information about the statistical significance.	☐	☐
	The selected model is adequate for the design of the study.	☐	☐
	To assess when multivariate models are used: The strategy of inclusion of variables is appropriate and is based on a conceptual framework or model.	☐	☐
	There is no selective reporting of results.	☐	☐
	Continuous variables are reported or appropriate (i.e., not data-dependent) cut-points are used.	☐	☐

To score 'yes' on a potential bias item at least 75% of the assessment criteria should be scored 'yes'.
Abbreviations: RTP, return to play; MRI, magnetic resonance imaging.

The detailed score sheets for each individual study are presented in Electronic Supplementary Material Appendix S1.

There was 100% agreement between the two reviewers on the classification of the studies into high or low risk of bias. For the specific items for opportunity of bias there was disagreement on 18 out of the 264 assessed items (6.8%), for which consensus was reached by the two reviewers.

MRI finding and association with time to return to play

Table 4.6 presents an overview of all the reported MRI findings, their association with RTP and the corresponding level of evidence according to the best evidence synthesis.

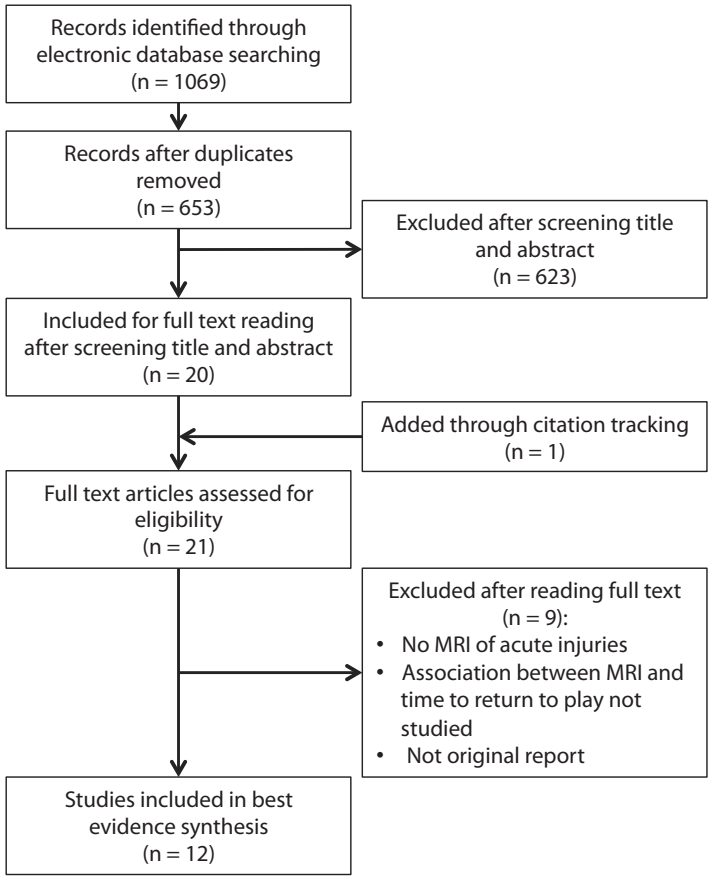

Figure 4.1. Study selection flow diagram

MRI negative injury

Moderate evidence was found that the absence of any focal hyperintensity on fluid sensitive sequences (MRI negative injury) is associated with a reduced time to RTP. Six studies showed that MRI negative injuries had a significantly shorter time to RTP than MRI positive injuries[20,52,63,77,203,216,231].

Number of muscles involved

There is conflicting evidence for the association of the number of muscles injured and time to RTP, as there were no consistent findings in the two studies reporting this finding. Silder et al. reported that a higher number of muscles injured was significantly correlated with a longer time to RTP (r=0.50, p=0.010)[213]. Gibbs et al. reported no difference in the time to RTP between the athletes with a single muscle and those with two muscles injured (p=0.73)[77].

Muscle involved

Moderate evidence was found that there is no association between involvement of the different hamstring muscles and time to RTP. Connell et al. and Schneider-Kolsky et al. reported that an injury of the biceps femoris was associated with longer time to RTP (p=0.049)[52,203]. Three studies reported no difference between time to RTP and involvement of the different hamstring muscles (p=0.33 to 0.86)[51,63,216].

Distance of injury to the muscle origin

Conflicting evidence was found that the distance of the injury to the muscle origin is associated with time to RTP. Different methods were used to measure the distance of the injury to the muscle origin. Four studies measured the distance between the ischial tuberosity and the most cranial point of the hyperintensity[15,17,20] or the maximum hyperintensity[213]. Three of these studies reported a significant association of the distance to the ischial tuberosity (r=0.44 to 0.74, p=0.001 to 0.043) with a longer time to RTP[15,20,213] and one found no association (p>0.05)[17]. Slavotinek et al. assessed whether the injury was observed proximal or distal in the hamstring, with using the femoral origin of the short head of the biceps femoris as a reference point. They reported no difference in time to RTP between proximally and distally located injuries (p=0.17)[216].

Proximal free tendon involvement

Moderate evidence was found for an association between involvement of the proximal tendon and time to RTP. Two studies reported that time to RTP was significantly longer in injuries with proximal tendon involvement than without (p<0.01)[15,20]. The proximal free tendon was considered injured if it was thickened, had an intratendinous high signal or a collar of high signal around it on a fluid sensitive sequence.

Table 4.3 Characteristics of included studies

Study	Population, timing of MRI examination and RTP characteristics	MRI finding	Association with time to RTP	
			Significant association[a]	**Non-significant association**
Askling et al. 2007[11]	n=17 Sprinters, national or international; Timing MRI: 4d after injury; RTP: train or compete at pre-injury level; Time to RTP: median 16w (range, 6-50)	Proximal free tendon involvement	Involved 34.8w vs not involved 13w (p=0.009) *r* =- 0.544 (p=0.044)	
		Distance to origin	Proximal 25.6w vs distal 9.5w (p=0.028)	
		Longitudinal length		*r* = 0.505 (p=0.055)
		Cross-sectional area	*r* = 0.695 (p=0.004)	
		Volume	*r* = 0.608 (p=0.016)	
		Antero-posterior extent	*r* = 0.584 (p=0.022)	
		Medio-lateral extent		*r* = 0.395 (p=0.146)
Askling et al. 2007[12][b]	n=12 Dancers, professional Timing MRI: 4d after injury; RTP: train or compete at pre-injury level Time to RTP: median 50w (range, 30-76)	Involved muscle site		*r* = 0.008 to 0.625 (p=0.053 to 0.981) for all MRI findings
		Distance to origin		
		Longitudinal length		
		Cross-sectional area		
		Volume		
		Antero-posterior extent		
		Medio-lateral extent		

Table 4.3 Characteristics of included studies (continued)

Study	Population, timing of MRI examination and RTP characteristics	MRI finding	Association with time to RTP	
			Significant association[a]	Non-significant association
Askling et al. 2013[13]	n=75 Football, professional; Timing MRI: ≤5d after injury; RTP: full participation in team training and availability for match selection; Time to RTP: L-protocol mean 28d (±15) C-protocol mean 51d (±21)	Hyperintensity	Absence 6d (±3) vs presence 23d (±11) (p<0.001)[c]	
		Proximal free tendon involvement	L-protocol: Involved > not involved (p<0.01) C-protocol: Involved > not involved (p<0.001)	
		Distance to origin	L-protocol: r = - 0.736 (p<0.001) C-protocol: r = -0.717 (p<0.001)	
		Longitudinal length	L-protocol: r = 0.817 (p<0.001) C-protocol: r = 0.320 (p<0.001)	
Comin et al. 2012[14]	n=62 Australian Football & Rugby, national; Timing MRI: NA; RTP: return to competition; Time to RTP: median 21d (IQR, 14-42)	Muscle injured		BF 21d (IQR, 12-56) vs SM 32d (IQR, 21-35) vs ST 14d (IQR, 12-22) (p=0.33)
		Central tendon disruption	Disruption 72d (IQR, 42-109) vs no disruption 21d (IQR, 9-28) (p<0.01)	
Connell et al. 2004[15] AND Schneider-Kolsky et al. 2006[16][d]	n=58 Australian Football, professional; Timing MRI: ≤3d after injury; RTP: return to competition; Time to RTP: median 21d (IQR, 4-56)	Hyperintensity	Absence 7d (IQR, 7-14) vs presence 21d (IQR, 4-56) (p<0.001)	
		Location within muscle	Musculotendinous junction involved < not involved r = NA (p<0.05)	
		Cross section area	r = NA (p<0.05)	
		Intramuscular fluid collection		r = NA (p>0.05)
		Extramuscular fluid collection		r = NA (p>0.05)
		Multivariate: - Longitudinal length - Muscle injured	r^2 = 37.9% (p=0.001) BF involved (p=0.049)	

Table 4.3 Characteristics of included studies (continued)

Study	Population, timing of MRI examination and RTP characteristics	MRI finding	Association with time to RTP	
			Significant association[a]	**Non-significant association**
Ekstrand et al. 2012[17]	n=207 Football, professional; Timing MRI: 1-2d after injury; RTP: clearance medical team for full training participation and match selection; Time to RTP: mean 19d (±17)	Hyperintensity	Absence (=grade 0) vs presence (=grade 1-3) (p<0.05)	
		Grading	Grade0 8d (±3), grade1 17d (±10), grade2 22d (±11), grade 3 73d (±60) (p<0.001) Pairwise comparison (p<0.05), except for grade 1 vs grade 2.	Grade1 vs grade2 (p=0.053)
		Muscle injured		BF 21d (±19) vs SM 19d (±11) vs ST 17d (±11) (p=0.79)
Gibbs et al. 2004[18]	n=31 Australian Football, professional; Timing MRI: 1-3d after injury; RTP: full participation in team training; Time to RTP: median 18d (IQR, 14-27)	Hyperintensity	Absence 6.6d (±8.2) vs presence 20.2d (±52.3) (p<0.001)	
		Longitudinal length	*r* = 0.84 (p<0.001)	
		Cross sectional area	*r* = 0.78 (p<0.001)	
		Number of muscles		Single vs double (p=0.73)
Rettig et al. 2008[19][e]	n=21 American football, professional; Timing MRI: NA; RTP: NA; Time to RTP: NA	Longitudinal length		
		Tendon separation at musculotendinous junction		
Silder et al. 2013[20]	n=25 Sports requiring high speed running; Timing MRI: ≤10d after injury; RTP: Completion of rehabilitation; Time to RTP: median 23d (IQR, 20-23)	Distance to origin	*r* = -0.44 (p=0.043)[f]	
		Longitudinal length	*r* = 0.41 (p=0.040)	
		Cross sectional area		*r* = 0.30 (p=0.182)[f]
		Number of muscles	*r* = 0.50 (p=0.010)[f]	

Table 4.3 Characteristics of included studies (continued)

Study	Population, timing of MRI examination and RTP characteristics	MRI finding	Association with time to RTP	
			Significant association[a]	Non-significant association
Slavotinek et al. 2002[21]	n=30 Australian Football, national or state; Timing MRI: 2-6d after injury; RTP: return to competition; Time to RTP: median 27d (range, 13-48)	Hyperintensity	absence vs presence: γ = -0.69 (p=0.04)	
		Muscles injured		BF vs ST (p=0.86)
		Distance to origin		Proximal vs distal (p=0.17)
		Cross-sectional area	r = 0.63 (p<0.001)	
		Volume	r = 0.46 (P=0.01)	
		Extramuscular fluid collection		r = 0.33 (p=0.12)
Verrall et al. 2003[22]	n=83 Australian Football, National or state; Timing MRI: 2-6d after injury; RTP: return in competition; Time to RTP: NA	Hyperintensity	Absence 16d vs presence 27d (p<0.01)	

a. Presented association measures are tested univariate, unless otherwise specified; p<0.05 is considered statistical significant; r, correlation coefficient; γ, gamma statistics, r^2, variance in time to RTP explained by the multivariate model.

b. Contact with corresponding author: no data available for correlation of each MRI finding and RTP separately.

c. As part of a randomised controlled trial, prognostic MRI variables assessed separately for treatment groups. L-protocol: lengthening exercises. C-protocol: conventional exercises.

d. Studies of Connell et al.[15] and Schneider-Kolsky et al.[16] used the same dataset and are therefore considered one study (confirmed by the corresponding author).

e. No statistical testing reported.

f. Association not determined in the original reports. A reviewer (GR) analysed association using the data presented in the report.

Abbreviations: RTP, return to play; MRI, magnetic resonance imaging; w, week; d, days; IQR, interquartile range; BF, biceps femoris; SM, semimembranosus; ST, Semitendinosus; NA, not available.

Table 4.4 Magnetic resonance imaging protocols used

Reference	Side	Magnetic field strength	Coil	Sequences	TR/TE	TI, ETL, flip angle	Thickness sections / gap (mm)	Field of view (cm)	Matrix (pixels)
Askling et al. 2007[15] & 2007[17] & 2013[20]	Bilateral	1.0-T[15,17] and 1.5-T[20]	Phased-array spine	Coronal STIR Sagittal STIR Axial STIR Axial T1 Axial T2	4000/30 4000/30 5035/30 722/20 5500/110	TI 150 ms TI 150 ms TI 150 ms	5/0.5 5/0.5 5/0.5 5/0.5 5/0.5	42.0x48.0 30.0x48.0 26.3x35.0 26.3x35.0 21.9x35.0	294x512 210x512 154x256 265x512 168x256
Comin et al. 2012[51]	NR	NR	NR	Proton density fat-saturation	NR	NR	NR	NR	NR
Connell et al. 2004[52] & Schneider-Kolsky et al. 2006[203]	NR	1.5-T	Phased-array shoulder	Axial and coronal oblique fast spin-echo Axial and coronal oblique fast spin-echo IR	4000/45 5000-6500 /35-55	ETL 8-12	5/0 5/0	20 20	512x384 256x224
Ekstrand et al. 2012[63]	NR	Minimum required: 1.5-T	NR	Minimum required: Axial and coronal T1 and T2-fat saturation or STIR	NR	NR	NR	NR	NR
Gibbs et al. 2004[77]	Bilateral	1.5-T	NR	Coronal T1 Coronal STIR Axial T2-fat suppression	NR	NR	4/1.5 10/0 7/3.5	NR	NR
Rettig et al. 2008[11]	Bilateral	NR		NR	NR	NR	NR	NR	NR
Silder et al. 2013[213]	Bilateral	1.5-T	Phased-array torso	Axial T2 Coronal T2	2200-3200 /70-88	NR	5/0 4/0.4	NR	512x512
Slavotinek et al. 2002[216]	NR	1.5-T	Polarized body array	Axial T1 Axial IR T2 Sagittal T1 Sagittal IR T2 Axial gradient-echo	802/12 5032/30 676/12 5000/30 610/18	ETL 3 ETL 7; TI 150 ms ETL 3 ETL 7; TI 150 ms Flip angle 20°	10/2 10/2 7/1.4 7/1.4 10/2	30-32x40-42.7 30-31.9x40-42.5 24x32 24x32 30-31.4x40-41.9	213x512 182x256 213x512 189x256 192x512
Verrall et al. 2003[231]	NR	1.5-T	NR	Axial and sagittal T1, T2 and gradient echo	NR	NR	NR	NR	NR

Abbreviations: TR, time to repetition; TE, time to echo; TI, time to inversion; ETL, echo train length; T, Tesla; STIR, short tau inversion recovery; NR, not reported; IR, inversion recovery.

Central tendon disruption

Limited evidence was found that involvement of the central tendon is associated with a longer time to RTP. Comin et al. reported that injuries with MRI findings of central tendon disruption, determined by the presence of a focal defect separating proximal and distal parts of the tendon or waviness of the tendon, had significantly longer time to RTP than those injuries without these findings ($p<0.01$)[51].

Musculotendinous junction involvement

Limited evidence was found that injuries not affecting the musculotendinous junction are associated with a longer time to RTP. Connell et al. reported that injuries at the musculotendinous junction had a significant longer recovery time than those that did not affect the musculotendinous junction($p<0.05$)[52].

Longitudinal length

Conflicting evidence was found for an association between the longitudinal length of hyperintensity on fluid sensitive sequences and the time to RTP. In an univariate analysis, a larger longitudinal length was shown to be associated with a longer time to RTP in three studies (r=0.32 to 0.84, p=0.001 to 0.040)[20,77,213]. No association was found in two studies (r=0.51, $p>0.05$)[15,17]. In a multivariate analysis the longitudinal length was found to be independently associated with time to RTP (p=0.001)[52,203].

Cross-sectional area

Conflicting evidence was found for an association of the cross-sectional area of hyperintensity on fluid sensitive sequences with time to RTP. All studies used a similar definition of the cross-sectional area: the maximal muscle cross-sectional area of hyperintensity expressed as a percentage of the total cross-sectional muscle area on the same axial image, measured on a fluid sensitive sequence. Four studies[15,52,77,203,216] reported a significant association with a longer time to RTP (r=0.70 to 0.84, p=0.001 to 0.05) and two studies[17,213] found no association with the time to RTP (r=0.30, p=0.182 and $p>0.05$).

Volume

Conflicting evidence was found for an association between the volume of the hyperintensity on fluid sensitive sequences and time to RTP. The volume in all three studies was calculated using the formula of an ellipsoid (volume ≈ cranio-caudal x antero-posterior x medio-lateral x 0.5)[15,17,216]. Two studies reported an association of a larger volume with a longer time to RTP (r=0.61 to 0.63, p=0.01 to 0.016)[15,216]. In a cohort of dancers Askling et al. found no significant correlation between the volume of the hyperintensity on fluid sensitive sequences and time to return to pre-injury level ($p>0.05$)[17].

Table 4.5 Risk of bias assessment

	Potential risk of bias item						
Reference	1	2	3	4	5	6	**Risk of bias[a]**
Askling et al. 2007[15]	+	+	+	–	+	+	High
Askling et al. 2007[17]	+	–	–	–	+	+	High
Askling et al. 2013[20]	+	+	–	–	+	+	High
Comin et al. 2012[51]	–	–	+	–	–	+	High
Connell et al. 2004[52]	+	+	+	–	–	+	High
Schneider-Kolsky et al. 2006[203]	+	–	–	–	–	+	High
Ekstrand et al. 2012[63]	–	–	–	–	–	+	High
Gibbs et al. 2004[77]	+	–	–	–	–	+	High
Rettig et al. 2008[11]	–	–	–	–	–	–	High
Silder et al. 2013[213]	+	+	+	+	–	+	Low
Slavotinek et al. 2002[216]	–	–	+	±	+	+	High
Verrall et al. 2003[231]	+	–	–	–	–	+	High

a. Low risk of bias requires positive scores for minimal 5 out of 6 items and for item 4; +, Potential risk of bias limited sufficiently; –, Potential risk of bias; ±, Potential risk of bias limited sufficiently, except for the finding 'hyperintensity absence or presence'.

Medio-lateral extent

Moderate evidence was found that there is no association between the maximal medio-lateral extent of hyperintensity measured on the axial images of fluid sensitive sequences and time to RTP, as Askling et al. found no significant correlations in both cohorts of sprinters and dancers (r=0.40, p=0.146 and p>0.05)[15,17].

Antero-posterior extent

Conflicting evidence was found for an association between the antero-posterior extent of hyperintensity measured on the axial images of fluid sensitive sequences and time back to pre-injury level. A study by Askling et al. in sprinters showed an association between a larger antero-posterior extent and a longer time to RTP (r=0.58, p=0.022)[15]. On the other hand, a study of Askling et al. in dancers showed no significant association (p>0.05)[17].

Fluid collection

There is moderate and limited evidence that extramuscular and intramuscular fluid collections respectively seen on MRI, suggestive for hematoma, are not associated with the time to RTP (r=0.33, p=0.12 and p>0.05)[52,203,216]. Connell et al. and Schneider-Kolsky et al. defined hematoma as a collection of fluid with abnormal signal intensity[52,203]. Slavotinek et al. considered extramuscular T2-hyperintensity to be extramuscular fluid[216].

Table 4.6 Overview of the studied MRI findings and their association with the time to return to play, and the corresponding level of evidence according to the best evidence synthesis.

MRI finding	Univariate		Multivariate	Best evidence synthesis[a]	
	Low risk of bias	High risk of bias	High risk of bias	Association	Level of evidence
Hyperintensity absence		−[20,52,63,77,203,216,231]		Yes	Moderate
Number injured muscles	+[213]	=[77]		Unknown	Conflicting
Location					
Muscle injured		=[51,63,216]	+[52,203]	No	Moderate
Distance to origin	+[213]	+[15,20], =[17,216]		Unknown	Conflicting
Proximal free tendon involvement		+[15,20]		Yes	Moderate
Central tendon disruption		+[51]		Yes	Limited
Musculotendinous junction involvement		−[52,203]		Yes	Limited
Hyperintensity extent					
Longitudinal length	+[213]	+[20,77], =[15,17]	+[52,203]	Unknown	Conflicting
Cross-sectional area	=[213]	+[15,52,77,203,216], =[17]		Unknown	Conflicting
Volume		+[15,216], =[17]		Unknown	Conflicting
Antero-posterior (depth)		+[15], =[17]		Unknown	Conflicting
Medio-lateral (width)		=[15], =[17]		No	Moderate
Fluid collection					
Intramuscular		=[52,203]		No	Limited
Extramuscular		=[52,203,216]		No	Moderate
Grading					
Grade 0-3		+[63]		Yes	Limited
Grade 1 vs grade 2		=[63]		No	Limited

−, Association with shorter time to return to play (negative association); +, Association with longer time to return to play (positive association); =, No association with time to return to play.
a. The studies of Connell et al.[52] and Schneider- Kolsky et al.[203] used the same dataset and are therefore considered as one study in the best evidence synthesis.
Abbreviations: MRI, magnetic resonance imaging.

Grading

Grading was studied in one report[63], using the following classification: grade 0) negative MRI without any visible pathology, grade 1): hyperintensity on fluid sensitive sequences without evidence of a macroscopic tear, grade 2): hyperintensity on fluid sensitive sequences with a partial tear, grade 3): total muscle or tendon rupture. Pairwise comparison showed that there was a significant difference in time to RTP between the grades of injury ($p<0.001$), except between grade 1 and 2 injuries ($p=0.053$). This implies that there is limited evidence for an association with the time to RTP and a grading that differenti-

ates between: i) MRI negative injuries, ii) MRI positive injuries without a total muscle or tendon rupture, and iii) injuries with a total muscle or tendon rupture.

DISCUSSION

The major findings of our systematic review are that there is moderate evidence that the absence of any hyperintensity on fluid sensitive sequences is associated with a shorter time to RTP and that proximal free tendon involvement is associated with a longer time to RTP. There is currently no strong evidence for any MRI finding that can guide sports physicians and radiologists in predicting the prognosis for the time to RTP after an acute hamstring injury, as only one of the twelve studies included had a low risk of bias.

In the current clinical setting MRI is considered as a valuable tool in athletes with hamstring injuries and there are high demands from the athletes and their medical staff to provide a prognosis on recovery time based on the MRI findings. However, our review shows that the sports physicians and radiologist cannot satisfy these high expectations from an evidence based point of view.

Return to play

The definition for RTP differed in the included studies: return to competition[51,52,203,216,231], return to full team training[77], full training participation and availability for match selection[20,63], performing at a pre-injury level[15,17] and completion of rehabilitation[213] These different definitions for time to RTP complicate comparison of the studies.

RTP is generally accepted as the primary outcome measure for acute muscle injuries, as it is the most clinically relevant outcome in athletes with these injuries[103,193]. However, there are still no validated objective criteria to guide progression through rehabilitation protocols and assess readiness for RTP. Decision making for progression through rehabilitation protocols and clearance for RTP are therefore substantially affected by subjective judgments of athletes and medical staff involved. In the absence of well-defined RTP criteria, knowledge about the results of the MRI findings introduces a major potential source of bias. We therefore considered adequately measured time to RTP, by clearly defined RTP criteria and blinding of subjects and clinicians involved in the rehabilitation or RTP decisions, compulsory for a low risk of biased results (domain 4 of the risk of bias assessment tool). Only two of the studies included reported blinding of the subjects and managing clinicians for the prognostic MRI findings studied[213,216].

Confounding factors

The type of sport or injury mechanism, whether it was a new or recurrent injury and the treatment/rehabilitation protocol were considered to be important potential confound-

ers in the prognostic value of MRI findings for time to RTP that should be appropriately accounted for in the analysis or study design to sufficiently limit potential biased results (domain 5 of the risk of bias assessment tool).

Askling et al. reported more extensive MRI abnormalities and shorter time to RTP in sprinting athletes compared to stretch type injuries in dancers[15,17]. As this difference between sprinters and dancers may be caused by the type of sport or the injury mechanism, we considered the potential bias of this confounder sufficiently limited if either the type of sports or the injury mechanism was accounted for.

Re-injuries are a potential confounder, because they are associated with both more extensive MRI abnormalities and a longer time to RTP[125]. To prevent confounding the treatment/ the rehabilitation protocol should be the same in all studied subjects or appropriately accounted for in the analysis.

In four of the studies these important potential confounders were appropriately accounted for[15,17,20,216].

Reliability of MRI measures

Only one study presented any information on the reliability of the performed MRI measures: Comin et al. reported 100% agreement between the two radiologists on the presence or absence of central tendon disruption[51]. None of the other studies included provided or referred to any information on reliability of the MRI measures and methods, introducing a risk of misclassification bias.

Limitations

We performed a qualitative analysis (best evidence synthesis) instead of a quantitative analysis (meta-analysis of the data), because of the heterogeneity of the studies with regard to the MRI findings, reported outcome measures and methodological quality. This systematic review does not provide a quantitative synthesis on the strength or magnitude of the associations of the MRI findings with RTP, but is limited to whether there is evidence for a statistical significant association or not. This limits the interpretation of the magnitude and clinical relevance of the reported associations. If we for example consider the difference between MRI negative and positive injuries, studies reported a wide range of days to RTP: 6(±3) versus 23(±11)[20], 7 (interquartile range, 7-14) versus 21 (interquartile range, 4-56)[52,203], 8(±3) versus 20(±14)[63], 7(±8) versus 20(±52)[77] and 16 versus 27[231] for MRI negative versus MRI positive injuries respectively. One study reported gamma statistics, a measure of rank correlation, with a correlation coefficient of 0.69 between MRI positive injuries and time to RTP. Although these different outcome measures cannot be appropriately pooled, a general overview of these numbers and their variability measures indicate that a MRI negative injury may take several days up to weeks and MRI positive injuries may take several days up to months to return to play.

For systematic reviews on prognostic findings there is currently no standardized risk of bias assessment method and there are no generally accepted limits to determine whether a study has a high or low risk of bias. Instead, it is recommended that risk of bias criteria for prognostic studies should be applied on the basis of the relevance to the research question[101]. We used risk of bias criteria, which we thought the most appropriate for studies on the prognostic value of MRI findings in acute hamstring injuries. With this approach we aimed to perform a best available systematic risk of bias analysis.

The sample size of some of the studies included might have been insufficient to show statistical significance of clinically important associations, potentially introducing a type II error. The sample sizes of studies reporting no significant association on the number of muscles involved, distance to the muscle origin, and the hyperintensity extent measures varied between 12 to 31[15,17,77,213,216], and are therefore unable to detect weak to moderate associations[24]. When the sample size is large enough to show statistical significance the outcome of the best evidence synthesis could change from conflicting evidence to moderate evidence. On the other hand, large sample sizes can lead to statistical significant, but clinically irrelevant associations.

The majority of prognostic MRI findings are analysed with simple univariate statistical approaches, with only one of the studies using multivariate statistical analysis[203,231]. In absence of multivariate analysis it remains unknown to what extent the MRI findings are independently associated with the time to RTP. This is because the majority can be expected to be related to each other, for example larger longitudinal length is likely to have a larger volume.

Future directions

This systematic review showed a lack of high quality studies on the prognostic value of MRI in acute hamstring injuries. Common methodological limitations are the low number of participants, insufficient information about losses to follow-up, lack of blinding of subjects and clinicians to the MRI results, insufficient accounting for potential confounders, lack of information on the reliability of MRI measures used, and the use of simple univariate statistical analysis. Future studies should account for these methodological flaws.

The use of different definitions for time to RTP, as an outcome measure, limits the comparability of the studies. Consensus on the definition of RTP is required to improve the comparability of studies using RTP as an outcome measure.

CONCLUSION

There is currently no strong evidence for any MRI finding that can guide sports physicians and radiologists in predicting prognosis for the time to RTP after an acute hamstring injury, as only one of the twelve studies included had a low risk of bias. There is only moderate evidence that injuries without hyperintensity on fluid sensitive sequences are associated with a shorter time to RTP and that injuries involving the proximal free tendon are associated with a longer time to RTP. Limited evidence was found for an association between central tendon disruption, injury not affecting the musculotendinous junction and total hamstring ruptures with a longer time to RTP. The other MRI findings studied showed either no association with time to RTP or there was conflicting evidence.

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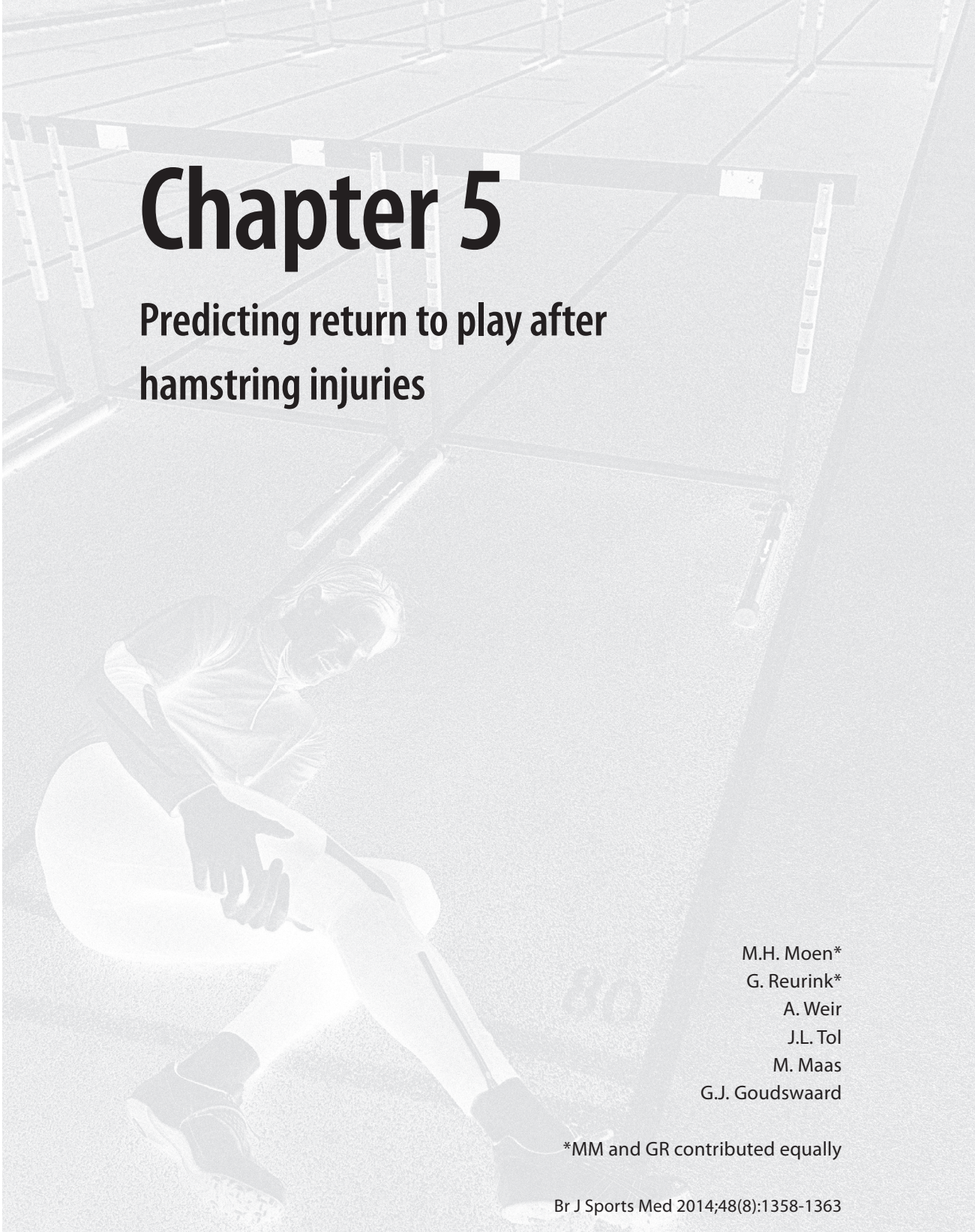
Chapter 5

Predicting return to play after hamstring injuries



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ABSTRACT

Background – Previous studies on the prognostic value of clinical and MRI parameters for the time to return to play (TTRTP) in acute hamstring injuries showed only limited to moderate evidence for the various investigated parameters. Some studies had multiple methodological limitations, including retrospective designs and the use of univariate analysis only. The aim of this study was to assess the prognostic value of clinical and MRI parameters for TTRTP using multivariate analysis.

Methods – Twenty-eight clinical and MRI parameters were prospectively investigated for an association with TTRTP in 80 non-professional athletes with MRI positive hamstring injuries undergoing a standardized rehabilitation program. The association between possible prognostic parameters and TTRTP was assessed with a multivariate linear regression model. Parameters that had a p-value < 0.2 on univariate testing were included in this model.

Results – 74 athletes were available for analysis. A total of 9 variables met the criteria for the multivariate analysis: intensity of sports, level of sports, self-predicted TTRTP by the athlete, length of discomfort on palpation, deficit in passive straight leg raise, pain score on isometric knee flexion, isometric knee flexion strength deficit and distance of the proximal pole of the MRI hyperintensity to the tuber ischiadicum. Of these, only self-predicted TTRTP by the athlete and a passive straight leg raise deficit remained significantly associated with TTRTP after stepwise logistic regression.

Conclusion – The clinical parameters self-predicted TTRTP and passive straight leg raise deficit are independently associated with the TTRTP. MRI parameters in grade 1 and 2 hamstring injuries, as described in the literature, are not associated with TTRTP. For clinical practice, prognosis of the TTRTP in these injuries should better be based on clinical parameters.

INTRODUCTION

After acute hamstring injury, the primary question of the athlete, medical and coaching staff is how long it will take to return to play. The large variation of 1 day[61] to 104 weeks[18]in time needed to return to play (TTRTP) makes estimating the prognosis a challenge. Few studies evaluated the prognostic value of findings on clinical assessment for the TTRTP, showing limited evidence that a visual analogue pain score of the injury,[231] time taken to walk pain free[238] and stretching mechanism of injury are associated with the TTRTP.

A substantial number of studies have identified possible prognostic MRI parameters.[11,15,17,20,51,52,63,77,203,213,216,231] There is only limited to moderate evidence for an association of a hyperintensive signal on T2-weighted images, involvement of the proximal or central tendon, injury not affecting the musculotendinous junction and a total rupture with a longer TTRTP[11,15,17,20,51,52,63,77,203,213,216,231]

Methodological limitations of some of these studies are the relative low number of subjects, retrospective study designs, lack of blinding and the use of simplistic univariate statistical analysis. As none of the studies used multivariate analysis in which both clinical and MRI findings were analysed, it remains therefore unknown to what extent MRI findings are independently associated with the TTRTP and complementary to clinical predictors. Additionally, in none of the studies both athletes and decision makers for return to play were blinded for the clinical or MRI assessment, introducing a substantial risk of bias.

Therefore, the aim of this study was to assess the prognostic value of clinical and MRI parameters for the TTRTP after acute hamstring injury. For this objective, a prospective design, multivariate analysis and blinding of both athletes and decision makers for return to play were ensured.

METHODS

Subjects

The athletes in this study took part in a previously published multicentre randomized controlled trial on the effect of platelet rich plasma in hamstring injuries (Dutch trial register number 2771). This trial started in and was conducted between February 2011 and May 2013 at the sports medicine departments of a general district hospital, a university hospital and at the FIFA medical centre of excellence of the national football association in the Netherlands. In this study, athletes were randomized into an intervention group or a control group. The intervention group received two injections of 3 ml platelet-rich plasma (Autologous Conditioned Plasma, Biocore, Arthrex Inc, Karlsfeld, Germany) and

the control group received two injections of 3 ml saline at the site of the injury. The first injection was performed within five days of the injury and the second injection five to seven days later. Injections were performed using a sterile ultrasound guided technique into the region of maximal muscle injury determined by MRI. All athletes completed a standardized physiotherapy programme, including range of motion exercises, progressive strength exercises, core stability training and agility exercises.[103,208] The exercises were all supervised by a specially instructed sports physiotherapist. There were no differences between the intervention and the control group on the primary outcome measure TTRTP.

All athletes provided written informed consent prior to the start of the study. Approval was obtained from the Regional Ethical Committee of South West Holland.

Eligibility criteria

Athletes were included if they met the following criteria: age of 18 to 50 years; a clinical diagnosis of an acute hamstring injury defined as: a history of acute posterior thigh pain within the past five days, localized discomfort on palpation, localized pain on passive stretching of the hamstrings and increased pain on isometric contraction of the hamstring; a visible hamstring lesion on magnetic resonance imaging (MRI) (within 5 days of injury), defined as an increased signal on fluid sensitive sequences.

Athletes were excluded if they were not capable of performing an active exercise program; if they had already received an injection for the injury; if they had no intention to return to full sports activity; if they did not want to receive one of the two therapies in the trial; if the cause of the injury was an extrinsic trauma (contusion injury); if they had chronic hamstring complaints, defined as recurrent tenderness of the hamstring muscles in the previous 2 months; if they had chronic low back pain; if they had a contraindication for MRI; or if there was a total rupture and/or avulsion seen on MRI.

Baseline assessment

All baseline assessments were performed at the same day within 5 days of the occurrence of the injury and before any injections were given.

Questionnaire

Patient characteristics, level and intensity of sports participation, information on history of previous hamstring injuries, history of anterior cruciate ligament surgery using a hamstring graft, the injury mechanism, the ability to walk pain free within one day and the self-predicted days to RTP indicated by the patient were obtained using a structured questionnaire.

Clinical examination

Manual muscle palpation

With the patient in a prone position the complete posterior thigh was carefully palpated from the hamstring origin at the ischial tuberosity to the insertions medial at the pes anserinus and lateral at the head of the fibula. The total longitudinal length of the discomfort area, the distance between the proximal border of the discomfort area on palpation of the hamstrings and the ischial tuberosity and the distance between the point of maximal discomfort on palpation and the ischial tuberosity were recorded.

Hamstring flexibility testing

Hamstring flexibility was assessed with the active knee extension test[140,189] and the passive straight leg raise test[22]. Athletes were tested in a supine position with an inclinometer placed on the anterior border of the tibia. For the active knee extension test positioned the hip of the tested leg in 90° flexion and were instructed to extend the knee until maximal tolerable stretch, with the contralateral leg remaining flat on the examination table. At the endpoint of maximal tolerable stretch, the absolute knee angle was measured. For the passive knee extension test athletes were instructed to completely relax the leg, while the researcher lifted the leg with the knee in full extension until maximal tolerable stretch, with the contralateral leg remaining flat on the examination table. At the endpoint of maximal tolerable stretch, the angle between the leg and the horizontal was measured. For both tests the absolute flexibility deficit was calculated by subtracting the recorded angle of the injured leg from the uninjured leg. Additionally athletes were asked whether they experienced normal stretch or localized pain during the tests.

Isometric knee flexion force

Isometric knee flexion force was measured using handheld dynamometry[128]. were tested in a prone position with the knee in 15° of knee flexion. The researcher placed the dynamometer at the heel of the subject and applied force to the heel, gradually increasing in 3-5 seconds. Athletes were instructed to resist the force applied by the researcher (brake test). At the point that the subject could not resist the force anymore the test was terminated and the dynamometer was read out. Each leg was tested 3 times. For each angle the highest force value was recorded. The relative strength deficit was calculated by dividing the recorded maximal force value of the injured leg by maximal force value of the uninjured leg. Additionally athletes were asked to whether they experienced localized pain during the test.

MRI assessment

The used protocol was a modified version of the protocol described by Askling et al.[15]. To locate the area of the injury the entire hamstring of the injured limb was visualized by obtaining coronal and sagittal short tau inversion recovery (STIR) images from the ischial origin of the hamstring muscles to the insertion on the fibula and the tibia (repetition time/echo time (TR/TE) of 3500/31 ms, field of view (FOV) of 300 mm and a 256x320 matrix). The uninjured leg was not depicted. Subsequently, transversal STIR (repetition time/echo time (TR/TE) of 3500/31 ms, field of view (FOV) of 300 mm and a 205x256 matrix), T1-weighted (TR/TE of 500/12 ms, FOV of 300 mm and a 355x448 matrix) and T2-weighted (TR/TE of 4080/128 ms, FOV of 300 mm and a 355x448 matrix) images were obtained from the injured area. The thickness of the slices for all sequences was 5mm. MR images were obtained with a 1.5-T magnet system (Magnetom Essenza, Siemens) with the use of a body matrix coil.

Each MRI was assessed by one radiologist, specialized in musculoskeletal radiology, who was blinded for all information except that there was a clinical diagnosis of a hamstring injury. For assessment of the MRIs we used standardised scoring forms based on the literature.[15,52,63,96,216] We recorded the involved muscle(s) and performed grading of the injury using the three-graded classification of Hancock et al.:[96] grade 1): increased signal intensity on fluid sensitive sequences without evidence of a macroscopic tear, grade 2): increased signal intensity on fluid sensitive sequences with a partial tear, grade 3): total muscle or tendon rupture. When no abnormalities were found, we regarded this as a grade 0 injury. We measured the increased T2 signal intensity for the affected hamstring muscle in cranio-caudal, transverse and anterior-posterior dimensions on the fluid sensitive sequences (STIR). Increased signal intensity was defined as an abnormal intramuscular increased signal compared to the unaffected surrounding muscle tissue. We recorded the longitudinal length (cranio-caudal) and calculated the involved cross sectional area as a percentage of the total muscle cross sectional area in the transversal plane and the total volume using the formula of a prolate ellipsoid ($4/3\pi$ x length x width x depth). We measured the distance of the most cranial pole of the intramuscular increased signal intensity to the distal tip of the ischial tuberosity and recorded whether there was extramuscular fluid present. Good to excellent inter- and intra-observer reliability was found for the used MRI parameters in a previous study.[36]

Outcome measure

The outcome was the time to return to play (TTRTP), defined as the number of days between injury and return to unrestricted sports activity in training and/or match play.[73] On a daily basis the athletes performed a progressive phased, criteria-based rehabilitation program, which was based on the best available evidence[103,208]. Patients were instructed to contact the coordinating researcher at the moment of return to unrestricted sports

activity. The definite clearance for RTP was given by the supervising physiotherapist once the patient completed the rehabilitation program including unrestricted functional sport specific testing. Both the athletes and the supervising physiotherapists were blinded to the clinical and MRI parameters assessed at baseline. We contacted athletes that did not return to play yet at 1, 3, 4, 8, 10, 16 and 26 weeks after inclusion to assess TTRTP. Athletes that sustained another non-hamstring injury before RTP were excluded from the analysis.

Statistical analysis

We performed statistical analyses with SPSS software (version 20.0; SPSS, Chicago, Illinois). We analyzed baseline patient characteristics using descriptive statistics. If the data was normally distributed continuous variables were presented as a mean with a standard deviation (SD), otherwise a median and inter quartile range (IQR) are used.

We analysed the association between the possible predictive variables measured at baseline and the TTRTP with a linear regression model. Variables that had a p-value < 0.2 on univariate testing were included in a multivariate backward linear regression model. We used a probability of F for removal of 0.10. We calculated adjusted regression coefficients (β-coefficients) and 95% confidence intervals (CIs) for the included predictive variables. Finally, the total variance of these predictive variables for TTRTP explained by the model was calculated.

RESULTS

Study patients and follow-up

Between February 2011 and November 2012 80 patients were included. Five patients did not achieve RTP within the study period and were excluded from the analysis: four patients sustained another non-hamstring injury before RTP, 1 patient did not manage to RTP because of ongoing posterior thigh complaints. There was one subject with a time to RTP of 149 days that was considered an outlier and was therefore excluded from the analysis (Figure 5.1). Of the 74 patients included in the analysis the sports played were football (n=55, 74%), field hockey (n=12, 16%), track and field athletics (n=4, 5%), fitness (n=1,1%), American football (n=1, 1%) and tennis (n=1, 1%). The majority of the athletes had a non-professional, competitive level (74%), the other athletes competed recreationally. The median time between injury and baseline assessment was 3 days (IQR, 2-4). Other baseline characteristics are presented in Table 5.1. The mean time to RTP was 44 days (±18).

Association of clinical and MRI assessment with TTRTP

The association of the baseline assessment with the TTRTP analysed with univariate linear regression model is presented in Table 5.1. There were 9 variables with a p-value < 0.2 that were included in the multivariate analysis: intensity of sports, level of sports, self-predicted TTRTP by the athlete, length of discomfort on palpation, passive straight

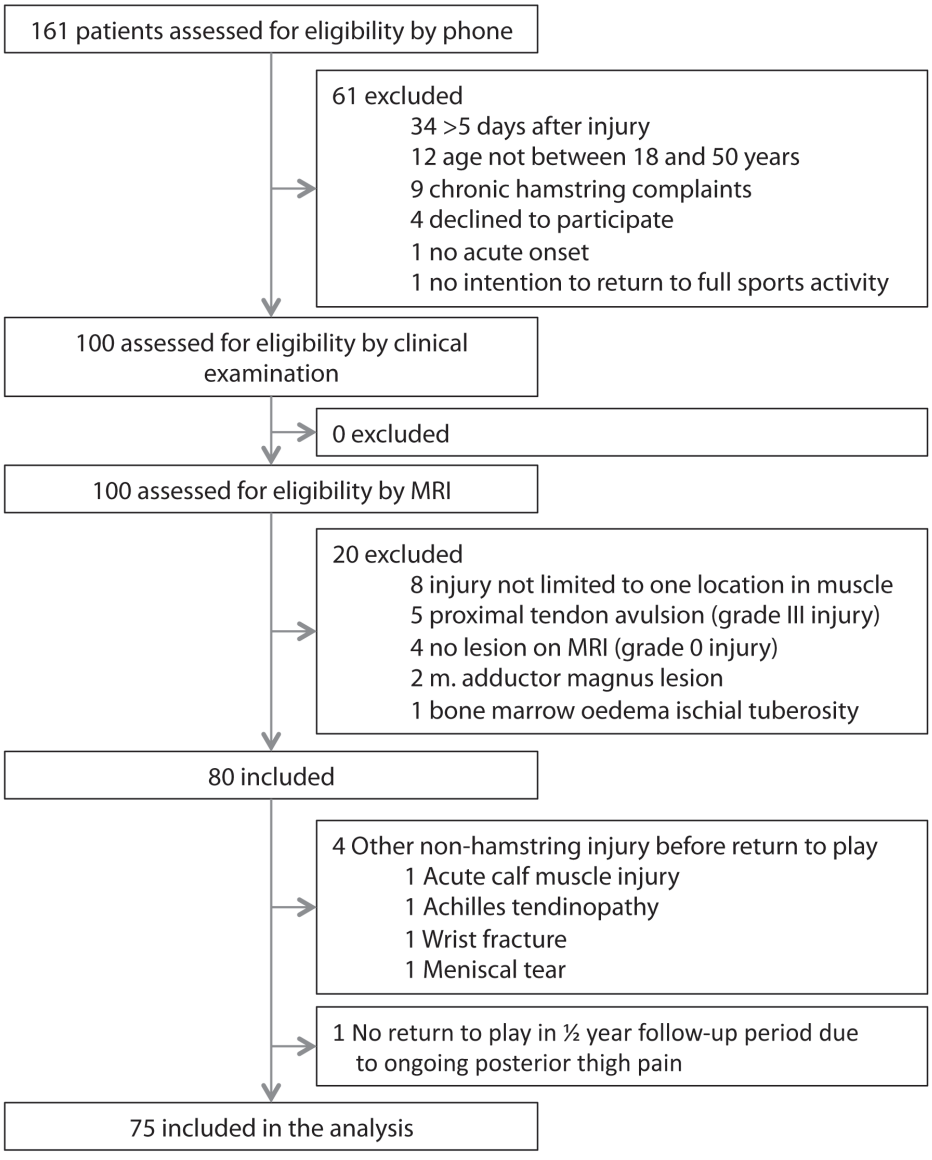


Figure 5.1 Patient flow diagram

leg raise deficit, isometric knee flexion strength testing pain score, isometric knee flexion strength testing force deficit, distance of proximal pole of the hyperintensity seen on MRI.

After backward regression three variables were included in the model, of which two were independently statistically significant associated with the TTRTP (Table 5.2): the deficit in passive straight leg raise in degrees (β-coefficient 0.70; 95% CI, 0.13 to 1.27; p=0.017) and the self-predicted TTRTP indicated by the patient in days (β-coefficient 0.36; 95% CI, 0.01 to 0.71; p=0.045). The variance in TTRTP explained by the model was 20% (R^2 = 0.20).

DISCUSSION

This prospective study on acute hamstring injury revealed after multivariate analysis that only athletes' self-predicted TTRTP and passive straight leg raise deficit were independently associated with TTRTP. None of the MRI parameters were independently associated with the TTRTP. Our findings reflect the value of clinical parameters.

Clinical parameters

Most of the previous studies on the value of clinical predictive parameters used univariate analysis. In absence of multivariate analysis it remains unknown to what extent the predictive parameters are independently associated with the time to RTP, as the majority can be expected to be mutual correlated. To assess the different clinical parameters independently, we used multivariate analysis.

Due to the limited number of studies examining clinical parameters for their prognostic value, the possibility to compare our results with findings in the literature is limited. The value of self-predicted TTRTP was assessed in one study, although unpublished[12]. 18 athletes (sprinters) self-estimated the time to be back at pre-injury level. The self-predicted time to return at pre-injury level was 4 weeks (median, range 2-12), while the actual time to return was significantly longer (median 16 weeks, range 6-50). However, no measure of association between self-predicted time to be back at pre-injury level and TTRTP was reported. Our study found a significant association between self-predicted TTRTP and reported TTRTP. A possible explanation might be that over 60% of the athletes had a previous hamstring injury. This previous experience might be used by the athlete as reference standard, possibly leading to bias.

Additionally, a previous study showed that the predicted TTRTP by a sports physician based on clinical examination was as good as predicting TTRTP with MRI, providing more leverage for clinically assessing TTRTP.[203] Contrary to the two previous studies, we found that passive straight leg raise deficit was significantly associated with TTRTP[21,238]. Warren

Table 5.1 Baseline assessment and their association with time to return to play in univariate analysis.

	Baseline measure*	β-coefficient (95% CI)	p-value	Trend TTRTP prognosis
Questionnaire				
Age, years	29 (±7)	.14 (-.44 to .73)	.622	X
Intensity of sport				
< 3 times per week (reference)	**15 (20%)**			
≥ 3 times per week	**59 (80%)**	**-7 (-18 to 3)**	**.177**	↓
Level of Sports				
Recreational (reference)	**19 (26%)**			
Competitive	**55 (74%)**	**-8 (-17 to 2)**	**.099**	↓
Mechanism of injury				
Stretching (reference)	6 (8%)			
No stretching	68 (92%)	-5 (-21 to 10)	.520	X
Mechanism of injury				
Sprinting (reference)	54 (73%)			
No sprinting	20 (27%)	4 (-5 to 14)	.379	X
Previous hamstring injury				
No (reference)	29 (39%)			
Yes	45 (61%)	-3 (-12 to 6)	.473	X
Previous ipsilateral hamstring injury				
No (reference)	36 (49%)			
Yes	38 (51%)	-1 (-9 to 8)	.901	X
Hamstring injury within previous year				
No (reference)	51 (69%)			
Yes	23 (31%)	3 (-6 to 12)	.533	X
Ipsilateral hamstring injury within previous year				
No (reference)	54 (73%)			
Yes	20 (27%)	2 (-7 to 12)	.632	X
Previous ipsilateral hamstring ACL-graft harvesting				
No (reference)	60 (81%)			
Yes	14 (19%)	-3 (-14 to 7)	.487	X
Time to walk pain-free				
≤1 day (reference)	8 (11%)			
> 1 day	66 (89%)	3 (-11 to 16)	.713	X
Self-predicted time to RTP indicated by the patient	**32 (±12)**	**.51 (.16 to .86)**	**.005**	↑
Clinical examination				
Length of discomfort on palpation, cm	**11.9 (±6.8)**	**.60 (-.01 to 1.21)**	**.053**	↑
Distance proximal border of discomfort area to ischial tuberosity, cm	**15.5 (±7.2)**	**-.53 (-1.11 to 0.05)**	**.072**	↓

Table 5.1 (continued)

	Baseline measure*	β-coefficient (95% CI)	p-value	Trend TTRTP prognosis
Distance maximal discomfort palpation to ischial tuberosity, cm	19.8 (±6.8)	-.36 (-1.01 to .28)	.265	X
Pain on active knee extension test				
Negative (reference)	14 (19%)			
Positive	60 (81%)	0 (-10 to 11)	.934	X
Active knee extension deficit, degrees	11 (±13)	-.02 (-.30 to .34)	.914	X
Pain on passive straight leg raise				
Negative (reference)	37 (50%)			
Positive	37 (50%)	-2 (-11 to 6)	.574	X
Passive straight leg raise deficit, degrees	**4 (±7)**	**.86 (.29 to 1.42)**	**.003**	↑
Isometric knee flexion strength testing: pain score	**4.4 (±2.5)**	**1.63 (-.04 to 3.29)**	**.055**	↑
Isometric knee flexion strength testing: force deficit	**28 (±25)**	**.19 (.03 to .36)**	**.025**	↑
MRI characteristics				
Grading				
Grade I (reference)	19 (26%)			
Grade II	55 (74%)	3 (-7 to 13)	.544	X
Injured muscle				
Lateral/BF (reference)	65 (88%)			
Medial/ST or SM	9 (12%)	-1 (-14 to 12)	.827	X
Cross sectional area, % of total muscle	37 (±28)	.05 (-.11 to .20)	.545	X
Longitudinal length, cm	11.6 (±5.9)	-.14 (-.86 to .59)	.704	X
Distance from tuber, cm	**15.2 (±7.8)**	**-.58 (-1.2 to .06)**	**.075**	↓
Volume	317 (±409)	.00 (-.01 to .01)	.666	X
Extramuscular fluid				
No (reference)	14 (19%)			
Yes	60 (81%)	-1 (-12 to 10)	.899	X

*For continuous variables data is presented in mean (± standard deviation) and for categorical variables the number (%) of athletes within each category.

Abbreviations: ACL, anterior cruciate ligament; RTP, return to play; TTRTP, time to return to play; MRI, magnetic resonance imaging; BF, biceps femoris; ST, semitendinosus, SM, semimembranosus. ↑ = trending towards a longer time to RTP; ↓ = trending towards a shorter time to RRP; X = not associated with a trend in time to RTP (p>0.2).

Table 5.2 Multivariate analysis.

	Adjusted β-coefficient (95% CI)	p-value
Passive straight leg raise deficit, degrees	.70 (.13 to 1.27)	.017
Self-predicted time to RTP indicated by the patient	.36 (.01 to .71)	.045
Level of Sports		
Recreational (reference)		
Competitive	-8 (-17 to 1)	.081

Abbreviations: RTP, return to play.

et al., not finding such an association, investigated 59 Australian Football players with an acute hamstring injury and used stepwise logistic regression. Possibly, the different findings of Warren et al. are due to methodological differences. Warren et al. assessed a deficit in passive straight leg raise dichotomously (≤ 10 degrees and > 10 degrees), while we scored continuously[238]. Additionally, our study included athletes with an MRI positive, while Warren et al. included clinically positive injuries. Askling et al. reported no statistical significant association between a deficit in passive straight leg raise and TTRTP in 18 elite sprinters and 15 professional dancers[21]. The absence of association might potentially be caused by the relative low sample size.

Several other clinical parameters were reported in the literature to be associated with TTRTP. The significant associated parameters reported were: time to walk pain free[238], active knee extension deficit > 10 degrees, discomfort on hamstring palpation localized more cranial to the tuber ischii[15,20], stretching type hamstring injury[20,21] and maximum pain experienced with the injury[231]. But in these studies usually the sample size was small, outcome assessors were not blinded for the studied prognostic parameter and / or no multivariate analysis was used[15,20,21,140,231]. The reported association was not confirmed in our cohort.

Overall the estimated TTRTP and deficit in passive straight leg raise explained only 20% of the total explained variance. To describe the clinical relevance of our findings an example for clinical practise is provided below.

The mean TTRTP for the group was 44 ± 18 days, indicating that approximately 95% of the athletes returned to play between a range of 8 and 80 days (mean ± 2 times the standard deviation). With the self-predicted and passive straight leg raise deficit we could only narrow the range down slightly. For an athlete, with a self-estimated TTRTP of 42 days and a passive straight leg raise deficit of 10 degrees the 95% CI for the estimated TTRTP by the model is 16 to 83 days, instead of 8-80 days. This wide confidence interval implies that future studies are needed to reveal additional prognostic parameters to increase the percentage of the explained variance.

MRI parameters

In this study both patients and decisions makers for RTP were blinded for the MRI results, thus keeping the risk of bias low. In other studies on the prognostic value of MRI parameters in acute hamstring injuries, this blinding was not ensured or not described. Multiple studies have investigated the association between one or more MRI parameters in acute hamstring injuries and TTRTP[11,15,17,20,51,52,63,77,213,216,231] with correlation coefficients ranging from 0.39-0.74 to assess the extent of the injury. In these studies, blinding of the patients and decision makers for RTP, blinding was not ensured or not described.

None of these studies used a multivariate analysis and therefore it remains unknown to what extent the MRI parameters have any prognostic value additional to the parameters obtained by clinical evaluation. The findings of our study suggest that the prognostic capacity of an MRI scan for acute hamstrings injuries might not be so strong as previously stated in the literature. In the present study none of the MRI parameters were significantly associated with TTRTP after multivariate analysis.

We have to emphasize that in our study no hamstrings were included that showed no abnormalities (grade 0) on MRI. Also, we excluded total hamstring ruptures (grade 3). Therefore, only grade 1 and 2 lesions were included[96]. Ekstrand et al. found that grade 0 lesions had a shorter TTRTP than grade 1 and 2 lesions[63]. They also found that grade 1 and 2 lesions were the most common grades of injury (respectively 57% and 27% of the total hamstring injuries). In addition, they found that grade 3 lesions displayed the longest TTRTP. Due to the nature of our inclusion criteria (MRI positive hamstring injuries (grade 1 and 2) and exclusion of total ruptures (grade 3)), no comparison with the grade 0 and grade 3 injuries from the Ekstrand et al. study was possible[63].

When comparing our results with findings in the literature Hallen and Ekstrand, in the large Union of European Football Associations (UEFA) and Champions League study, did find a difference in TTRTP between grade 1 and grade 2 injuries on MRI (median 15 days for grade 1 injuries (IQR 14 days) and median 21 days for grade 2 injuries (IQR 19 days); $p<0.0001$),[86]. This difference can possibly be explained by difference in the study population (professional versus non-professional), the number of subjects and the statistical analysis used in the studies.

Unfortunately, no comparison between the prognostic value of the involvement of the free proximal tendon, was possible. In two studies, that investigated the prognostic value of the involvement of the proximal free tendon, comparison with the uninjured leg was used[15,17]. Our limitation is that we only depicted the injured leg, which excluded direct comparison. For the future, the association of involvement of the free proximal tendon and TTRTP should be investigated more extensively. Possibly, new MRI techniques, such as 3 Tesla scans might enhance the prognostic value of MRI scans.

Strength of the study

This study has several strengths. Firstly, the size of the athletic population was quite large and the design of the study was prospective. Secondly, multivariate linear regression was used to examine the possible prognostic parameters for their independent association. Furthermore, treatment of the athletes was not influenced by the baseline characteristics, since treatment was allocated randomly. In addition, the decision maker for TTRTP was blinded to the baseline characteristics, including MRI .

Limitations

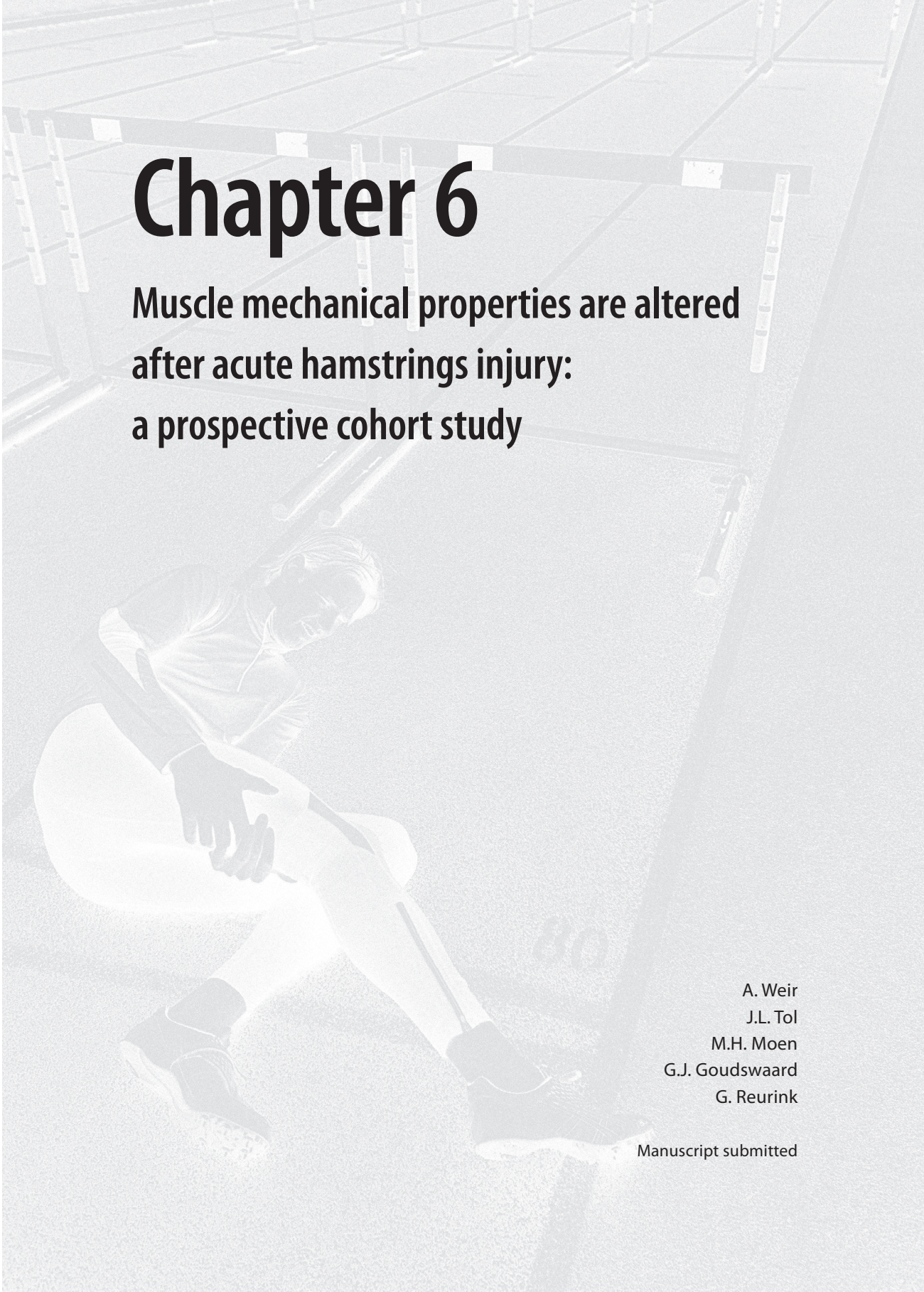
Although 74 athletes were included in this study, there could be a lack of power to detect weak associations with TTRTP. Because no professional athletes were included in the study, caution has to be taken in generalizing the results of this study to a professional athletic population. As no grade 0 and grade 3 injuries were included in this study, no comparison with other studies that looked at the association of the different grades of injury of the hamstring and our study was possible.

CONCLUSION

The clinical parameters self-predicted TTRTP and passive straight leg raise deficit are independently associated with the TTRTP. MRI parameters in grade 1 and 2 hamstring injuries, as described in the literature, are not associated with TTRTP. For clinical practice, prognosis of the TTRTP in these injuries should better be based on clinical parameters.

Chapter 6

Muscle mechanical properties are altered after acute hamstrings injury: a prospective cohort study



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ABSTRACT

Background/aim – It is common practice to examine injured muscles using palpation to assess mechanical properties like stiffness and tone. The effect of acute muscle injury on these muscle properties has never been examined. The aim of the study was to investigate the time course of changes in muscle mechanical properties after acute hamstrings injury.

Methods – Twenty five athletes with acute injuries to the biceps femoris muscle, confirmed on clinical examination and MRI, both performed within five days of the injury were included. They were examined by a single observer who measured the range of motion, strength, and the muscle mechanical properties: stiffness (N/m), tension (Hz) and elasticity using a myometer. Athletes were examined at inclusion, after one week, at return to play and after 26 weeks.

Results – The majority were competitive athletes (20/25) who played football (14/25) with a mean age of 30 (SD7) years. Most of the injuries were due to sprinting (18/25). Five were grade 1 (only increased signal on MRI but no tear) and 20 grade 2 (partial tear) injuries. At initial examination the muscle stiffness and tension were reduced in the injured leg and this normalized at return to play and remained so at 26 weeks. The muscle elasticity was not found to be different at any time.

Conclusions – The stiffness and tension, but not the elasticity, of the biceps femoris muscle are significantly reduced after acute injury. There are no significant differences remaining between the injured and uninjured leg at the time of return to play.

INTRODUCTION

Muscle injuries are common in sports especially football, track and field and Australian rules football[8,62,170]. A professional football team can be expected to have around 15 muscle injuries in a single season[62] and muscle injuries account for one third of all time lost due to injuries in football. The hamstring muscle is the most commonly injured muscle in sport.

Systematic reviews have highlighted that there is a paucity of good quality evidence to help guide the management of acute hamstrings injuries despite their high incidence[143,194]. Once an athlete sustains an acute hamstring injury the diagnosis is usually made using clinical examination involving palpation together with stretching and strength testing of the hamstrings muscles[121]. When palpating muscles the examiner feels for the location, extent and severity of the pain. Along with pain the muscle mechanical properties, such as stiffness or tone[119], can be palpated. Traditionally it has been difficult to quantify muscle mechanical properties in a reliable manner using palpation alone. Recent advances in technology have meant that muscle mechanical properties can be measured using muscle myometers. This gives the opportunity to reliably measure muscle mechanical properties in a research setting[4,31]. These devices have not been widely used in the clinical setting and the meaning of the measurements has not yet been studied in detail. Before these devices can be used in a clinical setting, observational and normal data are needed to be able to interpret the findings in a meaningful way.

The aim of this study was to observe if there was a measurable change in muscle mechanical properties over time after acute hamstrings injury, and if these normalized after rehabilitation.

METHODS

Study design

The design was a prospective cohort study. The patients in this study were part of a cohort of a double blind randomised controlled trial (RCT) on the effect of platelet rich plasma in hamstring injuries: Dutch trial register number 2771[188]. The local ethics committees gave permission for the study and all patients provided written informed consent. This multicentre RCT started in February 2011 and was performed at the sports medicine departments of a large general district hospital, a university hospital and the medical centre of the national football association. In this study subjects were randomized into a control group or an intervention group. The intervention group received two injections of 3 ml platelet-rich plasma (Autologous Conditioned Plasma, Biocore,

ArthrexInc, Karlsfeld, Germany) and the control group received two injections of 3 ml saline at the site of the injury. The first injection was performed within 5 days of the injury and the second injection 5 to 7 days later. The injections were performed using a sterile ultrasound guided technique into the region of maximal muscle injury, as determined by Magnetic Resonance Imaging (MRI). Three separate depots of 1 ml were injected. All subjects completed a standardized physiotherapy programme, including range of motion exercises, progressive strength exercises, core stability training and agility exercises which was supervised by a sports physiotherapist. All subjects gave written informed consent and the medical ethical committee of South West Holland approved the study. The randomized study showed that there was no difference in outcome between the two groups[188].

Patients were included if they met the following criteria: age of 18 to 50 years; a clinical diagnosis of an acute hamstring injury defined as; a history of acute posterior thigh pain within the past five days, localized pain on palpation, localized pain on passive stretching of the hamstrings and increased pain on isometric contraction of the hamstring; an isolated hamstring lesion in the biceps femoris on magnetic resonance imaging (MRI) (within 5 days of injury), defined as an increased signal on fluid sensitive sequences.

Patients were excluded if they were not capable of performing an active exercise program; if they had already received an injection for the injury; if they had no intention to return to full sports activity; if they did not want to receive one of the two therapies in the trial; if the cause of the injury was an extrinsic trauma (contusion injury); if they had chronic hamstring complaints, defined as recurrent tenderness of the hamstring muscles in the previous 2 months; if they had chronic low back pain; if they had a contraindication for MRI; or if there was a total rupture and/or avulsion seen on MRI, or the injury was located in the medial hamstrings group.

Patients were examined at inclusion with clinical examination, MRI and muscle mechanical property testing, the details of which are given below. The clinical examination and muscle mechanical property testing were repeated after one week at the appointment where the second injection was given, and again when the patients returned to playing their sports again and once again after 26 weeks.

Examination protocol

History

All history and examinations were performed by a single physician researcher who was trainedin the techniques used before the start of the study. A standardized form was used to record all data in a structured fashion. The age and sex of the patient was recorded as was the type of sport, the level and the number of times a week. The injury time and date was recorded along with the mechanism which was classified as acute onset during sprinting, acute onset during stretching or another mechanism.

The time to return to play was determined as the number of days between the initial injury and the completion of the full rehabilitation program under the supervision of the sports physiotherapist and following this the completion of full sports specific training without complaints during or afterwards.

Clinical examination

Manual muscle palpation

With the patient lying prone the complete posterior thigh was palpated from the hamstring origin at the ischial tuberosity to the insertions medially and laterally. The point of maximal pain on palpation, total longitudinal length of the painful area and the distance between the point of maximal pain on palpation and the ischial tuberosity were recorded.

Hamstring flexibility testing

Hamstring flexibility was assessed with the active knee extension test (AKET)[190]. This method has been shown to be reliable in acute injuries (ICC 0.89). Subjects were tested in a supine position with an inclinometer placed on the anterior border of the tibia. Subjects positioned the hip of the tested leg in 90° flexion and were instructed to extend the knee until maximal tolerable stretch was achieved, with the contralateral leg remaining flat on the examination table. At maximal tolerable stretch, the absolute knee angle was measured. The absolute flexibility deficit was calculated by subtracting the recorded angle of the injured leg from the uninjured leg.

Isometric knee flexion strength

Handheld dynamometry was used to measure isometric knee flexion strength[129]. Subjects were tested lying in a prone position with the knee in 15° of knee flexion. The researcher placed the dynamometer (MicroFET, Hoggan Health Industries, Inc., Draper, Utah, U.S.) on the subject's heel and applied force, gradually increasing over 3-5 seconds. Subjects were instructed to resist the force applied by the researcher (break test). Once the subject could not resist the force anymore the test was terminated and the reading was taken. Each leg was tested 3 times in 15° of knee flexion and the highest force value was recorded. The relative strength deficit was calculated by dividing the recorded maximal force value of the injured leg by maximal force value of the uninjured leg. Additionally subjects were asked to rate hamstring pain during testing on a 0-10 numeric rating scale.

MRI examination

The protocol was a modified version of the protocol described by Askling et al.[16]. MR images were obtained with a 1.5-T magnet system (MagnetomEssenza, Siemens) with

the use of a body matrix coil. To locate the area of the injury the entire hamstring of the injured limb was visualised by obtaining coronal and sagittal short tau inversion recovery (STIR) images from the ischial origin of the hamstring muscles to insertion on the fibula and the tibia (repetition time/echo time (TR/TE) of 3500/31 ms, field of view (FOV) of 300 mm and a 256x320 matrix). The thickness of the slices for all sequences was 5mm. Subsequently, transversal STIR (repetition time/echo time (TR/TE) of 3500/31 ms, field of view (FOV) of 300 mm and a 205x256 matrix), T1-weighted (TR/TE of 500/12 ms, FOV of 300 mm and a 355x448 matrix) and T2-weighted (TR/TE of 4080/128 ms, FOV of 300 mm and a 355x448 matrix) images were obtained from the injured area. The MRI was performed within 5 days of the occurrence of the injury and before any injections were given.

A grade 1 injury was defined as presence of oedema without a fibre disruption and a grade 2 injury was diagnosed if there was oedema and fibre disruption. The reliability of the grading of hamstrings injuries and other possible prognostic factors on MRI has been shown to be excellent[92]. The MRI images were also assessed for the longitudinal length on axial images and the maximal cross sectional area of the intramuscular oedema. Grade 0 (no visible abnormalities) and grade 3 (complete ruptures) were excluded from the study.

Muscle mechanical properties

Muscle stiffness, tension and elasticity were measured with a Myoton-PRO (MYO) (Myoton, Tallinn, Estonia). The MYO gives the muscle a short mechanical impulse and records the mechanical response through an acceleration probe(8,9). The muscle responds to the mechanical impact with damped oscillations. From the acquired acceleration waveform the frequency, decrement, and stiffness of the oscillation are calculated.

The stiffness (S) is shown as $S=m*a_1/dL$ (N/m), where m is the moving mass of the measuring mechanism (kg), dL is the maximum deformation of the probe (mm) calculated from the acceleration curve and $a_1$is the positive peak of the damped acceleration. The stiffness parameter characterizes muscle's ability to resist force that is deforming it. The higher the value is the more energy is needed to deform the shape of the tissue.

The tension (T) which is represented by oscillation frequency (F) is shown as F=1/T (Hz), and it is supposed to characterize the state of the muscle under mechanical stress. The higher the tension the faster the rate at which the muscle will oscillate.

The muscle elasticity can be measured using the logarithmic decrement of oscillation(D), which is shown as $D=\ln(a_1-a_3)$, where a_1 and a_3 are the first and third peak of the oscillation. The logarithmic decrement value is supposed to characterize muscle's ability to dissipate mechanical energy in the muscle structure. The decrement is inversely proportional to elasticity, thus the less elastic the muscle the quicker the oscillations will dampen. The complete theoretical concepts of MYO and are described fully

elsewhere[74].The MYO has proved to have good test–retest reliability for rectus femoris muscle (intraclass correlation coefficient, ICCs 0.84-0.85) while measuring the stiffness from a resting muscle[31] and more recently in the quadriceps muscle[4].

The MYO readings were performed with the patient lying prone. The position of the probe of the MYO was determined by measuring the distance between the proximal insertion of the biceps on the tuberosity and the distal insertion on the head of the fibula. A line was drawn transversely across the thigh at the halfway mark. The patient then contracted the hamstrings group and the lateral edge of the biceps femoris was located. Using manual palpation the center of the muscle belly at the halfway mark was determined and marked. Each measurement consisted of ten readings of which the highest and lowest are automatically discarded by the MYO. The reading was only accepted if all the readings varied less than 3%. All measurements at inclusion and after the first week were performed before the injections were given.

Figure 6.1 shows the measurement technique for the myometry.

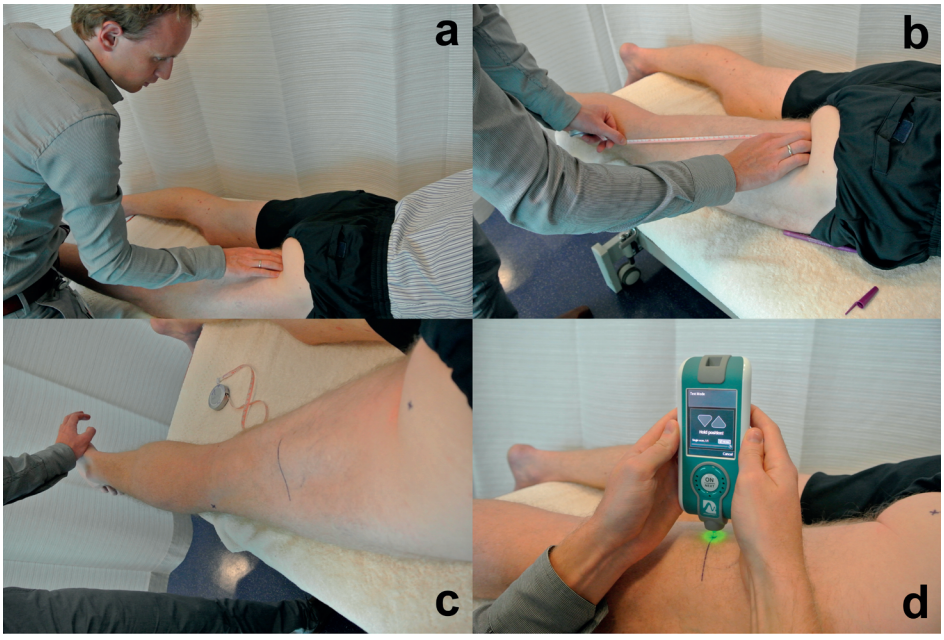


Figure 6.1. a) Palpation of the proximal insertion of the right hamstring complex in prone position. b) Measuring the total length of the biceps femoris. c) Contraction of the biceps femoris muscle to find the centre of the muscle belly. d) Using myometer to measure muscle mechanical properties.

Statistical analysis

Descriptive statistics are used to present the patient characteristics at baseline. If the data was parametric then it is presented as a mean with a standard deviation (SD) and if it was non-parametric then a median and inter quartile range (IQR) are used.

As there were some missing measurements in the longitudinal analysis, linear mixed models were used to analyze the repeated measures of muscle mechanical properties obtained with the MYO over time. The follow-up visit, the tested side (injured-uninjured) and their interaction were modeled as fixed-effects and intercept and tested side as random effects. To account for multiple comparisons, a Sidak confidence interval adjustment was used.

Differences in muscle mechanical properties at return to play between athletes who remained injury free and those who sustained a re-injury after return to sport were tested with an independent-samples Mann-Whitney U test. All calculations were performed using SPSS version 19.0.0 (SPSS Inc, Chigaco, Illinois, USA).

RESULTS

There were 25 male patients included from February 2012 until November 2012 within 5 days of an acute injury to the biceps femoris muscle. Their mean age was 30 years and the majority played competitive football. The patient characteristics are shown in Table 6.1. There were no patients lost to follow up during the study.

The findings on clinical examination and on the MRI scans are shown in Table 6.2.

On a number occasions there was missing data from clinical examination or the Myoton, due to a technical problem or because subjects did not attend, and an overview of this is given below in Table 6.3.

The results of the muscle mechanical property measurements, at all points in the study are shown in Table 6.4. The 5 athletes who sustained a re-injury are not included in the analysis at 26 weeks as their muscle properties were presumed to have been altered again by the new injury.

After completion of the rehabilitation protocol five of the athletes sustained a re-injury during the following two months. The results of the measurements taken at return to sport in those who remained injury free and those who sustained a re-injury are shown in Table 6.5. There was no significant difference found for any of the three muscle mechanical properties measured between the two group.

Table 6.1 Patient characteristics (n = 25)

Mean age (SD)	30 (±7)
Gender Male / Female	25/0
Sports	
- Football	14
- Field hockey	8
- Athletics	1
- Tennis	1
- American Football	1
Level of sports	
- Professional	0
- Competitive	20
- Recreational	5
Intensity of sports	
- >4/week	2
- 3-4/week	19
- 1-2/week	4
Injury mechanism sprint/stretch/other	18/2/4
Median days injury to initial exam (IQR)	3 (2-4)

Table 6.2 Findings on initial clinical examination and MRI

Length (in cm) from insertion to maximal pain on palpation	13.5 (IQR 8.8-24.8)
Length of painful area on palpation (in cm)	11.2 (±7.6)
Active knee extension	
- Score injured leg	123° (±15)
- Score uninjured leg	139° (±12)
- Deficit	16° (±14)
NRS pain score on isometric contraction	4 (±3)
Handheld dynamometry (in 15° knee flexion)	
- Force injured leg (in N)	182 (±76)
- Force uninjured leg (in N)	246 (±65)
- Force deficit (in % of injured leg)	26 (±27)
Severity of injury on MRI	
- Grade 1/Grade 2	5/20
- Cranio-caudal length (in cm)	11.1 (±7.0)
- Cross sectional area – (as percentage of total cross sectional area)	39% (31%)

Table 6.3 Overview of missing data.

	Missing data	Missingness characteristics
Baseline	2	Missing MYO measurement on available subject
Week 1	2	Missing MYO measurement on available subject
RTP	4	3 subject did not attend for examination at follow-up 1 missing MYO measurement on available subject
Week 26	3	Missing MYO measurement on available subject

Table 6.4 Results of the muscle mechanical property measurements.

	Baseline			Week 1			RTP			Week 26		
	Uninjured	Injured	Between side difference (95% CI)	Uninjured	Injured	Between side difference (95% CI)	Uninjured	Injured	Between side difference (95% CI)	Uninjured	Injured	Between side difference (95% CI)
Stiffness	339 (±30)	318 (±28)	20 (8 to 33)*	334 (±30)	315 (±35)	17 (6 to 31)*	324 (±29)	319 (±26)	5 (-5 to 22)	336 (±40)	330 (±33)	8 (-8 to 21)
Tension	17.9 (±1.3)	16.8 (±1.2)	1.1 (.5 to 1.6)*	17.6 (±1.2)	16.6 (±1.2)	.9 (.4 to 1.5)*	17.3 (±1.2)	16.9 (±1.1)	.4 (-.1 to 1.0)	17.9 (±1.6)	17.5 (±1.4)	.3 (-.1 to 1.1)
Elasticity	1.27 (±.16)	1.31 (±.15)	-.04 (-.11 to .03)	1.28 (±.16)	1.35 (±1.2)	-.07 (-.13 to .00)	1.31 (±.18)	1.31 (±.18)	.00 (-.07 to .07)	1.32 (.17)	1.30 (±.18)	.02 (-.06 to 0.09)

* statistical significant difference ($p<0.05$)

Table 6.5 Muscle mechanical properties at return to play between athletes who remained injury free and those who sustained a re-injury after return to play.

	No re-injury (n = 17, 3 missing data)	Re-injury (n = 4, 1 missing data)	
Stiffness			
- **Injured**	319 (305 to 336)	302 (273 to 320)	p=.148
- **Difference**	6 (-7 to 15)	7 (2 to 23)	p=.496
Tension			
- **Injured**	17.1 (16.1 to 17.6)	16.4 (15.8 to 16.7)	p=.268
- **Difference**	0.4 (-0.4 to 1.0)	0.1 (-0.1 to 0.8)	p= 1.00
Elasticity			
- **Injured**	1.33 (1.21 to 1.46)	1.30 (0.95 to 1.43)	p=.670
- **Difference**	0.01 (-0.10 to 0.08)	0.16 (-0.07 to 0.25)	p=.148

DISCUSSION

This prospective cohort study examining the changes in muscle mechanical properties in athletes with acute hamstrings injuries shows that muscle stiffness and tone, but not elasticity, are significantly reduced after injury and return to normal by the time athletes return to play.

The fact that the stiffness and tone are altered after injury and normalize by the time that athletes return to play again is an interesting observation. There may be a potential role in monitoring recovery and it may even assist in return to play decision making in the future. As this is the first study to systematically examine how muscle mechanical properties are altered after acute injury it is hard to compare the results to those in the existing literature.

While no previous studies have examined muscle mechanical properties after acute injury, alterations have been reported when muscle length changes and at different levels of force production, as can be expected[31]. In another study on muscle mechanical properties the application of cold packs to the muscle of healthy volunteers showed that cooling altered these properties[159].

Palpation of the hamstring muscle is common practice after injury and often used to help make the diagnosis. The presence of pain on palpation of the muscle is considered by many as a key requirement in diagnosing an acute hamstrings injury. During palpation to examine for the presence of pain the examiner also receives tactile feedback on the muscle mechanical properties. Some authors recommend examining for the feeling of tightness on palpation when examining the hamstrings muscles[119]. While others describe "When palpating muscle, assess tone, focal areas of thickening…"[37]. The use of a myometer allows the measurement of the mechanical properties of the muscle in an objective way for research purposes.

Muscle stiffness and tension were both reduced after injury in this study. This could be due to one of two possible mechanisms or a combination of both. The first possibility is that the stretching and/or tearing of the muscle causes mechanical alterations in the properties. This would fit with a decrease in tension and stiffness after injury. A reduced elasticity would also be expected which was not observed. We have no good explanation for this fact. The second possibility is that the pain after the injury causes a reflex inhibition of the muscle, which could also alter the mechanical properties. As we did not perform additional electromyographic recordings whether this was the case or not cannot be ascertained. In future studies a concomitant EMG would allow the investigation of the resting electrical activity in the muscle after injury during myometric examination.

It is interesting to note that while the muscle mechanical properties were not different to the uninjured leg when the athletes returned to play, suggesting a normalization of the muscle mechanical properties, the MRI images at this time are often still abnor-

mal[191]. This suggests that persistent MRI abnormalities are not associated with altered mechanical properties. The reason for this discrepancy between abnormal MRI images and the return to normal of the mechanical properties is unclear. In the current study five athletes had a re-injury after they returned to play. There were no significant associations of the mechanical properties and re-injury measured at return to play. As the groups are very small the study would only have been able to detect a very large difference between the groups. A larger group of athletes will allow for a proper assessment of whether measuring the muscle mechanical properties has any predictive value for the occurrence of re-injuries after return to sport.

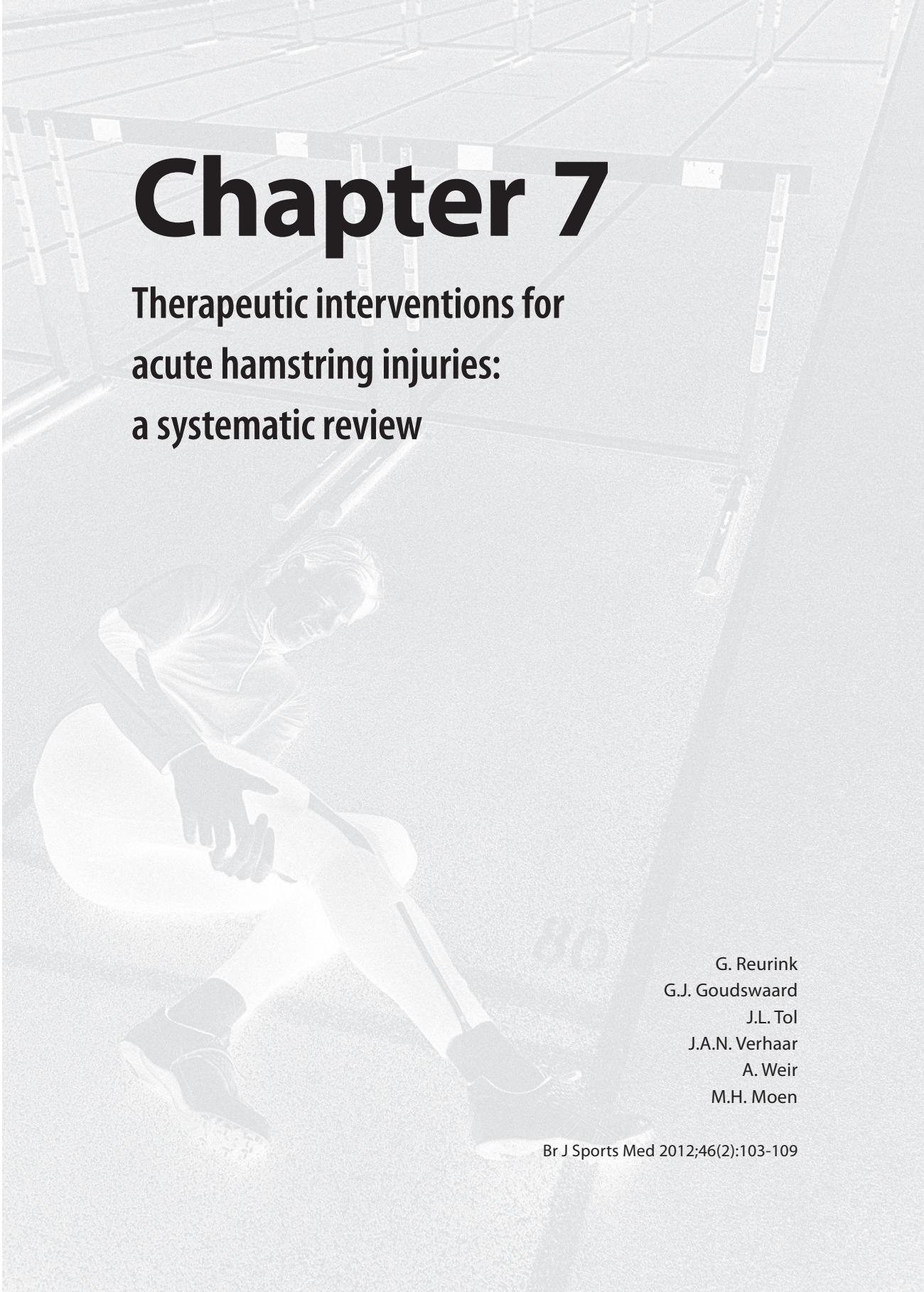
The strengths of this study are the use of a single observer, clinical and MRI confirmation of an acute injury, the location in a single hamstrings muscle and the use of a reliable myometer to measure the muscle mechanical properties. The study has some limitations as well. The fact that only injuries in the biceps femoris were included limits the generalizability of the findings with regard to the medial hamstring group. The medial hamstring group was not included as we felt that it is harder to distinguish between the semimembranosus and semitendinosus on clinical examination to ensure good placement of the myometer on the correct muscle belly. The relatively small group means that the study is underpowered to ascertain whether any differences in mechanical properties in the muscle would be predictive of re-injury or the time to return to play, although this was not the aim, it is advisable to have a larger group to investigate this in future studies.

CONCLUSION

The stiffness and tension, but not the elasticity, of the biceps femoris muscle are significantly reduced after acute injury. There are no significant differences remaining between the injured and uninjured leg at the time to return to play. Future studies can investigate if these altered muscle mechanical properties can be used to predict re-injury or guide return to play decision making.

Chapter 7

Therapeutic interventions for acute hamstring injuries: a systematic review



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Br J Sports Med 2012;46(2):103-109

ABSTRACT

Background – Despite the high injury rate there is no consensus on the management of hamstring injuries, with a large number of different interventions used. Recently several new injection therapies have been introduced.

Objectives – The purpose of this study is to systematically review the literature on the effectiveness of therapeutic interventions for acute hamstring injuries.

Data sources – The databases of PubMed, EMBASE, Web of Science, Cochrane library, CINAHL and Sportdiscus were searched in May 2011.

Study eligibility criteria – Prospective studies comparing the effect of an intervention with another intervention or a control group without intervention, in subjects with acute hamstring injuries were included.

Data analysis – Two authors independently screened the search results and assessed risk of bias. Quality assessment of the included studies was performed using the Physiotherapy Evidence Database score. A best evidence synthesis was used to identify the level of evidence.

Main results – Six studies were included in this systematic review. There is limited evidence for a positive effect of stretching, agility and trunk stability exercises, intramuscular Actovegin injections or slump stretching in the management of acute hamstring injuries. Limited evidence was found that there is no effect for non-steroidal anti-inflammatory drugs or manipulation of the sacroiliac joint.

Conclusion – There is a lack of high quality studies on the treatment of acute hamstring injuries. Only limited evidence was found to support the use of stretching, agility and trunk stability exercises, intramuscular Actovegin injections or slump stretching. Further research is needed, using an appropriate control group, randomisation and blinding.

INTRODUCTION

The acute hamstring injury is common in the athletic population. In different types of sports, like football, Australian Rules football and rugby, 12-16% of all injuries are hamstring injuries[35,61,66,169,240]. These injuries have significant consequences for the performance of players and their clubs: a professional athlete with a hamstring injury cannot perform in match play for an average of 14-27 days[61,216,231]. Despite the high injury rate there is no consensus on the best management due to a lack of scientific evidence for the effectiveness[171]. This is underlined by the diversity of different interventions that are used in the management of hamstring injuries; RICE (Rest, Ice, Compression, Elevation)[6], use of non-steroidal anti-inflammatory drugs (NSAID's)[150], exercise therapy[103], mobilisation and manipulation therapy[107], injection therapies including corticosteroids[132], autologous blood products[91,134] and Traumeel/Actovegin injections[134,171]. Traumeel is a homeopathic formulation containing botanical and mineral components to which anti-inflammatory effects are ascribed. Actovegin is a deproteinised haemodialysate obtained from filtered calf blood. It is suggested that Actovegin contains active components with muscle regenerating promoting effects[134,171]. The most recent systematic review on management of hamstring injuries was published by Harris et al. in 2011[97]. This was a systematic review on operative treatment compared to non-operative treatment in acute proximal hamstring ruptures. The most recent systematic review on conservative therapeutic interventions for acute hamstring injuries was published by Mason et al. in 2007[145]. This was a systematic review on rehabilitation interventions in hamstring injuries based on only three studies. Since the publication of Mason et al., additional studies have been published on therapeutic interventions in hamstring injuries and new injection therapies have been introduced[91,134].

The purpose of this study is to systematically review the literature on the effectiveness of therapeutic interventions for acute hamstring injuries.

METHODS

Literature search

A comprehensive systematic literature search was performed in May 2011. The databases of PubMed, EMBASE, Web of Science, Cochrane library, CINAHL and Sportdiscus were searched without any time limits. The complete electronic search strategy is presented in Table 7.1. Additionally citation tracking was performed by manually screening of the reference list of eligible studies.

Study selection

Two reviewers (GR and MM) independently assessed potential eligible trials identified by the search strategy. The inclusion criteria are presented in Table 7.2. All titles and abstracts were assessed by two reviewers (GR and MM), and relevant articles were ob-

Table 7.1 Search strategy

Search strategy	Records
Pubmed (hamstring injur*[tw] OR hamstring muscle injur*[tw] OR hamstring muscle strain*[tw] OR hamstring rupt*[tw] OR hamstring strain*[tw] OR hamstring tear*[tw]) AND (therapeutics[mesh] OR therapy[sh] OR therapy[tw] OR therapeut*[tw] OR rehabil*[tw] OR treat[tw] OR treated[tw] OR treatment*[tw] OR manag*[tw] OR intervent*[tw])	139
EMBASE (((hamstring* OR thigh OR semitendin* OR semimembran* OR 'femoral biceps' OR 'biceps femoris') NEAR/3 (injur* OR tear* OR rupt* OR strain*)):ti,ab,de) AND (therapy/exp OR therapy:lnk OR therap*:ti,ab,de OR rehabil*:ti,ab,de OR treat*:ti,ab,de OR manag*:ti,ab,de OR intervent*:ti,ab,de)	336
Web of Science ((hamstring* OR semitendin* OR semimembran* OR "biceps femoris" OR "femoral biceps") SAME (injur* OR tear* OR rupt* OR strain*)) AND (therap* OR rehabil* OR treat* OR manag* OR intervent* OR physiother*)	352
Cochrane library (((hamstring* OR thigh* OR semitendin* OR semimembran* OR 'femoral biceps' OR 'biceps femoris') NEAR/3 (injur* OR tear* OR rupt* OR strain*)) AND (therap* OR rehabil* OR treat* OR manage* OR intervent*)) In all text. Restricted to clinical trials.	22
CINAHL (EBSCOhost Research Databases) TX ((((hamstring* N3 injur*) OR (hamstring* N3 tear*) OR (hamstring* N3 rupt*) OR (hamstring* N3 strain*) OR (thigh* N3 injur*) OR (thigh* N3 tear*) OR (thigh* N3 rupt*) OR (thigh* N3 strain*) OR (semitendin* N3 injur*) OR (semitendin* N3 tear*) OR (semitendin* N3 rupt*) OR (semitendin* N3 strain*) OR (semitemembran* N3 injur*) OR (semitemembran* N3 tear*) OR (semitemembran* N3 rupt*) OR (semitemembran* N3 strain*) OR (femoral biceps N3 injur*) OR (femoral biceps N3 tear*) OR (femoral biceps N3 rupt*) OR (femoral biceps N3 strain*) OR (biceps femoris N3 injur*) OR (biceps femoris N3 tear*) OR (biceps femoris N3 rupt*) OR (biceps femoris N3 strain*)) AND (therap* OR rehabil* OR treat* OR manage* OR intervent*)))	377
Sportdiscus (EBSCOhost Research Databases) TX ((((hamstring* N3 injur*) OR (hamstring* N3 tear*) OR (hamstring* N3 rupt*) OR (hamstring* N3 strain*) OR (thigh* N3 injur*) OR (thigh* N3 tear*) OR (thigh* N3 rupt*) OR (thigh* N3 strain*) OR (semitendin* N3 injur*) OR (semitendin* N3 tear*) OR (semitendin* N3 rupt*) OR (semitendin* N3 strain*) OR (semitemembran* N3 injur*) OR (semitemembran* N3 tear*) OR (semitemembran* N3 rupt*) OR (semitemembran* N3 strain*) OR (femoral biceps N3 injur*) OR (femoral biceps N3 tear*) OR (femoral biceps N3 rupt*) OR (femoral biceps N3 strain*) OR (biceps femoris N3 injur*) OR (biceps femoris N3 tear*) OR (biceps femoris N3 rupt*) OR (biceps femoris N3 strain*)) AND (therap* OR rehabil* OR treat* OR manage* OR intervent*)))	388

tained. All relevant articles were read independently in full text by two reviewers (GR and MM) to assess whether they met the inclusion criteria. If there was a difference in opinion on eligibility, a consensus was reached by consulting a third reviewer (JT).

Table 7.2 Inclusion criteria

Subjects in the study had have an acute hamstring injury, diagnosed by physical examination, MRI or ultrasound;
The study design was a prospective comparative study; randomised controlled trial (RCT) or non-randomised controlled clinical trial (CCT);
There was a well described therapeutic intervention which was compared to another intervention or a control group;
Full text of the article was available;
The article was written in English, German or Dutch;
In the article at least one of the following outcome measures had to be reported: • Time to return to sport or normal function • Re-injury rate • Pain scores • Hamstring force: isometric or isokinetic testing • Hamstring flexibility testing • Subjective patient satisfaction • Adverse effects

Data extraction

One reviewer recorded the study design, population, intervention, outcome measure and outcome using standardised data extraction forms. To assess the efficacy of the interventions, mean values of the continuous outcomes and dichotomous values were extracted from the published articles. When a study had more multiple measurements of an outcome measure at different moments during the follow-up period, the results of the last recorded follow-up were used.

Quality assessment

The studies included were scored using the PEDro (Physiotherapy Evidence Database) score by two reviewers (GR and HM)[138,157]. The PEDro score is an 11 point list using yes and no answers. The first statement pertains to the external validity of the study and is not used to compute the final quality score. The score (0-10) is the number of positive answers on questions 2-11. The PEDro items are shown in Table 7.3. The reliability of the PEDro score is fair to good[138]. A PEDro score of six or higher is considered to represent a high quality study and a score of five or lower is considered to represent a low quality study[65]. If there was a difference in opinion on a PEDro item score, a consensus was reached by consulting a third reviewer (JT).

Table 7.3 PEDro scale

1. Eligibility criteria were specified
2. Subjects were randomly allocated to groups
3. Allocation was concealed
4. The groups were similar at baseline regarding the most important prognostic indicators
5. There was blinding of all subjects
6. There was blinding of all therapists who administered the therapy
7. There was blinding of all assessors who measured at least one key outcome
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analysed by 'intention-to-treat'
10. The results of between-group statistical comparisons are reported for at least one key outcome
11. The study provides both point measures and measures of variability for at least one key outcome

The score is the number of positive answers on questions 2-11 (0-10).

Best evidence synthesis

Because the studies were considered heterogeneous with regard to the interventions, outcome measures and methodological quality, it was not possible to perform a meta-analysis of the data. Instead a best evidence synthesis was used[215]. The results of the quality assessments of the individual trials were used to classify the level of evidence[229]. This qualitative analysis was performed with five levels of evidence based upon the quality and results of clinical studies:

1. Strong evidence: provided by generally consistent findings in multiple high quality studies (≥ 75% of the studies reported consistent findings).
2. Moderate evidence: provided by generally consistent findings in one high quality study and one or more lower quality studies, or by generally consistent findings in multiple low quality studies (≥ 75% of the studies reported consistent findings).
3. Limited evidence: provided by only one study (either high or low quality).
4. Conflicting evidence: inconsistent findings in multiple studies (<75% of studies reported consisting findings).
5. No evidence: no randomised controlled trials (RCTs) or non-randomised controlled clinical trials (CCTs).

RESULTS

Literature search

The search yielded 975 records. Eight studies were identified as possibly relevant after screening the titles and/or abstracts for which full text articles were retrieved. Citation tracking added one possibly relevant study. After review of the full text three studies[176,224,241] were excluded and six studies[48,123,131,141,196,208] met the inclusion criteria (Figure 7.1).

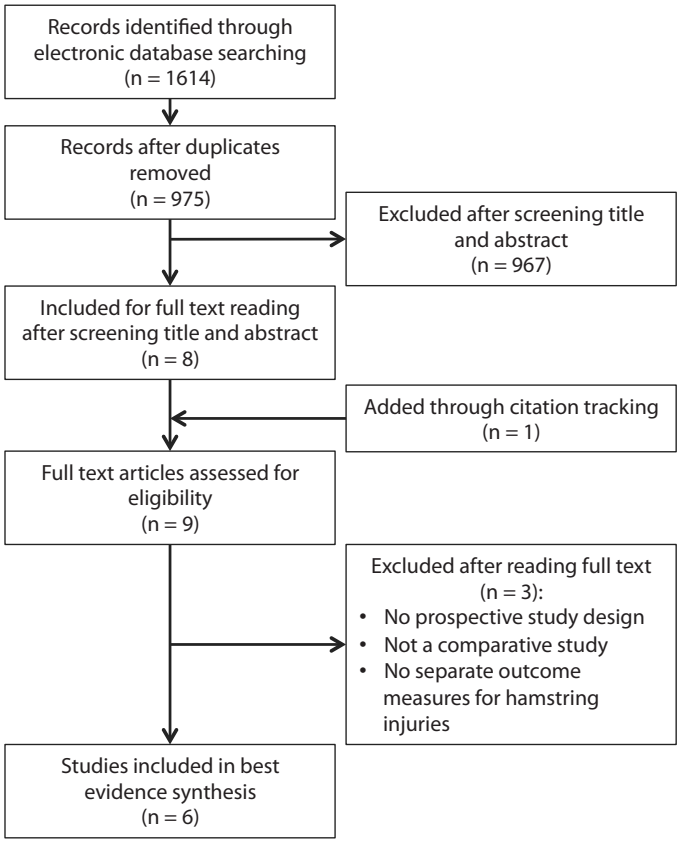


Figure 7.1. Study selection flow diagram

Study design

There were two CCT[123,131] and four RCT's with an adequate randomisation design[48,141,196,208]. None of the included studies reported a sample size calculation.

Description of included studies

Table 7.4 presents the characteristics of the six included studies[48,123,131,141,196,208].

Table 7.4 Characteristics of the included studies

Reference	N	Study design	Population	Intervention(s)	Follow-up	Primary outcome	Results
Cibulka et al. 1986[26]	20	RCT	Clinical diagnosis of hamstring strain and evidence of sacroiliac dysfunction	I: Manipulation of sacroiliac joint in addition to moist heat and passive stretching C: Moist heat and passive stretching	After intervention	Isokinetic testing (peak torque) Flexibility (passive knee extension)	I: 45.7 ± 22.70 foot-pounds C: 46.4 ± 17.47 foot-pounds I: 155.0° ± 14.2° C: 144.6° ± 16.7°
Kornberg et al. 1989[27]	28	CCT	Australian rules football professionals, with grade I hamstring strain and positive slump test	I: Slump stretching in addition to 'traditional treatment methods' C: 'traditional treatment methods'	RTS	≥ 1 missed games (dichotome)	I: 9.1% (1/11) C: 100% (16/16)
Lee et al. 2011[28]	11	CCT	Football professionals with grade I or II hamstring injuries, confirmed with MRI	I: Intramuscular Actovegin injections and exercise therapy C: exercise therapy	RTS	Time to RTS	I: 12 ± 2.94 days * C: 20 ± 4.45 days *
Malliaropoulos et al. 2004[29]	80	RCT	Athletes with grade II hamstring strain, confirmed with ultrasound	I1+I2: during first 48 h PRICE followed by rehabilitation program I1: once daily session of static hamstring stretches I2: four times daily session of static hamstring stretches	RTS	Time required for full rehabilitation Time to return to full ROM (passive knee extension)	I: 13.27 ± 0.71 days * C: 15.05 ± 0.81 days * I: 5.57 ± 0.71 days * C: 7.32 ± 0.81 days *
Reynolds et al. 1995[30]	44	RCT	Sports related tear of the hamstring, included within 48 h after injury	I1: meclofenamate + diclofenac placebo for 7 days I2: diclofenac + meclofenamate placebo for 7 days C: diclofenac placebo + meclofenamate placebo for 7 days	7 days	Pain score (sum of VAS pain score on: previous 24h, movement, walking, running, palpation)	I1: 7.9 ± 6.6 I2: 8.8 ± 7.7 C: 3.9 ± 3.3
Sherry & Best 2004[31]	24	RCT	Athletes with clinical diagnosis of grade I or II sport related hamstring strain	I1: static stretching, isolated progressive resistance exercises, and icing I2: progressive agility and trunk stabilization exercises and icing	1 year after RTS	Time to RTS Re-injury rate	I1: 37.4 ± 27.6 days I2: 22.2 ± 8.3 days I1: 70% (7/10) * I2: 7.7% (1/11) *

Abbreviations: RCT, randomised controlled trial; CCT, non-randomised controlled clinical trial; I, intervention group; C, control group; PRICE, protection - rest - ice - compression - elevation; RTS, return to sport / return to full function; ROM, range of motion.

* statistical significant difference between studied groups

Quality assessment

The PEDro scores for the six studies are shown in table 7.5. The scores ranged from 3 to 7 with an average of 5.0. Two studies were assessed as high quality (PEDro score ≥ 6)[196,208] and four studies were of low quality (PEDro score < 6)[48,123,131,141]. All studies reported the eligibility criteria.

Table 7.5 Pedro score of the included studies

	Item PEDro score											
Reference	1	2	3	4	5	6	7	8	9	10	11	**Total score**
Cibulka et al. 1986[48]	+	+	-	-	-	-	-	+	+	+	+	5/10
Kornberg et al. 1989[123]	+	-	-	-	-	-	-	+	+	+	-	3/10
Lee et al. 2011[131]	+	-	-	-	-	-	-	+	+	+	+	4/10
Malliaropoulos et al. 2004[141†]	+	+	-	+	-	-	-	-	-	+	+	4/10
Reynolds et al. 1995[196]	+	+	+	+	+	+	-	-	-	+	+	7/10
Sherry & Best 2004[208*]	+	+	+	+	-	-	-	+	+	+	+	7/10

The total score was defined by the number of positive answers on questions 2-11 (0-10)

† Unable to contact research group for additional information; when the answer on a question is unclear the item is scored negative.

* Contact with research group for additional information to determine score on item 3

Participants

The mean number of subjects was 34.5 (SD 24.8) with a range of 11-80. One study was on Australian rules football professionals[123], one study on football (soccer) professionals[131], three studies evaluated athletes of different sports[141,196,208] and one study did not report the sports activity of the participants[48]. Participants in all studies were diagnosed as having an acute hamstring injury. Four studies used clinical examination alone to make the diagnosis[48,123,196,208] and two studies used additional imaging techniques to confirm diagnosis; one study used MRI[131] and one study used ultrasound[141]. One study included only patients with a positive Slump test, defined as reproduction of symptoms during slump stretch[123].

The slump stretch consists of combining vertebral flexion, straight leg raise and ankle dorsiflexion, aimed at stretching pain sensitive structures in the vertebral canal and intervertebral foramen. In one study all patients had evidence of sacroiliac dysfunction, defined as pelvic asymmetry between the left and right innominates, a positive flexion standing test, and a positive prone knee-flexion test[48].

Four studies reported the grade of the hamstring injury as an inclusion criterion; three studies used a clinical assessment[123,131,208] and one study used ultrasound for grading[141]. However, no uniform grading system was used in these studies, making comparison unreliable. Participants with total ruptures of the hamstring were not included in these studies.

Interventions and outcome

The effects of interventions on outcome measures in the studies included are summarised in Table 7.6. All six studies investigated different interventions: manipulation of sacroiliac joint[48], slump stretching[123], intramuscular Actovegin injections[131], static hamstring stretching[141], non-steroidal anti-inflammatory drugs (meclofenamate and diclofenac)[196], and comparison of rehabilitation program of static stretching and resistance exercises with rehabilitation program of progressive agility and trunk stabilisation[208].

Table 7.6 Effect of interventions on outcome measures

Intervention	Outcome measure	High quality*	Low quality*	Best evidence synthesis
Manipulation of sacroiliac joint	hamstring flexibility		=[48]	Limited
	isokinetic testing		=[48]	limited
Slump stretching	missed games		+[123]	limited
Actovegin injection therapy	time to RTS		+[131]	Limited
	adverse effects		=[131]	limited
Stretching exercises	time to RTS		+[141]	limited
	hamstring flexibility		+[141]	limited
NSAIDs	pain score	=[196]		limited
	isokinetic testing	=[196]		limited
Agility and trunk stabilization vs Stretching and resistance exercises	time to RTS	=[208]		limited
	re-injury	+[208]		limited

*High quality studies are studies with PEDro score ≥ 6; Low quality studies are studies with PEDro score < 6
+ Positive effect of intervention on outcome measure; = No effect of intervention on outcome measure; - Negative effect of intervention on outcome measure
Abbreviations: RTS, return to sport; NSAIDs, non steroidal anti-inflammatory drugs

Manipulation of sacroiliac joint

In the study of Cibulka et al.[48] there was no difference on peak hamstring torque and passive knee extension test immediately after a single manipulation of the sacroiliac joint between the experimental group (peak torque 45.7 ± 22.70 foot-pounds, passive knee extension 155.0° ± 14.2°) and the control group (peak torque 46.4 ± 17.47 foot-pounds, passive knee extension 144.6° ± 16.7°) . A significant difference between the experimental and control group in change in hamstring peak torque is reported in the article. This is due to a lower pre-test peak torque of 8.4 foot-pounds in the experimental group.

Slump stretching

Kornberg et al.[123] reported a significant effect of slump stretching on games missed in 28 patients with hamstring injuries and a positive slump test. Kornberg et al. used games

missed as an indirect measure of time to return to sport. To obtain a dichotomous variable one game missed was used as a cut off point in the study. In the slump stretching group 11 patients missed no games and one player missed ≥ one game compared to no players missing any games and 16 players missing ≥ one game in the control group (difference statistical significant p<0.001). Approximation of time to return to sport is not possible, because of lack of information about frequency of matches during the study period.

Actovegin injection therapy

In the study of Lee et al.[131] four patients with grade I injuries treated with Actovegin injections returned to play at average after 12 days (± 2.94) compared to 20 days (± 4.45) for four patients with grade I injuries in the control group, a statistical significant difference (p=0.033). Three patients with grade II injuries in Actovegin group returned to play at average after 18.7 days (± 4.93). There were no patients in the control group with grade II injuries, therefore no statistical analysis was performed on grade II injuries.

Stretching exercises

In the study of Malliaropoulos et al.[141] the group which performed a more intensive stretching programme was found to regain full active knee extension compared to the uninjured side earlier than the group which performed a less intensive stretching programme; respectively 5.57 ± 0.71 days and 7.32 ± 0.525 days. Time needed for rehabilitation was also statistical significantly shorter (p<0.001) in the intensive stretching group (13.27 ± 0.71 days) compared to the less intensive stretching group (15.05 ± 0.81 days).

Non-steroidal anti-inflammatory drugs

Reynolds et al.[196] found no statistical significant effect of treatment with NSAIDs (meclofenamate and diclofenac) on pain score and isokinetic hamstring testing (peak torque, average power and total work) compared with placebo. Pain score's measured with visual analogue scale after one week were 7.9 ± 6.6, 8.8 ± 7.7 and 3.9 ± 3.3 for the meclofenamate, diclofenac and placebo group respectively.

Adverse events were reported by 13 patients (29%), 12 gastro-intestinal and 1 headache. Adverse events were reported by 5 of 13 patients (38%) in meclofenamate group, 6 of 17 patients (35%) in the diclofenac group and 2 of 14 patients (14%) in the placebo group. No statistical analysis was performed on the number of adverse events.

Stretching and resistance exercises versus agility and trunk stabilisation exercises

Sherry and Best[208] found no statistical significant difference in time to RTS (p=0.2455) between a group performing stretching and isolated progressive hamstring resistance exercises and a group performing progressive agility and trunk stabilisation exercises;

37.4 ± 27.6 days and 22.2 ± 8.3 days respectively. This study reported statistical significant re-injury rates in favour of the progressive agility and trunk stabilisation group at two weeks (p=0.0343) and at one year (p =0.0059) after RTS . At two weeks 6 (54.5%) of the 11 patients in the stretching and isolated progressive hamstring resistance exercises group suffered a hamstring re-injury compared to none of the 13 patients in the progressive agility and trunk stabilization. At one year re-injury rate was 70% (7/10) in the stretching and isolated progressive hamstring resistance exercises group and 7.7% (1/13) in the progressive agility and trunk stabilisation exercises group.

DISCUSSION

This systematic review shows limited evidence for a positive effect of stretching, agility and trunk stability exercises, intramuscular Actovegin injections and slump stretching in the management of acute hamstring injuries. Limited evidence was found that there is no effect for NSAID's and manipulation of the sacroiliac joint.

Only six studies met the criteria for inclusion in this systematic review; two CCT's[123,131] and four RTC's[48,141,196,208], of which three were classified as high quality. These six studies all investigated different interventions, thereby limiting comparison of the studies and pooling of the results.

Despite hamstring injuries being very common in the athletic population, this comprehensive systematic literature search revealed a lack of high quality studies on the management of hamstring injuries. All interventions reported in these clinical studies have been investigated once, thereby limiting the amount of evidence on the efficacy of these interventions.

There was limited evidence for a positive effect of stretching on the time required for rehabilitation. Malliaropoulos et al.[141] reported a positive effect of static stretching on the rehabilitation time. In contrary, the stretching and progressive resistance group in the study of Sherry and Best showed a tendency for prolonged rehabilitation time compared to the agility and trunk stabilisation group. However, no conclusions can be drawn on the effect of stretching as an isolated intervention with the results of the study of Sherry and Best[208], because resistance exercises was another variable which may influence the outcome besides stretching.

There is limited evidence that agility and trunk stabilization exercises compared to progressive resistance and stretching resulted in less re-injuries at two weeks and one year follow-up. The re-injury rate of 70 % at one year follow-up found in the progressive resistance and stretching group in the study of Sherry and Best[208] is higher than reported

in the literature for hamstring injuries[77,231,232]. This may indicate that the rehabilitation programme in this group has a detrimental effect on the outcome of rehabilitation.

There is limited evidence that the use of NSAID's has no effect on pain scores and isokinetic strength testing in acute hamstring injuries. Similar to these results, a number of reviews found NSAID's to be no more effective than placebo in the management of acute soft tissue injuries[6,150,244]. Furthermore, concerns have been raised about the possible harmful effect of NSAID's on muscle healing after acute muscle injuries by delaying muscle regeneration and promoting fibrosis[207,244]. Despite the widespread use of NSAID's in acute muscle injuries there is no evidence for their efficacy in hamstring injuries.

Kornberg et al.[123] reported a reduced number of games missed using stretching of neural structures (slump stretching) in athletes with grade I hamstring injuries and a positive slump test. Grade I injury was defined as pain and tenderness in hamstring, pain and decreased strength on isometric contraction and decreased hamstring length. Diagnosis was not confirmed by ultrasound or MRI. In the experimental group treated with the slump stretching technique 11 of the 12 athletes missed no games. Compared to rehabilitation times for grade I injuries found in the literature it is remarkable that these players did not miss any games. This raises the question whether these injuries actually contained hamstring muscle pathology or there is another cause of the injury, such as neural tension pathology.

Cibulka et al.[48] reported an increase in peak hamstring torque after manipulation of the sacroiliac joint measured with a pre- and post-intervention test. The control group did not increase in peak hamstring torque. However, there was a baseline difference in peak hamstring torque in favour of the control group. At the post-test the groups were similar. This significant baseline difference makes the interpretation of the outcome difficult and causes a substantial risk of bias. Furthermore there are several other limitations in this study: no information is provided about the sport activity of the participants, the criteria for the diagnosis of sacroiliac dysfunction are not clear and there is no rehabilitation outcome presented in measurements of time to return to sport and re-injuries.

In recent years injection therapies are gaining popularity in the treatment of muscle injuries, such as Actovegin[131,171] and growth factor injections[134,241]. Lee et al.[131] reported a significant shorter rehabilitation time for treatment of acute hamstring injuries with Actovegin compared to no injection therapy. However, there is a substantial risk of bias in this study due to serious methodological limitations; no randomisation, no blinding and the allocation of patients who refused the injection therapy to the control group. Therefore, no conclusions can be drawn on the efficacy of Actovegin injections in hamstring injuries.

Injection therapies with growth factors have been proposed as a new treatment modality for muscle injuries[134,241]. No studies on growth factor injections met the inclusion criteria of this review. One study with platelet rich plasma (PRP) has been conducted in

muscle injuries, including hamstring injuries, but was excluded from this review because the control group used was a retrospective analysis of patients treated previously. Additional shortcomings of this study are lack of blinding, no quantification of lesions and no follow-up after return to sport[241].

Surgical treatment have been advocated to repair complete ruptures of the hamstring muscles and is increasingly used in the management of these injuries[49,97,126]. Although a surgical intervention was not an exclusion criterion, no studies on surgical treatment of acute hamstring injuries were included in the analysis of this systematic review. In the literature search no prospective controlled studies were identified on surgical interventions for acute hamstring injuries. This highlights a the lack of high quality scientific evidence in the surgical management of acute hamstring injuries.

Future directions

This systematic review highlights a lack of good quality studies on the treatment of acute hamstring injuries. Common methodological limitation are the small number if participants and the lack of an appropriate control group, randomisation and blinding of patients, therapists and assessors.

Grading systems are used for classification of severity of acute hamstring injuries[96,177]. However, there seems to be no uniform classification system for these injuries: grading is performed using clinical examination[123,131,208], MRI[96] and/or ultrasound[141,177]. In a general sense these grading systems share common classification categories: grade 0, no abnormality; grade 1, no/minimal tear; grade 2, partial tear; grade 3, total rupture. The precise definitions of the grading categories vary between the classification systems. The exact distinction between no, minimal and partial tear is not uniform. Of the studies included, four graded the injuries using different classification systems[123,131,141,208], making comparison unreliable. The reliability of these classification systems in clinical practice has not been investigated. This highlights the need for a uniform, reliable and validated classification system which increase the comparability of outcomes of studies and which can be used by sport physicians for management planning, prognosticating and return to sport decisions.

The outcome measures used in different studies on hamstring injuries are heterogeneous, limiting the comparability of the studies. The most common outcome measure reported is the time to return to sport. In the practice of sports medicine this is an important measure of the success of treatment, especially in professional athletes. Regarding the high re-injury risk of hamstring injuries another important outcome measure for assessing the effect of an intervention is the re-injury rate in the follow-up period after return to sport. An intervention may seem to be successful when athletes can return to play earlier. However, if the risk of re-injury is elevated, the success of the intervention is at least questionable. It is suggested that both time to return to sport and re-injury rate

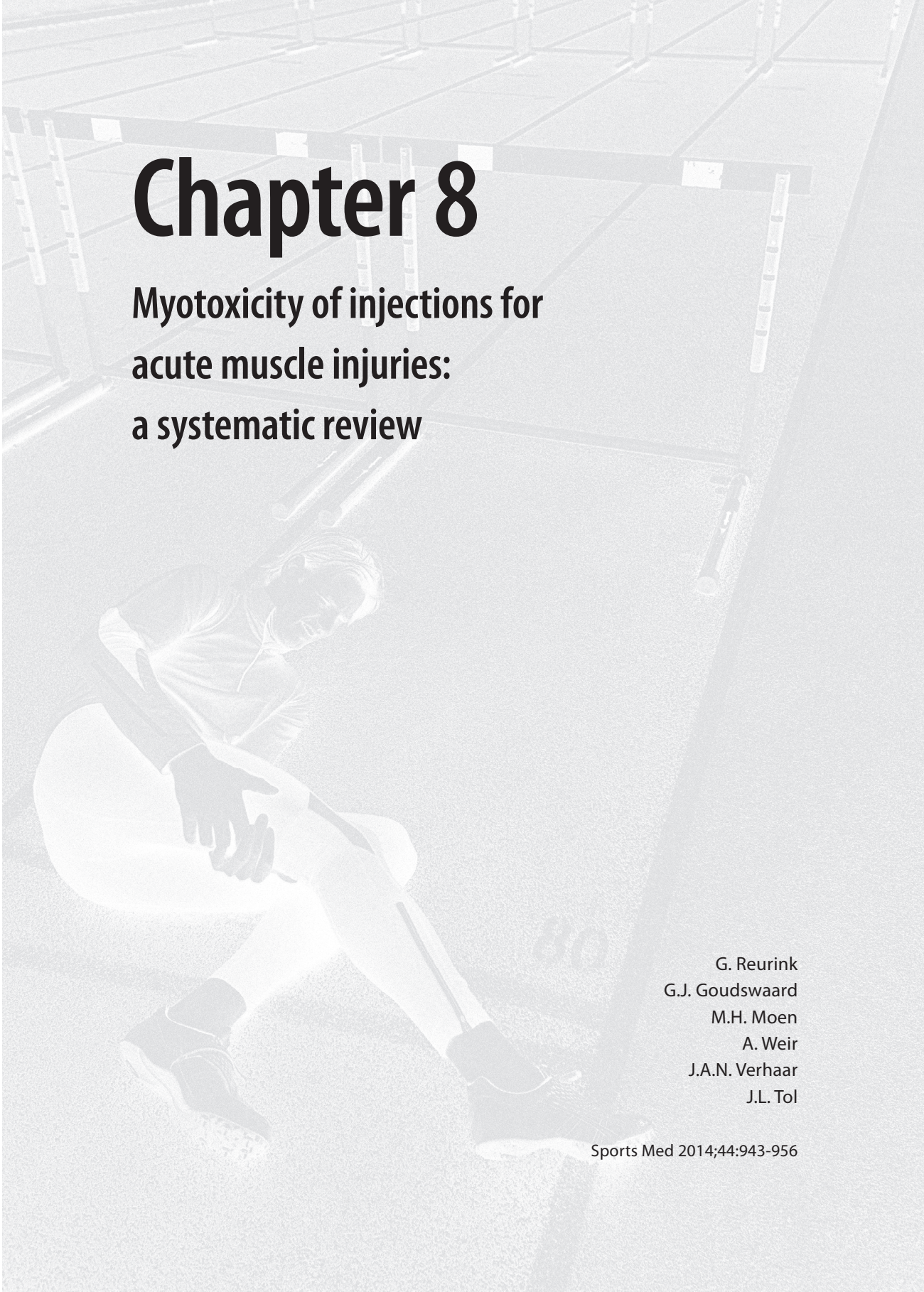
should be measured to determine the efficacy of an intervention in athletes with acute hamstring injuries. Three of the studies included reported time to return to sport[131,141,208] and only one reported the re-injury rate[208]. In the future validated outcome measures need to be developed.

CONCLUSION

Despite acute hamstring injuries being common in the athletes, there is a lack of high quality studies on their treatment. In this review only limited evidence was found for a positive effect of stretching, agility and trunk stability exercises, intramuscular Actovegin injections and slump stretching as treatments. Limited evidence was found that there is no effect of NSAID's and manipulation of the sacroiliac joint. Further research is needed, using an appropriate control group, randomisation and blinding. It is recommended that future studies assess the efficacy of interventions with time to return to sport as well as re-injury rate.

Chapter 8

Myotoxicity of injections for acute muscle injuries: a systematic review



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ABSTRACT

Background – Injection therapies are widely used for muscle injuries. As there is only a limited evidence for their efficacy, physicians should be aware of the potential harmful effects of these injected preparations.

Objectives – The purpose of this review is to systematically review the literature on the myotoxic effects of commonly used intramuscular injection preparations used in acute muscle injuries.

Data sources – The databases of PubMed, EMBASE, Web of Science, Cochrane library, CINAHL and Sportdiscus were searched in March 2013.

Study eligibility criteria – Studies reporting histological evaluation or creatine kinase activity after intramuscular injection with local anesthetics, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), platelet-rich plasma (PRP), Traumeel® and Actovegin®, or combination preparations were eligible for inclusion.

Data analysis – Two authors independently screened the search results and assessed risk of bias. A best evidence synthesis was used to identify the level of evidence.

Results – Forty-nine studies were included in this systematic review. There is strong to moderate evidence that intramuscular injected local anesthetics and NSAIDs are myotoxic, and conflicting evidence on the myotoxicity of PRP. There is limited evidence that single corticosteroids injections are not myotoxic, but have a synergistic myotoxic effect together with local anesthetics. There is no information to assess whether Actovegin® and Traumeel® are myotoxic.

Conclusion – Local anesthetics and NSAIDs injections are not recommended for the treatment of muscle injuries in athletes as they are myotoxic. The possible myotoxic effects of corticosteroids, PRP, Traumeel® and Actovegin® should be assessed in future research.

BACKGROUND

Muscle injuries are among the most common time-loss injuries in soccer, American and Australian football[61,69,169,206]. These injuries have significant consequences for the performance of players and their clubs, as athletes are not able to train or compete for several weeks or even months and have an increased risk of recurrent injury after they have returned to play[61,69,169,206,234].

Especially in elite sports, physicians face substantial external pressure from coaching staff, press and injured players themselves, to get players with acute muscle injuries ready to return to play quickly. Injection therapies have been suggested to speed up recovery and reduce the risk of recurrence. Corticosteroids[132,218], non-steroidal anti-inflammatory drugs (NSAIDs)[244], platelet enriched plasma products[30,91,186,241], and Traumeel® and/or Actovegin® injections[131,179,241], as single or combination preparations are reported as treatment of muscle injuries. Although intramuscular injections are widely used, there is only a limited evidence base for the efficacy[30,90,91,131,132,171,179,186,193,209,218,241,244].

Clinical and histopathological studies have shown the potential myotoxicity of intramuscular injections in both animals and humans[32,184,185,245], with pain at the injection site and histopathological changes of inflammation, necrosis and fibrosis[32,184,185,245]. Besides histological changes, local or plasma creatine kinase (CK) concentration is the most commonly used valid marker for skeletal muscle myotoxicity[56,164,166].

With a paucity of high level evidence of their efficacy and the "Primum non nocere" ("first do no harm") dogma of Hippocrates, knowledge about the potential myotoxic effect should be considered before injecting intramuscular preparations for acute muscle injuries. The purpose of this review is to systematically review the literature on the possible myotoxic effects of commonly used preparations injected intramuscularly for acute muscle injuries.

METHODS

Literature search

A comprehensive systematic literature search was performed in March 2013. The databases of PubMed, EMBASE, Web of Science, Cochrane library, CINAHL and Sportdiscus were searched without any time limits. The complete electronic search strategy is presented in Table 8.1. Additional citation tracking was performed by manually screening the reference lists of eligible studies.

Table 8.1 Search strategy

Search strategy	Records
PubMed Muscle[All fields] AND inject*[tw] AND (intramuscular inject*[all fields] OR local injection[All fields] OR local therapy[All fields] OR local administration[All fields] OR myotoxi*[tw] OR tolerability[tw] OR histolog*[tw] OR "muscles/ultrastructure"[mesh] OR "Histological Techniques"[Mesh]) AND (Bupivacaine [all fields] OR lidocaine[all fields] OR mepivacaine[all fields] OR corticosteroid[all fields] OR Platelet rich plasma[All fields] OR autologous conditioned plasma[tw] OR autologous conditioned serum[tw] OR platelet enriched plasma[tw] OR autologous blood[tw] OR Traumeel®[tw] OR Actovegin®[tw] OR Anti-Inflammatory Agents, Non-Steroidal[Mesh]	648
EMBASE Muscle:ti,ab,de AND inject*:ti,ab,de AND ('intramuscular drug administration'/syn OR 'local therapy'/exp OR myotoxi*:ti,ab,de OR tolerability:ti,ab,de OR histolog*:ti,ab,de) AND ('bupivacaine'/syn OR 'lidocaine'/syn OR 'mepivacaine'/syn OR corticosteroid*:ti,ab,de OR 'thrombocyte rich plasma'/syn OR 'autologous conditioned serum':ti,ab,de OR 'autologous conditioned plasma':ti,ab,de OR 'platelet enriched plasma':ti,ab,de OR 'autologous blood':ti,ab,de OR Actovegin®/syn OR Traumeel®:ti,ab,de OR 'nonsteroid antiinflammatory agent'/mj)	836
Web of Science TS = (Muscle$ AND inject* AND (intramuscular injection* OR (local* NEAR/2 (therap* OR injection* OR administration)) OR myotoxi* OR tolerability OR histolog*) AND (bupivacain$ OR lidocain$ OR mepivacain$ OR corticosteroid* OR (((platelet* OR thrombocyt*) NEAR/2 (rich OR enriched)) NEAR/2 (plasma OR serum) OR Autologous NEAR/2 (serum OR plasma OR blood)) OR Actovegin® OR Traumeel® OR ((nonsteroid* OR non-steroid*) NEAR/2 (anti-inflammator* OR antiinflammator*))))	307
Cochrane library (Muscle* AND inject* AND (intramuscular injection* OR (local* NEAR/2 (therap* OR injection* OR administration)) OR myotoxi* OR tolerability OR histolog*) AND (bupivacain* OR lidocain* OR mepivacain* OR corticosteroid* OR (((platelet* OR thrombocyt*) NEAR/2 (rich OR enriched)) NEAR/2 (plasma OR serum) OR Autologous NEAR/2 (serum OR plasma OR blood)) OR Actovegin® OR Traumeel® OR ((non NEXT steroid*) OR nonsteroid*) NEAR/2 ((anti NEXT inflammator*) OR antiinflammator*))):ti,ab,kw In all text. Restricted to clinical trials.	83
CINAHL (EBSCOhost Research Databases) Muscle* AND inject* AND (intramuscular injection* OR (local* N2 (therap* OR injection* OR administration)) OR myotoxi* OR tolerability OR histolog*) AND (bupivacain* OR lidocain* OR mepivacain* OR corticosteroid* OR (((platelet* OR thrombocyt*) N2 (rich OR enriched)) N2 (plasma OR serum) OR autologous N2 (serum OR plasma OR blood)) OR Actovegin® OR Traumeel® OR ((non steroid* OR nonsteroid* OR non-steroid*) N2 (anti inflammator* OR anti-inflammator* OR antiinflammator*)))	99
SPORTDiscus Muscle* AND inject* AND (intramuscular injection* OR (local* N2 (therap* OR injection* OR administration)) OR myotoxi* OR tolerability OR histolog*) AND (bupivacain* OR lidocain* OR mepivacain* OR corticosteroid* OR (((platelet* OR thrombocyt*) N2 (rich OR enriched)) N2 (plasma OR serum) OR autologous N2 (serum OR plasma OR blood)) OR Actovegin® OR Traumeel® OR ((non steroid* OR nonsteroid* OR non-steroid*) N2 (anti inflammator* OR anti-inflammator* OR antiinflammator*)))	36

Table 8.2 Eligibility criteria

Inclusion criteria
• The article had to be an original report that studied an intramuscular injection in skeletal muscles with one of the following drugs: o Local anesthetic bupivacaine, lidocaine or mepivacaine; o Corticosteroids; o Non-steroidal anti-inflammatory drug o Platelet enriched plasma products; o Traumeel® and/or Actovegin®; o Combined preparation of one of the abovementioned drugs
• In the article at least one of the following outcome measures had to be reported: o Description of morphologic changes of muscle tissue at injection site in hematoxylin and eosin stained histological sections; o Creatine kinase activity in muscle tissue at injection site or in plasma
• Full text of the article was available
• The article was written in English, Dutch or German
Exclusion criteria
• Case reports: studies reporting isolated cases
• Combined preparation with other than abovementioned drugs
• Injection with drugs not registered for use in humans
• Injection in ocular muscles
• Injection in dystrophic muscles

Study selection

Two reviewers independently assessed potential eligible studies identified by the search strategy. The eligibility criteria are presented in Table 8.2. All titles and abstracts were assessed by 2 reviewers, and relevant articles were obtained. All relevant articles were read independently in full text by 2 reviewers to assess whether they met the inclusion criteria. If there was a difference in opinion on eligibility, the independent assessment on eligibility of a third reviewer was decisive.

Data extraction

One reviewer recorded the study design, population, intervention, outcome measure, maximum follow-up time and outcome using standardized data extraction forms. Descriptive histopathology findings were extracted from the studies included, and when available continuous and dichotomous outcomes were extracted of quantitative measures. Descriptive histopathology findings were considered indicative for myotoxicity whenever histopathologic changes of tissue degeneration, inflammatory infiltrate or necrosis were described.

Risk of bias assessment

Two reviewers independently assessed the risk of bias of the studies included using questions from existing assessment tools[157,230]. The 4 risk of bias items are presented in Table 8.3. Each item was scored as 'yes', 'no' or 'unsure'. If there was a difference in opinion

Table 8.4 Characteristics of the included studies

Reference	Study design	Population (n)	Injection	Outcome measure	Outcome	Myo-toxic
Local anaesthetics						
Abe et al. 1987[1]	Case series	Rats (NA)	I: Bupivacaine	Histology	Completely degenerated fibers and inflammatory infiltrate	+
Akiyama et al. 1992[5]	CLS	Rats (52)	I: Bupivacaine C: Saline	Histology	I: Massive necrosis and inflammatory infiltrate C: Not reported	+
Basson and Carlson 1980[26]	CLS	Rats (75)	I1: Mepivacaine, single injection I2: Mepivacaine, six repeated injections C1: Saline, single injection C2: Needle only, six repeated injections C3: Saline, six repeated injections	Histology	I1: Lesion typically about 30% of muscle cross-sectional area; oedema and phagocytic degeneration I2: Lesions about 30-100% of muscle cross-sectional area; oedema and phagocytic degeneration, scarring and atrophied fibers C1-3: No significant damage	+
Beitzel et al. 2004[29]	CLS	Rats (73)	I: Bupivacaine C: No treatment	Histology	Fiber cross sectional area I<C ($p<0.05$)	+
Brazeau and Fung 1989[33]	CLS	Rats (NA)	I: Lidocaine C1: No treatment C2: Needle only C3: Saline	Local CK release	I: 9.19 ± 3.52 U/L x 10^2 C1: 0.10 ± 0.14 U/L x 10^2 C2: 0.70 ± 0.31 U/L x 10^2 C3: 1.47 ± 0.81 U/L x 10^2	+
Brazeau et al. 2011[34]	CLS	Rats (NA)	I: Bupivacaine C: Saline	Local CK release	I>C ($p<0.05$)	+
Carlson et al. 1990[40]	CLS	Monkeys (35)	I1: Bupivacaine I2: Lidocaine I3: Mepivacaine C: Saline	Histology	I1+I2+I3: Oedema, degeneration and inflammatory infiltrate C: Few damaged fibres along needle track	+
Cereda et al. 2012[42]	CLS	Rats (12-14)	I: Bupivacaine C: Saline	Histology (muscle damage score 0-3) Plasma CK	I: median (25^{th}-75^{th}): 1.9 (1.65-2.0) C: median (25^{th}-75^{th}): 0 (0-0) I > C: 5.5 fold higher ($p < .0001$)	+ +

Table 8.4 Characteristics of the included studies (continued)

Reference	Study design	Population (n)	Injection	Outcome measure	Outcome	Myotoxic
Chellman et al. 1990[43]	CLS	Rats (20)	I: Lidocaine C: Saline	Histology	I: Degeneration, necrosis, inflammatory infiltrate, oedema and haemorrhage C: Minimal lesions	+
				Plasma CK	I: Increase ($p<0.05$) C: CK no increase	+
Cherng et al. 2010[45]	CLS	Rats (24)	I1: Bupivacaine 0.25% I2: Bupivacaine 0.5% I3: Bupivacaine 1% C: saline	Histology	I1-3: Mild to severe muscle damage with inflammatory infiltrate. Ranked severity I3>I2>I1 C: No abnormality	+
Duguez et al. 2002[57]	CLS	Rats (n = 44)	I: Bupivacaine C: Saline	Histology	I: Necrosis, oedema and inflammatory infiltrate affecting 99% (± 1) of cross sectional area C: no signs of necrosis	+
Foster and Carlson 1980[70]	CLS	Rats (14-16)	I1: Bupivacaine I2: Lidocaine C: Saline	Histology	I1-2: Necrosis, degeneration, haemorrhage and inflammatory infiltrate I1: Up to 90% of muscle involved I2: Up to 50% of muscle involved C: Limited damage along the needle track	+
Fujikake et al. 2009[72]	CLS	Rats (n = 28)	I: Bupivacaine C: Saline	Histology	I: Necrosis and inflammatory infiltrate C: Limited changes along the needle track	+
Grim et al. 1988[80]	CLS	Rats (NA)	I1: Bupivacaine I2: Lidocaine 1% I3: Lidocaine 2% C: Saline	Histology	I1-3: Necrosis and inflammatory infiltrate I1: 29% (±4) of cross-sectional area affected I2: 15% (±1) of cross-sectional area affected I3: 58% (±4) of cross-sectional area affected C: Limited damaged along the needle track	+
				Plasma CK	Increase I1-3 > C ($p<0.05$)	+
Guttu et al. 1990[82]	CLS	Rats (10)	I: Bupivacaine C: Saline	Histology	I: Necrosis and mild inflammatory infiltrate. C: No abnormality	+
Hall-Craggs et al. 1974[85]	CLS	Rats	I1: Bupivacaine, single injection I2: Bupivacaine, three repeated injections C: Saline	Histology	I: Degeneration, haemorrhage, inflammatory infiltrate. Severity I2>I1 C: No abnormality	+

Table 8.4 Characteristics of the included studies (continued)

Reference	Study design	Population (n)	Injection	Outcome measure	Outcome	Myo-toxic
Horiguchi et al. 2002[106]	CLS	Rats (64)	I1: Bupivacaine C: Saline	Histology	I: Degeneration, necrosis, oedema and inflammatory infiltrate C: No abnormality	+
Ishiura et al. 1983[109]	CLS	Rats (40)	I1: Bupivacaine C: Saline	Histology	I: Necrosis and inflammatory infiltrate C: No abnormality	+
Ishiura et al. 1986[110]	CLS	Rats (NA)	I1: Bupivacaine C: Saline	Histology	I: Necrosis and inflammatory infiltrate C: Limited damage along the needle track	+
Jiménez-Díaz et al. 2012[112]	CLS	Rats (36)	I: Mepivacaine C: No treatment	Histology	I: Degenerating fibers, oedema, inflammatory infiltrate C: No abnormality	+
Jones et al. 1982[113]	CLS	Rats (87)	I1: Bupivacaine 0.5% I2: Bupivacaine 0.75% I3: Bupivacaine 1.0% I4: Bupivacaine 1.5% C: Saline	Histology	I2-4: Regions of ischemic muscle. Severity I4>I3>I2 I1: Essentially no ischemic muscle. C: Not described	+
Lagrota-Candido et al. 2010[127]	CLS	Mice (NA)	I: Bupivacaine C: not specified	Histology	I: Inflammatory infiltrate and regenerating fibers. C: Not described	+
Louboutin et al. 1996[135]	CLS	Rats (NA)	I: Bupivacaine C: No treatment	Histology	I: Necrosis and inflammatory infiltrate C: No abnormality	+
McNeill Ingham et al. 2011[149]	CLS	Rats (16)	I: Bupivacaine C: No treatment	Histology	I: Necrosis and inflammatory infiltrate C: Not described	+
Nepomnyashchikh et al. 2007[161]	CLS	Rats (38)	I: Bupivacaine C: No treatment	Histology	I: Necrosis, inflammatory infiltrate and haemorrhage C: Not described	+
Nonaka et al. 1983[162]	CLS	Rats (38)	I: Bupivacaine C: Saline	Histology	I: Necrosis and inflammatory infiltrate C: No fibers underwent massive necrosis	+

Table 8.4 Characteristics of the included studies (continued)

Reference	Study design	Population (n)	Injection	Outcome measure	Outcome	Myo-toxic
Nosaka et al. 1996[163]	CLS	Rats (30)	I1: Bupivacaine unilateral I2: Bupivacaine bilateral C1: No treatment C2: Saline	Histology	I1-2:Completely disorganised fibers and inflammatory infiltrate C1-2: not mentioned	+
				Plasma CK	I1-2: Increase ($p<0.01$) C1-2: No increase I1-2 > C1-2 ($p<0.05$) I1>I2 ($p<0.05$)	+
Nosaka 1999[165]	CCT	Healthy human (5)	I1: Bupivacaine 0.5% dose 2 ml I2: Bupivacaine 0.5% dose 10 ml I3: Bupivacaine 0.5% dose 20 ml	Plasma CK	I1-3: Increase ($p<0.01$); I3>I2>I1	+
Orimo et al. 1991[173]	CLS	Rats (60)	I: Bupivacaine C: Saline	Histology	I: Necrosis and inflammatory infiltrate C: Small number of inflammatory cells along needle track	+
Osawa et al. 1989[174]	CLS	Mice (NA)	I1: Lidocaine single injection I2: Lidocaine two repeated injections I3: Lidocaine three repeated injections I4: Lidocaine five repeated injections C: Saline	Histology	I1-4: Degeneration and necrosis; I1<I2<I3<I4 C: Little damage	+
Plant et al. 2006[180]	CLS	Mice (NA)	I: Bupivacaine C: No treatment	Histology	I: Up to 51% of the cross sectional area consisted of degenerated fibers C: Not described	+
Politi et al. 2006[181]	CLS	Rats (21)	I: Bupivacaine C: Saline	Histology	I: Necrosis and inflammatory infiltrate C: Not described	+
Rosenblatt et al. 1992[198]	CLS	Rats (256)	I: Bupivacaine C1: Saline C2: No treatment	Histology	I: Massive fiber degeneration and inflammatory infiltrate. After 21 days increased amount of connective tissue C1-2: No abnormality, except elevated water content at 1-2h in C1	+

Table 8.4 Characteristics of the included studies (continued)

Reference	Study design	Population (n)	Injection	Outcome measure	Outcome	Myo-toxic
Sadeh et al. 1984[200]	CLS	Rats	I: Bupivacaine C: No treatment	Histology	I: Complete disorganization of the muscle with inflammatory cells infiltrate C: Not described	+
				Local CK release	I < C ($p<0.001$)	+
Sadeh et al. 1985[199]	CLS	Rats (9)	I: Bupivacaine, repeated weekly for 5 months C: Saline	Histology	I: Increased fibrosis Fiber size : I (40±22 µm) < C (49±12 µm)	+
Sauerwein et al. 1975[202]	CCT	Human (24)	I: Lidocaine C: Saline	Plasma CK	I: Increase in 75% of subjects C: No increase	+
Steiness et al. 1978[217]	CCT & CLS	Heart failure patients (9), pigs (8) and rabbits (8)	I: Lidocaine C: Saline	Histology (pigs and rabbits)	I: Necrosis and inflammatory infiltrate C: No damage	+
				Plasma CK	I: Increase in all populations C: No increase in human and rabbits, increase in pigs	+
Tomas i Ferré et al. 1989[228]	CLS	Rats (24)	I: Bupivacaine C1: No treatment C2: Saline	Histology	I: Local necrosis, oedema and inflammatory infiltrate C: Not described	+
White et al. 2009[239]	CLS	Mice (NA)	I: Bupivacaine C: No treatment	Histology	Cross sectional area: I < C at 14 days ($p<0.05$)	+
Yildiz et al. 2011[243]	CLS	Rats (60)	I: Bupivacaine C: Saline	Histology	I: Oedema, necrosis and inflammatory cells infiltrate C: No abnormality	+

Table 8.4 Characteristics of the included studies (continued)

Reference	Study design	Population (n)	Injection	Outcome measure	Outcome	Myotoxic
Corticosteroids						
Guttu et al. 1990[82]	CLS	Rats (30)	I1: Triamcinolone I2: Bupivacaine I3: Triamcinolone + bupivacaine C: Saline	Histology	I1: Normal findings I2: Moderate necrosis and mild inflammatory infiltrate. Normalisation at 2 weeks I3: Extensive necrosis and marked inflammatory infiltrate. Little evidence of repair at 4 weeks Ranked severity: I2<I3 C: Normal findings	I1: - I2,I3: +
Non-steroidal anti-inflammatory drugs						
Chellman et al. 1994[44]	CLS	Rats (70)	I1: Ketorolac 10mg ml^{-1} I2: Ketorolac 30mg ml^{-1} I3: Diclofenac I4: Piroxicam I5: Ketoprofen I6: Metamizole C: Saline	Histology	I1-6: Muscle degeneration, inflammatory infiltrates, haemorrhage and oedema. Ranked severity: I1<I2<I5<I4<I3<I6 C: Normal findings I1,I2,I6,C: No change	+
				Plasma CK	I3-5: Increase ($p<0.05$)	I1,I2,I6: - I3-5: +
Ghozlan et al. 1996[76]	RCT	Rheumatoid and osteoarthritis patients (210)	I1: Meloxicam I2: Piroxicam	Plasma CK	I1: No change I2: 59% increase ($p = 0.01$)	I1: - I2: +
Guterres et al. 2000[81]	CLS	Rats (16)	I: Diclofenac C: Saline	Histology	I: Mildly severe lesions, inflammatory infiltrate C: not mentioned	+
				Plasma CK	I: Increase compared to C ($p<0.05$)	+
Lima et al. 2002[133]	CLS	Rats (12)	I: Diclofenac C: no treatment	Histology	I: Severe tissue damage; degeneration, myocytolysis, inflammatory infiltrate	+
				Plasma CK	I: Increase compared to C ($p<0.05$)	+

Table 8.4 Characteristics of the included studies (continued)

Reference	Study design	Population (n)	Injection	Outcome measure	Outcome	Myo-toxic
Narjes et al. 1996[160], study 1	RCT	Healthy human (32)	I1: Meloxicam 5mg I2: Meloxicam 10mg I3: Meloxicam 20mg I4: Meloxicam 30mg C: Saline	Plasma CK	I1-4, C: No increase	-
Narjes et al. 1996[160], study 2	Cross over RCT	Healthy human (12)	I: Meloxicam 15 mg C: Meloxicam 15 mg intravenous	Plasma CK	I, C: No increase	-
Pyörälä et al. 1999[183]	Cross over CCT	Cows (5)	I1: Ketoprofen I2: Metamizole C: Saline	Plasma CK	I1: Increase ($p<0.05$) I2: Increase ($p<0.05$) C: No change	+
Platelet-rich plasma						
Hammond et al. 2009[94]	CLS	Rats, muscle strain model (72)	I: Platelet-rich plasma C1: Platelet-poor plasma C2: no treatment	Histology (centrally nucleated fiber count)	I > C1 and C2, $p<.05$	-
Wright-Carpenter et al. 2004[242]	CLS	Mice, muscle contusion model (108)	I: Platelet-rich plasma C: Saline	Histology	I: Less necrosis and granulomatous tissue than in control	-
Harris et al. 2012[98]	CLS	Rabbits (18)	I: Platelet-rich plasma C: Saline	Histology	I: Inflammatory infiltrate, oedema, necrosis, fibrosis, calcium deposition C: Normal findings	+

Abbreviations: CLS, controlled laboratory study; RCT, randomised controlled trial; CCT, controlled clinical trial; NA, not available; I, intervention group; C, control group; CK, creatine kinase;

+ outcome indicative for myotoxicity, - outcome not indicative for myotoxicity

on an item score, the independent assessment of the third reviewer was decisive. Studies were considered to have a low risk of bias when 3 or more of the 4 items scored 'yes'.

All reviewers involved in the study selection, data extraction and risk of bias assessment were medical doctors.

Best evidence synthesis

As the studies were considered heterogeneous with regard to the interventions, outcome measures and methodological quality statistical pooling of the results was not possible. Instead a best evidence synthesis was used[215]. The results of the risk of bias assessments of the individual studies were used to classify the level of evidence[229]. This qualitative analysis was performed with 5 levels of evidence based on the risk of bias and results of the included studies:

1. Strong evidence: provided by two or more studies with low risk of bias and by generally consistent findings in all studies (≥ 75% of the studies reported consistent findings).
2. Moderate evidence: provided by one study with low risk of bias and/or two or more studies with high risk of bias and by generally consistent findings in all studies (≥ 75% of the studies reported consistent findings).
3. Limited evidence: provided by only one study with high risk of bias.
4. Conflicting evidence: inconsistent findings in multiple studies (<75% of the studies reported consistent findings).
5. No evidence: when no studies could be found.

RESULTS

Literature search

The search yielded 1386 records. After screening the titles and abstracts 87 studies were identified as possibly relevant, for which full text articles were retrieved. Citation tracking added no additional relevant studies. After review of the full text, out of these 87 studies 38 were excluded and 49 studies[82,1,5,26,29,33,34,40,42,43,45,57,70,72,80,85,106,109,110,112,113,127,135,149,161–163,165,173,174,180,181,198–200,202,217,228,239,243,44,76,81,133,160,183,94,98,242] met the eligibility criteria (Figure 8.1).

Study design

There were 4 studies in human subjects[76,160,165,202], 44 studies using animal models[82,1,5,26,29,33,34,40,42,43,45,57,70,72,80,85,106,109,110,112,113,127,135,149,161–163,173,174,180,181,198–200,228,239,243,44,81,133,183,94,98,242] and 1 study in both human subjects and animal models[217]. There were 2 randomized controlled trials[76,160], 3 clinical controlled trials[165,202,217], 43 controlled laboratory studies[82,5,

26,29,33,34,40,42,43,45,57,70,72,80,85,106,109,110,112,113,127,135,149,161–163,173,174,180,181,198–200,228,239,243,44,81,133,183,94,98,242

and 1 case series[1].

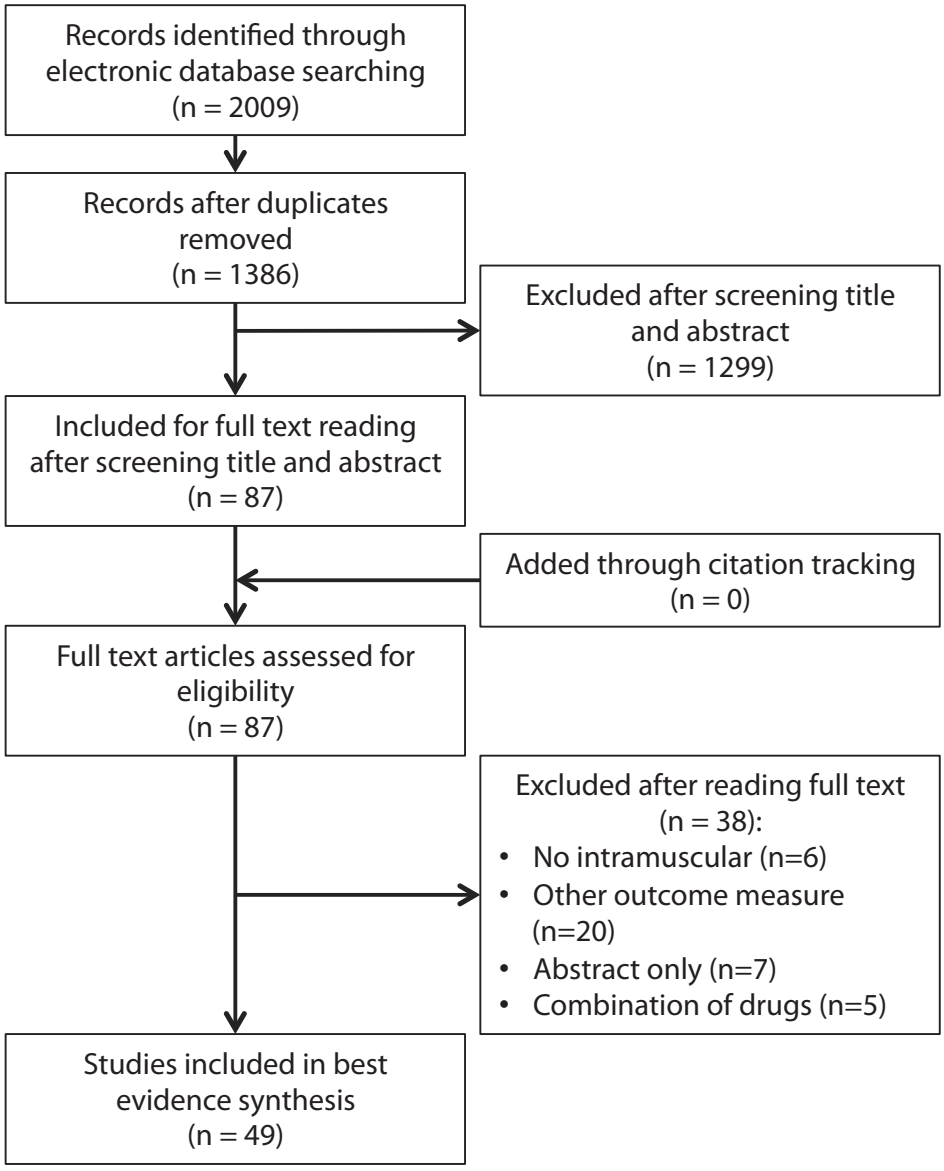

Figure 8.1. Study selection flow diagram

Description of included studies

Table 8.4 presents the characteristics of the included studies.

Risk of bias assessment

The scores of the studies included, on the 4 risk of bias items, are presented in Table 8.5. Nineteen studies were assessed as having a low risk of bias (score ≥ 3)[29,33,34,42,44,45,57,80,81,133,163,165,180,183,198,200,239,242,243] and 30 studies were assessed as having a high risk of bias (score < 3)[1,5,26,40,43,70,72,76,82,85,94,98,106,109,110,112,113,127,135,149,160–162,173,174,181,199,202,217,228].

Injected preparations and outcome

An overview of the best evidence synthesis is presented in Table 8.6. There were no studies on Actovegin® and/or Traumeel®, 1 study on the corticosteroid triamcinolone[82], 40 studies on the local anesthetics bupivacaine[1,5,29,34,40,42,45,57,70,72,80,82,85,106,109,110,113,127,135,149,161–163,165,173,180,181,198–200,228,239,243], lidocaine[33,40,43,70,80,174,202,217] and mepivacaine[26,40,112], 6 studies on the NSAIDs diclofenac[44,81,133], ketoprofen[44,183], ketorolac[44], meloxicam[76,160], metamizole[44,183] and piroxicam[44,76] and 3 studies on platelet-rich plasma[94,98,242].

Local anesthetics

There is strong evidence that the local anesthetics bupivacaine and lidocaine are myotoxic and moderate evidence that mepivacaine is myotoxic. All 40 studies included on the intramuscular injected local anesthetics reported outcomes indicative for myotoxicity of these drugs[1,5,26,29,33,34,40,42,43,45,57,70,72,80,82,85,106,109,110,112,113,127,135,149,161–163,165,173,174,180,181,198–200,202,217,228,239,243].

Thirty-six studies reported histology as an outcome measure[1,5,26,29,40,42,43,45,57,70,72,80,82,85,106,109,110,112,113,127,135,149,161–163,173,174,180,181,198–200,217,228,239,243]. Histology typically showed fiber degeneration, edema, inflammatory cell infiltration and necrosis after injection with local anesthetics. Near to complete normalization of histological changes were reported between 2 to 5 weeks[5,26,40,57,70,80,82,85,106,112,135,149,162,173,181,198,243]. In control muscles that received no injection or saline injection, studies reported no abnormalities or only limited damage around the needle track.

Ten studies reported CK levels as an outcome measure and found increased CK levels after intramuscular injection of the local anesthetics in plasma[42,43,80,163,165,202,217] or local CK release at the injection site[33,34,200]. The method to assess local CK release is performed by dissecting the injected muscle and placing it into a vial containing a balanced salt solution. Subsequently the CK level in the salt solution is determined over time as a measure of CK release of the muscle. Six studies studied different doses and all reported increased myotoxicity with higher doses, indicating a dose-dependent response[26,45,80,113,165,174].

Corticosteroids

There is limited evidence that single intramuscular injections of triamcinolone are not myotoxic. A combined preparation of triamcinolone and bupivacaine is more myotoxic than bupivacaine alone. There was only 1 study on intramuscular corticosteroid

Table 8.5 Risk of bias assessment

	Risk of bias items				
Reference	1	2	3	4	**Total score**
Abe et al. 1987[1]	+	-	-	-	1
Akiyama et al. 1992[5]	+	-	-	-	1
Basson and Carlson 1980[26]	+	-	-	-	1
Beitzel et al. 2004[29]	+	-	+	+	3
Brazeau et al. 1989[33]	+	+	+	-	3
Brazeau et al. 2011[34]	+	+	-	+	3
Carlson et al. 1990[40]	+	-	-	-	1
Cereda et al. 2012[42]	+	+	+	+	4
Chellman et al. 1990[43]	-	+	+	-	2
Chellman et al. 1994[44]	+	+	+	+	4
Cherng et al. 2010[45]	+	+	+	+	4
Duguez et al. 2002[57]	+	-	+	+	3
Foster and Carlson 1980[70]	+	-	-	-	1
Fujikake et al. 2009[72]	+	-	-	-	1
Ghozlan et al. 1996[76]	-	+	-	+	2
Grim et al. 1988[80]	+	+	+	-	3
Guterres et al. 2000[81]	+	+	+	+	4
Guttu et al. 1990[82]	+	+	-	-	2
Hall-Craggs et al. 1974[85]	+	-	-	-	1
Hammond et al. 2009[94]	-	-	+	+	2
Harris et al. 2012[98]	+	+	-	-	2
Horiguchi et al. 2002[106]	+	-	-	-	1
Ishiura et al. 1983[109]	+	-	-	-	1
Ishiura et al. 1986[110]	+	-	-	-	1
Jiménez-Díaz et al. 2012[112]	+	-	-	-	1
Jones et al. 1982[113]	+	-	-	-	1
Lagrota-Candido et al. 2010[127]	+	-	-	-	1
Lima et al. 2002[133]	+	+	+	-	3
Louboutin et al. 1996[135]	+	-	-	-	1
McNeill Ingham et al. 2011[149]	+	-	-	-	1
Narjes et al. 1996[160]	+	+	-	-	2
Nepomnyashchikh et al. 2007[161]	+	-	-	-	1
Nonaka et al. 1983[162]	+	-	-	-	1
Nosaka et al. 1996[163]	+	+	+	+	4
Nosaka 1999[165]	-	+	+	+	3
Orimo et al. 1991[173]	+	-	-	-	1
Osawa et al. 1989[174]	+	-	-	-	1
Plant et al. 2006[180]	+	+	-	+	3

Table 8.5 (continued)

	Risk of bias items				
Reference	1	2	3	4	**Total score**
Politi et al. 2006[181]	+	-	-	-	1
Pyörälä et al. 1999[183]	+	+	+	-	3
Rosenblatt et al. 1992[198]	+	-	+	+	3
Sadeh et al. 1984[200]	+	+	+	+	4
Sadeh et al. 1985[199]	+	-	+	-	2
Sauerwein et al. 1975[202]	+	+	-	-	2
Steiness et al. 1978[217]	+	+	-	-	2
Tomas i Ferré et al. 1989[228]	+	-	-	-	1
White et al. 2009[239]	+	-	+	+	3
Wright-Carpenter et al. 2004[242]	+	-	+	+	3
Yildiz et al. 2011[243]	+	+	+	+	4

Total score is the number of positive answers on the risk of bias items presented in table 8.3

injections that met the eligibility criteria[82]. Guttu et al. reported no abnormalities on histology of muscle tissue after injection with triamcinolone or saline in a rat model[82]. Triamcinolone and bupivacaine combination preparations resulted in more extensive muscular lesions than bupivacaine injections alone, indicating a synergistic myotoxic effect of triamcinolone and bupivacaine. The histology after 2 weeks showed normalization of the muscle tissue in the bupivacaine only group. In the group that received a combined preparation of bupivacaine with triamcinolone there was still evidence of regeneration of the degenerated tissue at the last evaluation at 4 weeks.

Non-steroidal anti-inflammatory drugs

For intramuscular NSAIDs, there is strong evidence for the myotoxicity of diclofenac, ketoprofen and metamizole and moderate evidence for myotoxicity of piroxicam and ketorolac. There is moderate evidence that meloxicam is not myotoxic. All studies reported plasma CK levels as an outcome measure[44,76,81,133,160,183] and 3 studies also reported histology as an outcome measure[44,81,133]. In the muscle tissue injected with NSAIDs on histological evaluation muscle degeneration, hemorrhage, edema, infiltration of inflammatory cells, and myocytolysis was observed up to 7 days after injection. Histology at later follow-up time intervals was not performed.

Platelet-rich plasma

There is conflicting evidence regarding the myotoxicity of intramuscular PRP injections. Two studies used an animal muscle injury model and reported increased signs of regeneration, less necrosis and less granulomatous tissue in the muscles injected with PRP

compared to control muscles on histological evaluation up to 2 weeks[94,242]. Harris et al. found that uninjured rabbit muscles injected with PRP showed edema, inflammatory cells infiltrate, necrosis and fibrosis up to 12 weeks after injection, indicating myotoxicity of PRP[98].

Actovegin® and/or Traumeel®

As there were no studies on possible myotoxic effects of intramuscular injection of Actovegin® and/or Traumeel®, there is no evidence available for assessing the myotoxicity of these drugs.

Table 8.6 Best evidence synthesis overview of myotoxicity of intramuscular injected drugs

Drugs	Low risk of bias	High risk of bias	Best evidence synthesis	Level of evidence
Local anaesthetic				
• Bupivacaine	+[29,34,42,45,57,80,163, 165,180,198,200,239, 243]	+[1,5,40,70,72,82,85,106,109,110,113, 127,135,149,161,162,173,181,199, 228]	Myotoxic	Strong
• Lidocaine	+[33,80]	+[40,43,70,174,202, 217]	Myotoxic	Strong
• Mepivacaine		+[26,40,112]	Myotoxic	Moderate
Corticosteroids				
• Triamcinolone		-[82]	Not myotoxic	Limited
• Triamcinolone + bupivacaine		+[82]	Myotoxic	Limited
Non-steroidal anti-inflammatory drugs				
• Diclofenac	+[44,81,133]		Myotoxic	Strong
• Ketoprofen	+[44,183]		Myotoxic	Strong
• Ketorolac	+[44]		Myotoxic	Moderate
• Meloxicam		-[76,160]	Not Myotoxic	Moderate
• Metamizole	+[44,183]		Myotoxic	Strong
• Piroxicam	+[44]	+[76]	Myotoxic	Moderate
Platelet-rich plasma	-[242]	-[94], +[98]	Unknown	Conflicting
Traumeel® and/or Actovegin®			Unknown	No evidence

+ Outcome indicative for myotoxicity; – Outcome not indicative for myotoxicity.

DISCUSSION

The major findings of this systematic review are that there is strong evidence for the myotoxicity of intramuscular injection of local anesthetics and some NSAIDs, conflicting evidence for myotoxicity of PRP and no evidence to assess whether Actovegin® and Traumeel® are myotoxic.

Injected preparations

Local anesthetics

Muscle injury models in basic science use local anesthetic injections to induce muscle lesions to study muscle regeneration. Considering this, it is remarkable that in sports medicine, whenever intramuscular injections with corticosteroids[132,218], PRP[241], Actovegin® and Traumeel®[171,179,241] are used, local anesthetics are commonly added. Although the muscle damage induced by local anesthetics is reversible, it seems contradictory to induce additional muscle damage when muscle repair is required.

Although the extent of muscular damage differs between specific agents and is dose dependent, the time course and histological changes observed appear to be rather uniform[245]. Within minutes after injection hypercontraction of the fibers occur, followed by degeneration of fibers, edema and infiltration of inflammatory cells and necrosis over the following days. The pathogenesis of the myotoxicity is complex and not completely understood. The pathological mechanism is thought to be an interaction of local anesthetics with the sarcoplasmic reticulum channels initiating increased intracellular Ca^{2+} levels and subsequent Ca^{2+}-activated pathways of cell death[245]. Initially the histological damage appears severe, but the necrosis of fibers is reversible and muscle regeneration usually occurs within 2 to 5 weeks.

Corticosteroids

Corticosteroids are sometimes used in muscle injuries, but scientific evidence for their efficacy is lacking[39,132,197,218]. In our systematic search we only found 1 study on intramuscular corticosteroids that met the eligibility criteria and it showed no myotoxic effect of injections with triamcinolone, resulting in limited evidence that this drug is not myotoxic[82]. The same study reported that triamcinolone and bupivacaine combined resulted in more extensive muscular lesions than bupivacaine injections alone, indicating a synergistic myotoxic effect of triamcinolone and bupivacaine. Although triamcinolone does not damage muscle tissue directly, it seems to delay regeneration of bupivacaine induced muscle damage. To what extent this delaying effect on regeneration can be generalized to muscle injuries in athletes remains unknown. Considering the lack of evidence for the efficacy of corticosteroids and the limited evidence of the myotoxicity, we suggest caution in their use as a treatment for acute muscle injuries.

Non-steroidal anti-inflammatory drugs

Traditionally NSAIDs have been widely used for muscle injuries[244]. Although their administration is usually oral, intramuscular injections are sometimes used[55,244]. The use of oral and injectable NSAIDs in muscle injuries is a subject of debate among experts[171], as

there is increasing evidence from basic science that NSAIDs may be counterproductive for muscle healing[244].

This review found moderate to strong evidence that intramuscular injections of NSAIDs are myotoxic. For meloxicam there was moderate evidence that this drug has no myotoxic effect. Histological changes consisting of muscle degeneration, edema, hemorrhage and inflammatory cell infiltration, and increased levels of plasma CK are observed after injection with myotoxic NSAIDs[44,76,81,133,160,183]. Considering the myotoxicity of NSAIDs found in the present review and the lack of support for their efficacy, intramuscular NSAIDs injections are not recommended for use in acute muscle injuries.

Platelet-rich plasma

Injections with autologous platelet-rich plasma products are a widely used therapy for muscle injuries, although evidence for their efficacy from clinical studies is lacking[9,90]. This review found conflicting evidence on the myotoxicity of intramuscular PRP injections. In animal muscle injury models there were signs of increased regeneration, less necrosis and less granulomatous tissue in the muscles injected with PRP compared to controls[94,242]. Harris et al. reported conflicting findings with histological changes consisting of inflammatory cell infiltration, edema and necrosis followed by fibrosis following intramuscular PRP injection[98]. The reason for this discrepancy is unclear. It may be related to the different injury models or PRP composition and further research is needed to clarify the possible myotoxicity and efficacy of PRP in muscle injuries.

Limitations

This review has some limitations. Firstly, we limited the outcome measures to histological evaluation on hematoxylin and eosin stained histological sections and CK activity in plasma or in muscle tissue at the injection site. There are a multitude of different staining methods for histopathological assessments. However, including multiple different staining methods would have considerably complicated the comparability of the studies. As hematoxylin and eosin staining is the most commonly used method for morphological assessment of tissue in medical diagnostics[226], histological outcome measures were limited to this staining method to ensure comparability of the outcomes of the studies included. Four studies on local anesthetic[122,154,204,221] and 1 on NSAIDs[155] were not included for this reason. As almost all studies on myotoxicity included this staining method in their protocol, the influence of excluding other staining methods on the outcome of present review is expected to be limited.

A second limitation is that this review does not provide a quantitative analysis of the degree of myotoxicity. Most histopathological evaluation is descriptive in nature and not expressed in quantitative measures, which makes interpretation more difficult.

Thirdly, mechanical alteration secondary to needle trauma or injected fluid volume might have contributed to the reported tissue damage. However, the studies using normal saline as a control clearly showed that muscle damage does not occur after injection of the corresponding volume and that the needle only causes minor damage along the needle track[26,33,34,40,42–45,57,70,72,80,82,85,98,112,162,174,217,243]. Thus, the potential for needle- and volume-induced damage is not expected to be clinically relevant.

A fourth limitation is that this review has several features that may limit the generalizability of its findings. For example, the majority of the studies included were performed in animal models; only 5 studies were performed in humans[76,160,165,202,217]. However, all studies involving local anesthetics indicated myotoxicity, both in animal models as in humans[165,202,217]. Furthermore, the NSAID meloxicam was studied in humans in 2 studies[76,160]. However, all other preparations were investigated in studies that were conducted in animal models and the generalizability to humans remains unknown. Another important consideration is that the majority of the studies were performed in uninjured muscle tissue; only two studies of PRP were conducted in muscle strain[94] or contusion[242] models. For the other preparations the generalizability to injured muscle tissue and the actual effects on clinical outcome in injured human subjects remain unknown.

Finally, it is important to remember that this review focuses on the general myotoxic effect of the drugs that are injected intramuscularly. However, in addition to this myotoxicity there are other rare, but clinical significant complications and adverse drug reactions that can occur after intramuscular injection of drugs[89,244]. Clinicians should consider the possibility of these complications, such as infection, hemorrhage and Nicolau Syndrome (an adverse reaction to a variety of intramuscular injected drugs, characterized by pain, skin changes and necrosis of the soft tissue) [89], prior to the use of intramuscular drug injections.

CONCLUSION

The main finding of this systematic review is that there is strong to moderate evidence that intramuscular local anesthetic and NSAIDs injections are myotoxic, limited evidence that corticosteroids are not myotoxic, and conflicting evidence on the myotoxicity of PRP. There is no information to assess whether Actovegin® and Traumeel® are myotoxic or not.

In acute muscle injuries the injection of local anesthetics and NSAIDs is not recommended. The possible myotoxic effects of corticosteroids, PRP, Traumeel® and Actovegin® should be assessed in future research and considering the lack of conclusive evidence on their myotoxicity and efficacy, we would currently not recommend their use as a treatment for acute muscle injuries.

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Chapter 9

Platelet-rich plasma injections in acute hamstring muscle injuries

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Rationale, secondary outcome scores and 1-year follow-up of a randomised trial of platelet-richplasma injections in acute hamstring muscle injury: the Dutch Hamstring Injection Therapy study
Br J Sp Med. 2015;49:1197-205

ABSTRACT

Background – Platelet-rich plasma (PRP) injections is an experimental treatment for acute muscle injuries. We examined whether PRP injections would accelerate return to play after hamstring injury.

Methods – In this three-centre, randomized, double-blind, placebo-controlled trial, we randomly assigned 80 competitive and recreational athletes with acute hamstring muscle injuries to PRP (intervention group) or isotonic saline placebo injections (control group) with both groups undertaking a standardized criteria-based rehabilitation program. The primary outcome measure was the time needed to return to play. Treatment differences were analysed with a Cox proportional-hazards model. Secondary outcome scores included re-injury at one year, alteration in clinical and MRI parameters, subjective patient satisfaction and the hamstring-outcome score.

Results – The median time to return to play was 42 days (interquartile range, 30 to 58) in the PRP-group, as compared to 42 days (interquartile range, 37 to 56) in the placebo-group (hazard ratio, 0.96; 95% CI, 0.61 to 1.51: p=0.66). The absolute between group difference for median time to return to play was 0 days (95% CI, -11 to 11). There was no significant between group difference in the 1-year re-injury rate (hazard ratio 0.89; 95% CI, 0.38 to 2.13; p=0.80) or any other secondary outcome measure. There were no serious adverse events.

Conclusions – At one year post injection we found no benefit of intramuscular PRP compared to placebo injections in patients with acute hamstring injuries in the time to return to play, re-injury rate, and alterations of subjective, clinical or MRI measures.

INTRODUCTION

Muscle injuries account for one third of all time-loss sports injuries, with the hamstring being the most commonly injured muscle in major sports like soccer, Australian football, American football, and track and field athletics[69,206,61,169,7]. Each team can expect 7 muscle injuries per season in amateur soccer[28] and up to 15 in professional soccer[61].

Despite both a high prevalence and risk of recurrence there is a lack of evidence for the effectiveness of any therapeutic intervention for muscle injuries[144,193]. Since the World Anti-Doping Agency permitted the intramuscular injection of platelet-rich plasma (PRP) in 2011, this experimental treatment has been used to treat acute muscle injuries[54,90]. PRP is derived from autologous whole blood using centrifuge separation systems to provide growth factor release from the alpha-granules of the platelets. The growth factors released are assumed to stimulate myoblast proliferation and accelerate myofiber regeneration[95,153,222,242]. PRP has been studied for a number of musculoskeletal disorders[209,156,236,114]. The use in muscle injury has been proposed more recently. Whether the ratio of growth factors in PRP is appropriate for muscle healing remains unproven. Despite uncertainty about the its effectiveness, there is a large commercial market for PRP, which is expected to increase from $45 million in 2009 to $126 million in 2016[79,209].

Two recent systematic reviews show uncertainty about the effectiveness of PRP injections for musculoskeletal indications[156,209]. We designed the Hamstring Injection Therapy (HIT) study to examine the efficacy of PRP injections in patients with acute hamstring muscle injuries.

METHODS

Study design

The Dutch HIT study was a parallel-group, three-centre, stratified, block-randomized, double-blind, placebo-controlled trial. The study was designed and conducted by the authors and the analyses were completed at the coordinating centre. The study protocol was approved by the Medical Ethics Committee of South West Holland. All participants provided written informed consent. The authors GR, AW and JT vouch for the accuracy and completeness of the data and all analysis, and for the fidelity of the report to the study protocol, which is available online along with the full text of this article. GR wrote the first draft. All authors made the decision to submit the manuscript for publication.

The study was sponsored by Arthrex Medizinische Instrumente GmbH (Garching, Germany) and the Royal Netherlands Soccer Association (Zeist, the Netherlands). The sponsors had no role in the study design or data analysis. Prior to submission the sponsors were allowed to review the manuscript and submit any suggestions for changes

as long as these did not affect the scientific character or neutrality of the publication. The sponsors provided no suggestions for changes prior to submission. There was no confidentiality agreement between the study sponsor and the investigators.

Study patients

We recruited patients with acute hamstring injuries nationwide and invited patients, physicians and therapists to contact the coordinating researcher by e-mail or phone in case of a suspected acute hamstring injury. The coordinating researcher provided information about the study and assessed potential eligibility by phone. Subsequently, a sports physician assessed eligibility by clinical assessment, followed by magnetic resonance imaging (MRI). Eligibility criteria are presented in Table 9.1.

Table 9.1 Eligibility criteria

Inclusion criteria
• Age 18 – 50 years
• Clinical diagnosis of an acute hamstring injury, defined as[15]:
o History of acute onset of posterior thigh pain, and
o Localized pain on palpation, and
o Localized pain on passive stretch of the hamstring, and
o Increasing pain on isometric contraction.
• Hamstring lesion on MRI, defined as increased signal intensity on STIR and/or T2-weighted images, limited to one location in the muscle.
Exclusion criteria
• Subject is not capable of doing an active exercise program
• Subject received injection therapy for this injury before
• Subject does not have the intention to return to full sports activity
• Subject does not want to receive one of the two therapies
• The cause of the injury is an extrinsic trauma on the posterior thigh
• Subjects has chronic low back pain
• There are contraindications for MRI
• Subject has chronic hamstring complaints, defined as recurrent tenderness of hamstring muscles during at least two months[38]
• There is a grade III lesion (total rupture) and/or avulsion on MRI

Abbreviations: MRI, magnetic resonance imaging; STIR, short-tau inversion recovery

Randomization and blinding

Randomization was performed by an independent statistician using a computer-generated permuted-block scheme, with patients stratified to centre with a fixed block size of four. Based on this randomization, an independent assistant prepared opaque sealed envelopes with the allocated intervention. At inclusion the next subject number was assigned to the patient. For each subject number there were two sealed opaque envelopes containing the same assigned treatment: an envelope for the first injection at inclusion and an envelope for the second injection 5 to 7 days after the first. For each patient the coordinating researcher prepared a syringe with PRP and a syringe with pla-

cebo (isotonic saline: 0.9% sodium chloride). After preparation a non-blinded physician assistant opened the envelope, selected the correct syringe, and blinded the syringe with a covering sheath. The patients, sports medicine physicians, physiotherapists and coordinating researcher were all blinded to the allocation of the intervention and to the contents of the syringe.

Study intervention

The intervention group received PRP injections (PRP-group) and the control group received placebo injections containing isotonic saline (placebo-group) with both groups performing an identical standardized rehabilitation program. Each patient received 2 injections: the first injection at inclusion within 5 days of the injury, and the second injection 5 to 7 days after the first. We instructed the patients to avoid the use of co-interventions and non-steroidal anti-inflammatory drugs until they returned to play.

PRP and placebo injections preparation

For each patient the coordinating researcher prepared a PRP and a placebo injection (isotonic saline: 0.9% sodium chloride). The PRP was prepared using a commercial available system (Arthrex double syringe ACP system, Arthrex Medizinische Instrumente GmbH, Garching, Germany) according to the manufacturer's instructions. Two double syringes of 12ml of venous blood were collected from the cubital vein. No anti-coagulant was added. After blood collection and 5 minutes of centrifugation 2 syringes with 3ml of PRP were obtained. No pre-activation substances were added. One syringe was used for evaluation of possible microbial contamination, platelet and leucocyte count. The other syringe and an identical syringe with 3ml of isotonic saline were prepared for injection by the coordinating researcher.

Injection procedure

At each clinic there were 2 blinded sport physicians available for the injections. The injection procedure was performed within 30 minutes of blood collection using a sterile ultrasound guided technique into the region of the muscle injury. The injection was given at the location of maximal muscle injury on MRI[91]. The exact injection location was determined using an oil capsule that has been placed as a skin marker prior to MRI. The distance and depth of the injection location in relation to the marker was determined on the MRI images. The positioning of the tip of the needle was verified with the ultrasound images before injection of the fluid. With a 22-gauge needle three separate depots of 1ml were injected: at the site of maximal muscle injury and approximately 1cm proximal and distal. No local anaesthetics were used. After the injections patients stayed in a prone position on the examination table for 15 minutes with additional ice application. Patients were instructed to refrain from exercise for the first 48 hours after the injections.

Rehabilitation program

Both study groups performed an identical daily progressive phased, criteria-based rehabilitation program, which was based on the best available evidence[103,144,208]. The program consisted of a daily home exercises and twice-weekly physiotherapist supervised training sessions. To improve and monitor adherence to the rehabilitation program, patients were instructed to keep daily logs in the supplied logbooks[115].

To stimulate an early return to play, the physiotherapists and patients were explicitly instructed to progress through the rehabilitation program as fast as possible according to the pre-specified functional progression criteria. Clearance for return to play was given by the supervising physiotherapist once the patient completed the rehabilitation program including unrestricted functional sport specific testing. The rehabilitation program is described in detail in the Supplementary Table of this thesis.

Outcome measures

Primary outcome: time to return to play

The primary efficacy outcome was the time to return to play, defined as the number of days between injury and return to unrestricted sports activity in training and/or match play[73]. Patients were instructed to contact the coordinating researcher at the moment of return to unrestricted sports activity. Patients underwent clinical assessment at 1 and 26 weeks and a questionnaire by telephone at 3, 4, 8, 10 and 16 weeks after inclusion.

Secondary outcome measures

The main secondary outcome measure was the re-injury rate within one year follow-up. Subjects were instructed to immediately contact the coordinating researcher in the event of a suspicion of re-injury and re-injury occurrence was monitored at 4, 8, 16, 26 and 52 weeks with phone calls to the subjects. Acute onset of posterior thigh pain that occurred on the same side as the initial injury and caused absence from play was counted as a re-injury.[61]

Other previously unreported secondary outcome measures were; the subjective patient satisfaction, perceived recovery, a numeric rating scale for posterior thigh pain at rest (0-10, where a higher score indicates more pain), pain and flexibility deficit measured with the active knee extension test[189] and the passive straight leg raise test[21], isometric knee flexion force deficit measured with handheld dynamometry in 15° and 90° of knee flexion[128], the hamstring outcome score (0-100, where a higher score indicates better hamstring function)[67], adherence to the rehabilitation programme, the amount of oedema on MRI at return to play.

Description of clinical examination

Clinical examination was performed at baseline, 1 week and 26 weeks follow-up.

Manual muscle palpation

With the patient in a prone position the complete posterior thigh was carefully palpated from the hamstring origin at the ischial tuberosity to the insertions medially at the pes anserinus and laterally at the fibula head. The total longitudinal length of the painful area and the distance between the point of maximal pain on palpation and the ischial tuberosity were recorded.

Hamstring flexibility testing

Hamstring flexibility was assessed with both the active knee extension[140,189] and the passive straight leg raise test[22]. Subjects were tested in a supine position with an inclinometer placed on the anterior tibial border. For the active knee extension test, subjects positioned the tested leg hip in 90° flexion and were instructed to extend the knee until maximal tolerable stretch, with the contralateral leg remaining flat on the table. At the endpoint of maximal tolerable stretch, the absolute knee angle was measured.

For the passive knee extension test subjects were instructed to completely relax the leg, while the researcher lifted the leg with the knee in full extension until maximal tolerable stretch. The contralateral leg remained flat on the table. At the endpoint of maximal tolerable stretch, the angle between the leg and the table was measured. For both tests, the absolute flexibility deficit was calculated by subtracting the recorded angle of the injured leg from the uninjured leg. Subjects were also asked if they experienced normal stretch or localized pain during the tests.

Isometric knee flexion force

Isometric knee flexion force was measured using handheld dynamometry[128]. Subjects were tested in a prone position with the knee in 15° and 90° of flexion. The researcher placed the dynamometer on the subject's heel and applied force to the heel, gradually increasing over 3-5 seconds. Subjects were instructed to resist the force applied by the researcher (break test). At the point that the subject could not resist the force anymore, the test was terminated and the reading taken. Each leg was tested 3 times in 15° and 90° of knee flexion. For each angle the highest force value was recorded. The relative strength deficit was calculated by dividing the recorded maximal force value of the injured leg by maximal force value of the uninjured leg. Additionally subjects were asked to rate hamstring pain during testing on a 0-10 numeric rating scale.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) was performed at inclusion within 5 days of injury and within 7 days after return to play.

MRI protocol

The protocol used was a modified version of that described by Askling et al.[15]. To locate the area of the injury, the entire hamstring of the injured limb was visualised by obtaining coronal and sagittal short tau inversion recovery (STIR) images from the ischial origin of the hamstring muscles to insertion on the fibula and the tibia (repetition time/echo time (TR/TE) of 3500/31 ms, field of view (FOV) of 300 mm and a 256x320 matrix). Subsequently, transverse STIR (repetition time/echo time (TR/TE) of 3500/31 ms, field of view (FOV) of 300 mm and a 205x256 matrix), T1-weighted (TR/TE of 500/12 ms, FOV of 300 mm and a 355x448 matrix) and T2-weighted (TR/TE of 4080/128 ms, FOV of 300 mm and a 355x448 matrix) images were obtained from the injured area. The thickness of the slices for all sequences was 5mm. MR images were obtained with a 1.5-T magnet system (Magnetom Essenza, Siemens) with the use of a body matrix coil.

MRI assessment

Each MRI was assessed by a single radiologist, specialized in musculoskeletal radiology. For assessment of the MRIs, we used standardised scoring forms.[15,52,63,96,216] We recorded the involved muscle(s) and performed grading of the injury using the three-graded classification of Hancock et al.[96]: grade 1) increased signal intensity on fluid sensitive sequences without evidence of a macroscopic tear, grade 2) increased signal intensity on fluid sensitive sequences with a partial tear, grade 3) total muscle or tendon rupture. We measured the increased T2 signal intensity for the affected hamstring muscle in cranio-caudal, transverse and anterior-posterior dimensions on the fluid sensitive sequences (STIR). We recorded the longitudinal length (cranio-caudal) and calculated the involved cross sectional area as a percentage of the total muscle cross sectional area in the transversal plane. We measured the distance of the most cranial pole of the intramuscular increased signal intensity to the distal tip of the ischial tuberosity. Increased signal intensity was defined as an abnormal intramuscular increased signal compared to the unaffected surrounding muscle tissue. Good to excellent inter- and intra-observer reliability for these MRI parameters has been reported.[36]

Statistical analysis

We calculated that a sample of 80 would be required to provide a power of 80% to detect a difference of 20% in the number of days to return to play, with a type 1 error rate of 0.05, assuming a mean time to return to play of 27 (SD 8) days in the control group[52,141,216,231] and an expected lost to follow-up of 15%. The choice of the 20% be-

tween group difference was based on 1) a 20% reduction in time to return to play among patients with muscle injuries treated with PRP, reported in a previous retrospective case control study[241], 2) feasibility, and 3) the clinical relevance that in most sports a one week earlier return to play implicates one extra match played.

Differences at baseline between groups were analysed with an independent t-test for continuous variables and Chi-square test for binary variables.

Using an intention-to-treat analysis we analysed the treatment effect on the time to return to play with a Cox proportional-hazards model. Patients sustaining a non-hamstring injury before return to play, that was assumed to be unrelated to the injection intervention, were censored in the analysis at the time of this injury (non-informative censoring). Patients lost to follow-up before return to play were censored at the time of the last available follow-up. Outcome measures were adjusted for baseline variables that changed ≥10% of the treatment effect (hazard ratio). We performed an additional sensitivity analysis to test the robustness of the treatment effect found in the initial analysis. In the sensitivity analysis the censored cases were considered not having reached return to play until the 6 months follow-up. Time-to-event curves were calculated with the Kaplan-Meier method.

We analysed the difference in re-injury rate between the treatment groups with a Cox proportional-hazards model. In this model the time (days) from return to play to the event (re-injury) or the end of the follow-up is the dependent variable. Subjects who sustained a severe injury (causing absence from training and matches >28 days[61,83]) during follow-up that was not considered a hamstring re-injury were censored at the time of this injury. Subjects lost to follow-up were censored at the time of their last available follow-up. Subjects completing the one year follow-up were censored at the time of the last follow-up measure. We adjusted for ipsilateral hamstring injuries in the preceding 12 months, as a history of hamstring injury is previously reported as a predictor for re-injury[235,238]. Time-to-re-injury curves were calculated with the Kaplan-Meier method.

The Hamstring Outcome Score was tested with a linear regression model. Continuous secondary outcome measures with repeated measures in time were tested with linear mixed models and binary secondary outcome measures with repeated measures in time were tested with generalized estimating equations. Secondary outcome measures were adjusted for the baseline measures. Adherence to the rehabilitation protocol was tested with an independent t-test.

The coordinating researcher and the independent statistician, who performed the analysis, were blinded for the allocated treatment. The analysis was performed using SPSS version 21.0.1 (SPSS Inc, Chigaco, Illinois, USA). All p-values are two-sided.

PRP samples analysis

Platelets and leucocytes count

We assessed the number of thrombocytes (platelets), leucocytes and leucocyte differentiation in whole blood and in PRP. Whole blood obtained from the cubital vein and 2 ml of PRP were collected in EDTA blood collection tubes. Directly after collection of the whole blood and PRP, the collection tubes were transported to the Clinical Chemistry Laboratory. Platelet and leucocyte counts were performed using the Sapphire blood analysis machine (Abbott Diagnostics, Hoofddorp, The Netherlands).

Microbial contamination

We tested the PRP samples for the presence of micro-organisms. One ml of PRP was collected in a BACTEC Peds Plus™/F culture vial. Before injection of the PRP into the vial, the top was disinfected using disinfection alcohol. Directly after collection the vial was transported to the Microbiology laboratory and stored in a stove at 35 °C for 7 days.

Design considerations

Rationale for age criteria

We set the lower boundary at 18 years, because of legislation issues related to medical research in minors. We chose an upper limit of 50 years for generalizability of the results to the athletic population seen in the sports medicine clinical practice, and to have a study population that would be comparable to previous published series in hamstring injuries.

Rationale for including MRI inclusion criteria

Patients with a clinical diagnosis of an acute hamstring injury without lesion on MRI (commonly diagnosed as grade 0 injuries) were not included, as there are no macroscopic signs of tissue damage and the location of the lesion cannot be determined. Furthermore, these injuries are associated with a short recovery time[63,77,216,233], limiting the clinical relevance of hastening recovery with an invasive intervention.

Complete muscle ruptures/tendon avulsions (commonly indicated as grade III injuries) were excluded, as these are rare, severe injuries that may require surgical intervention[97].

Therefore we only included MRI positive injuries that are not complete ruptures (often diagnosed as grade I/ II injuries[63]). It could be argued that PRP injections would have more potential in injuries with signs of macroscopic muscle tissue disruption (MRI grade II) than in injuries without (grade I). However, it has been shown previously that there is no significant difference in recovery time between MRI grade I and II injuries[63], suggesting that tissue healing may require the same time in grade I and II injuries. It is

therefore questionable to what extent MRI grade I and II injuries distinguish between the presence and absence of tissue disruption. We hypothesize that in grade I injuries the tissue damage does not result in a visible disruption, due to limited resolution of MRI. As there is evidence that there is no difference in injury severity, we included both grade I and II injuries in our study.

Rationale for number and timing of injections

The timing and the number of injections have been the subject of debate, as the tissue environmental milieu and the effect of growth factors changes over time during the healing process[108]. However, it remains unclear whether the timing and number of injections are important factors for the effect of PRP on muscle regeneration[90]. In usual clinical practice the first injection is performed shortly after the injury and repeated injections are performed at several days to one week later[30,186,241]. Concerns have been raised that during the biological healing phase of fibrosis, that starts 2-3 weeks after injury, TGF- β activity may be preferentially up regulated, thereby promoting fibrosis over regeneration[90,108]. There is therefore a theoretical contraindication to inject PRP 2-3 weeks after a muscle injury. Taking into account the possible pro-fibrotic effect of PRP and the generally used procedures, we performed the first injection within 5 days of injury and a second injection 5-7 days later.

RESULTS

Between February 2011 and November 2012, 80 patients were enrolled and randomly assigned to either the PRP (N=41) or placebo (N=39) group (Figure 9.1). All patients sustained their injury while participating in sports. All randomized patients received the allocated injections. The baseline characteristics of the patients are presented in Table 9.2. For the primary outcome analysis no patients were lost to follow-up. Four patients in the PRP-group and one in the placebo-group did not achieve return to play within the 26 weeks study period.

Primary outcome: time to return to play

The median time to return to play was 42 days (interquartile range, 30 to 58) in the PRP-group, as compared to 42 days (interquartile range, 37 to 56) in the placebo-group (hazard ratio, 0.96; 95% CI, 0.61 to 1.51: p=0.66, in favour of the placebo-group) (Figure 9.2a and Figure 9.2b). The absolute between group difference for median time to return to play was 0 days (95% CI, -11 to 11).

Three patients in PRP-group and one in the placebo-group sustained non-hamstring injuries before return to play that were assumed to be unrelated to the injection inter-

vention and were censored in the survival analysis at the time of this injury. An overview of these cases is presented Table 9.3. There were no baseline variables that changed the treatment effect on the primary outcome ≥10%. The sensitivity analysis showed that the outcome of the primary analysis was robust, as there was no relevant change in the treatment effect found: hazard ratio 0.94 (95% CI, 0.60 to 1.49) in favour of the placebo-group and a median time to return to play of 42 days in both groups.

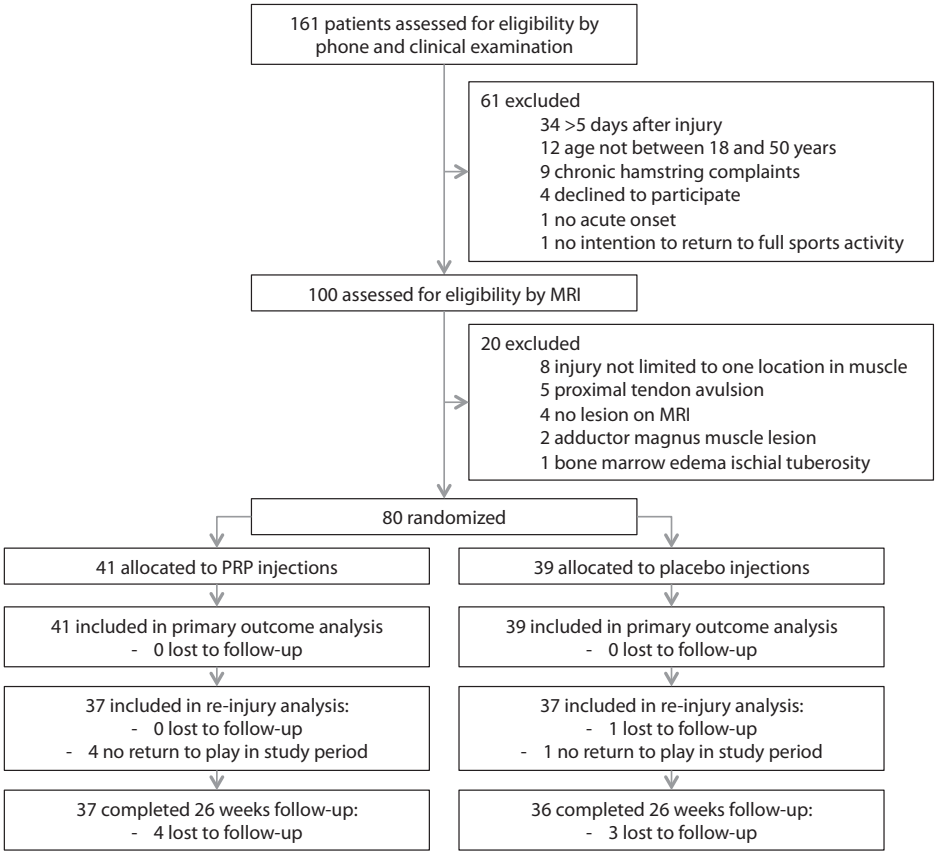


Figure 9.1. Patient flow diagram

Secondary outcome measures

Re-injuries during one year follow-up

Four patients in the PRP-group and two in the placebo-group were not included in the re-injury analysis: four patients sustained another injury before they returned to play, one patient in the PRP group did not achieve return to play within the study period

Table 9.2 Baseline characteristics of the patients*

	PRP-group (n = 41)	**Placebo-group** (n = 39)
Age, years	28±7	30±8
Male gender, no. (%)	39 (95)	37 (95)
Sports, no. (%)		
Soccer	30 (73)	27 (69)
Field hockey	5 (12)	7 (18)
Track and field athletics	3 (7)	1 (3)
American football	2 (5)	1 (3)
Fitness	0 (0)	2 (5)
Cricket	1 (2)	0 (0)
Frequency of sport, no. (%)		
< 3 times per week	6 (15)	10 (26)
≥ 3 times per week	35 (85)	29 (74)
Level of Sports, no. (%)		
Competitive	30 (73)	29 (74)
Recreational	11 (27)	10 (26)
Sprinting type of injury, no. (%)¥	35 (85)	24 (62)
Previous hamstring injury, no. (%)	27 (66)	23 (59)
Previous ipsilateral hamstring injury, no.(%)	24 (59)	18 (46)
Previous ipsilateral hamstring ACL-graft harvesting, no. (%)	5 (12)	2 (5)
Length of pain palpation, cm	12±7	12±6
Distance maximal pain palpation to ischial tuberosity, cm	21±7	19±7
Active knee extension deficit, degrees	12±12	12±15
Passive straight leg raise deficit, degrees ¥	2±6	6±8
Isometric knee flexion strength testing		
Force deficit, % relative to uninjured side		
in 15° knee flexion	31±25	29±25
in 90° knee flexion	18±22	18±24
Pain score		
in 15° knee flexion	4.5±2.6	4.4±2.4
in 90° knee flexion	3.2±2.5	3.5±2.4
MRI characteristics		
Grade I / grade II, no. (%)	11 (27) / 30 (73)	12 (31) / 27 (69)
Cross sectional area, % of total muscle	35±28	38±26
Longitudinal length, cm	11.1±6.0	12.7±6.0
Distance from tuber, cm	14.2±7.9	16.0±7.6
Days between injury and 1st injection – median (interquartile range)	3 (2-4)	3 (2-5)

* Plus-minus values are means ±SD. Abbreviations: no., number; cm, centimetres

¥ Statistical significant difference between study groups at $p<0.05$

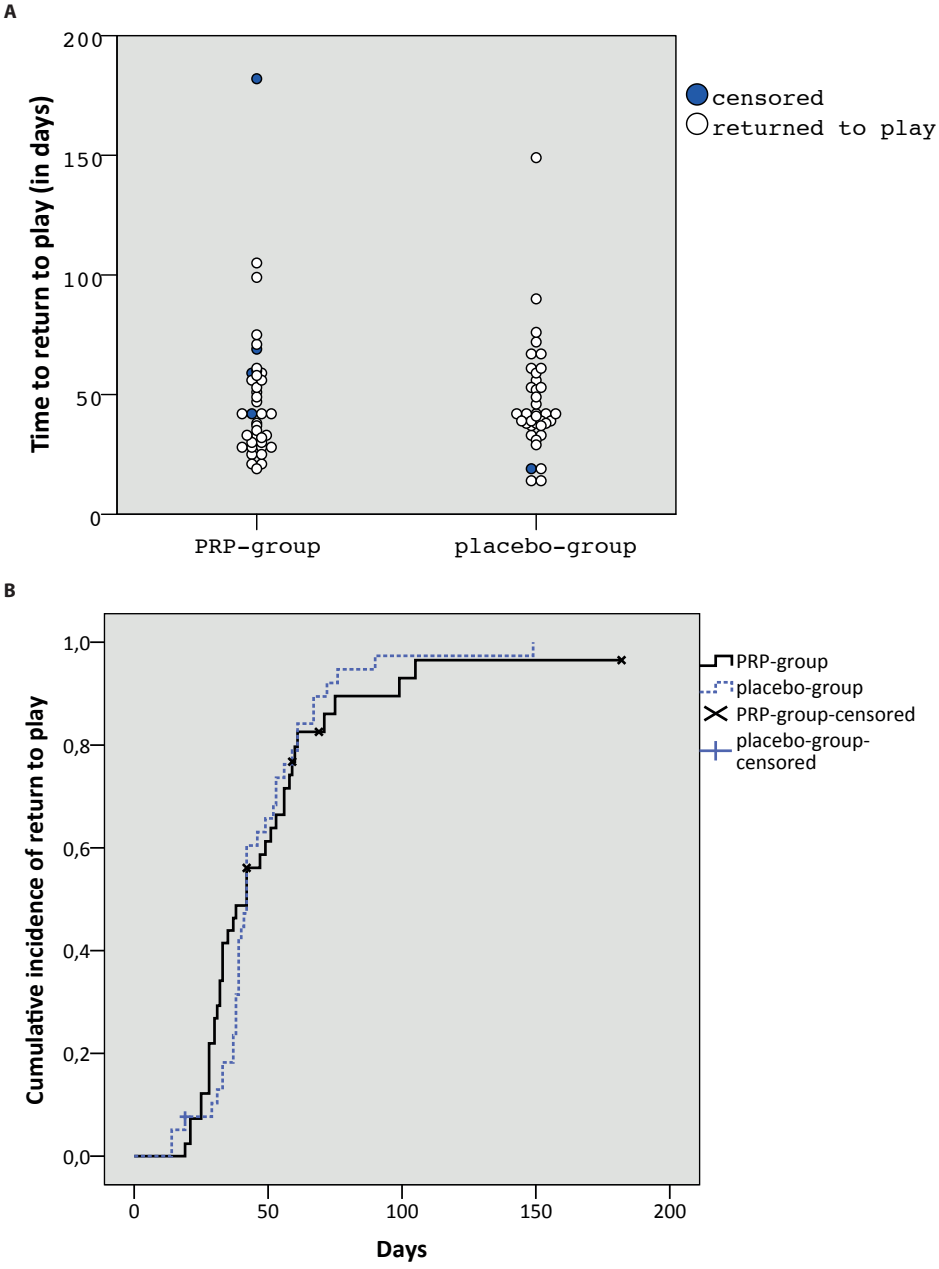


Figure 9.2a+b. The upper panel shows a scatter plot of the number of days that were required for patients to return to sport in the group receiving injections of platelet-rich plasma (PRP) and the placebo group. The lower panel shows Kaplan Meier curves for the cumulative probability of a return to sport. Data for patients who had a non-hamstring injury before they returned to sport were censored at the time of this injury.

Table 9.3 Overview of injuries sustained before RTP, assumed unrelated to injection intervention

Subject (group)	Diagnosis	Injury situation	Time*	Course during FU	Primary analysis
1 (PRP)	Acute calf muscle injury	Sprinting exercise	42d	Sustained a second acute calf injury. Lost to FU after 16w, no RTP	Censored at 42d
2 (PRP)	Achilles tendinopathy	Developed gradually during rehabilitation	69d	No RTP at 26w FU	Censored at 69d
3 (PRP)	Wrist fracture	Fell during football training	59d	Lost to FU after 16w, no RTP	Censored at 59d
4 (placebo)	Meniscal tear	Deep squat when lifting object	19d	No RTP at 26w FU	Censored at 19d

* Time interval of occurrence after initial hamstring injury
Abbreviations: PRP, platelet-rich plasma; RTP, return to play; FU, follow-up; d, days; w, weeks

and one patient in the placebo group was lost to follow-up after he returned to play. In the PRP-group 10 out of 37 patients (27%) and in the placebo-group 11 out 37 (30%) sustained a re-injury during the one year follow-up period. The adjusted hazard ratio for the PRP-group was 0.89 (95% CI, 0.38 to 2.13; p=0.80) (Figure 9.3).

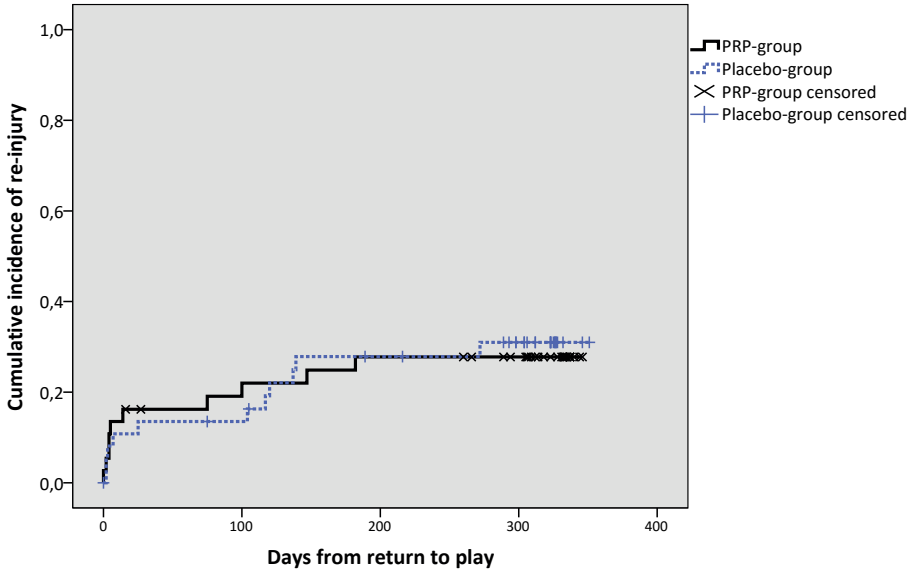


Figure 9.3. Kaplan Meier curves for the cumulative incidence of re-injury. Data for subjects who sustained a severe injury (causing absence from training and matches >28 days) during follow-up that was not considered a hamstring re-injury were censored at the time of this injury. Subjects that did not sustain a re-injury were censored at the time of their last available follow-up.

Subjective patient related outcome measures

There were no significant differences between the study groups on the subjective patient satisfaction, perceived recovery and the numeric rating scale for posterior thigh pain at rest at 1, 4 and 10 weeks follow-up (Table 9.4).

Table 9.4 Secondary outcome measures obtained by questionnaire at 1, 4, and 10 weeks*

	1 week			4 weeks			10 weeks		
	PRP (n=41)	placebo (n=39)	Between group difference (95% CI)	PRP (n=40)	placebo (n=39)	Between group difference (95% CI)	PRP (n=40)	placebo (n=38)	Between group difference (95% CI)
Good/excellent patient satisfaction – %	93%	82%	11 (-4 to 25)	93%	95%	-2 (-13 to 8)	93%	100%	-7 (-16 to 7)
Perceived full recovery – %	0%	3%	3 (-2 to 8)	28%	31%	3 (-17 to 23)	80%	76%	-4 (-22 to 15)
Pain score in rest – 0-10 rating scale (SD)	0.7±1.5	0.5 ±1.2	0.2 (-0.2 to 0.6)	0.2±0.8	0.2±0.8	0.0 (-0.4 to 0.4)	0.1±0.4	0.2±0.7	-0.1 (-0.5 to 0.3)

* Plus-minus values are means ±SD. Abbreviations: PRP, platelet-rich plasma; CI, confidence interval; SD, standard deviation.

Physical examination

At 1 and 26 weeks, there were no significant differences between the study groups on pain and flexibility deficit measured with the active knee extension test and the passive straight leg raise test, except for the active knee extension deficit at 1 week follow-up. There were also no significant differences on pain and isometric strength deficit measured with handheld dynamometry at 1 and 26 weeks (Table 9.5).

Hamstring outcome score

At 26 weeks there were no significant differences between the study groups on the overall hamstring outcome score and the subscales symptoms, soreness, pain, function in sports and quality of life (Table 9.6).

Oedema on MRI

There were no significant differences between the study groups on the extent of oedema on MRI at return to play (Table 9.7).

Table 9.5 Secondary outcome measures obtained by clinical examination at 1 and 26 weeks*

	1 week			26 weeks		
	PRP (n=41)	placebo (n=39)	Adjusted between group difference¶ (95% CI)	PRP (n=41)	placebo (n=39)	Adjusted between group difference¶ (95% CI)
Active knee extension deficit – degrees	3±10	7±9	-4 (-7 to -1)¥	-1±5	1±5	-2 (-5 to 1)
Passive straight leg raise deficit – degrees	2±5	2±3	0 (-2 to 3)	-2±6	0±6	-1 (-3 to 1)
Isometric knee flexion strength testing						
• Strength deficit in 15° knee flexion – %	13±21	13±20	-1 (-10 to 7)	-1±18	1±14	-2 (-11 to 6)
• Strength deficit in 90° knee flexion – %	11±17	7±18	2 (-5 to 9)	3±14	1±13	2 (-5 to 9)
• Pain score in 15° knee flexion	1.6±1.9	1.7±2.2	-0.1 (-0.8 to 0.7)	0.4±1.3	0.5±1.6	-0.1 (-0.9 to 0.7)
• Pain score in 90° knee flexion	1.3±1.7	1.9±2.3	-0.6 (-1.3 to 0.2)	0.4±1.3	0.5±1.6	0.1 (-0.7 to 0.9)

* Plus-minus values are means ±SD; ¶ Between group differences are adjusted for the baseline measure; ¥ Statistical significant difference (p = 0.01). Abbreviations: PRP, platelet-rich plasma; CI, confidence interval

Table 9.6 Hamstring Outcome Score at 26 weeks follow-up*

	PRP (n=41)	placebo (n=39)	Between group difference (95% CI)
Overall score (0-100)	86±19	88±21	-3 (-12 to 7)
Symptoms (0-100)	79±28	86±26	-7 (-20 to 6)
Soreness (0-100)	89±18	91±19	-2 (-11 to 7)
Pain (0-100)	91±18	90±20	1 (-9 to 10)
Function in sports (0-100)	95±14	92±22	4 (-6 to 13)
Quality of life (0-100)	77±27	82±26	6 (-18 to 7)

* Plus-minus values are means ±SD
Abbreviations: PRP, platelet-rich plasma; CI, confidence interval

Table 9.7 Oedema on MRI at return to play*

	PRP (n=33)	placebo (n=30)	Between group difference (95% CI)
Cross sectional area, % of total muscle	15±22	14±20	1 (-9 to 12)
Longitudinal length, cm	5.3±5.2	5.5±5.4	-0.2 (-2.8 to 2.4)

* Plus-minus values are means ±SD.
Abbreviations: PRP, platelet-rich plasma; CI, confidence interval

Adherence to the rehabilitation program

In the PRP-group 49% and in the placebo-group 51% of the patients kept and returned their daily logs of the rehabilitation program. There were no significant differences in reported adherence to the rehabilitation program between the study groups (Table 9.8).

Table 9.8 Adherence to the rehabilitation program*

	PRP (n=20)	placebo (n=20)	Between group difference (95% CI)
Supervised physiotherapy (% of performed sessions)	80±22	80±29	0 (-17 to 16)
Home exercise program (% of performed sessions)	68±17	59±21	9 (-4 to 21)

* Plus-minus values are means ±SD
Abbreviations: PRP, platelet-rich plasma; CI, confidence interval

PRP samples analysis

Mean platelet concentration in whole blood was within expected ranges (232, SD 48 10^3µL) and increased with a factor 1.9 in PRP (433, SD 125 10^3µL) (Table 9.9).

Two out of the 160 collected PRP samples were positive for microbial growth (*Micrococcus luteus* and *Staphylococcus Aureus*), suggestive for contamination of dermal microbes. There were no clinical signs of infection after the PRP injections of these samples.

Table 9.9 Platelet and leucocyte count in whole blood and PRP (in PRP-group) *

	Whole blood	**PRP**
Platelets	232±48	433±128
Leucocytes	6.5±3.6	1.9±2.1
Neutrophils	3.44±1.07	0.52±0.69
Lymphocytes	1.96±0.50	1.13±1.21
Monocytes	0.49±0.15	0.23±0.32
Eosinophils	0.16±0.13	0.02±0.06
Basophils	0.04±0.03	0.02±0.03

*All data is presented in 10^3µL; Plus-minus values are means ±SD
Abbreviations: PRP, Platelet-Rich Plasma; SD, standard deviation

Adverse events

There were no serious adverse events. Minor adverse events are reported in the Table 9.10.

Table 9.10 Adverse events (regardless of whether considered to be related to the intervention)*

	PRP (n=41)	**Placebo** (n=39)
Dermal hyperesthesia	1 (2%)	0 (0%)
Nausea	0 (0%)	1 (3%)
Other musculoskeletal injury:		
• Calf muscle injury	1 (2%)	0 (0%)
• Achilles tendinopathy	1 (2%)	0 (0%)
• Wrist fracture	1 (2%)	0 (0%)
• Meniscal tear	0 (0%)	1 (3%)
Total	4 (10%)	2 (5%)

* Values are presented as number (%)
Abbreviations: PRP, platelet-rich plasma.

DISCUSSION

In this double-blind, randomized, placebo-controlled trial we found that PRP did not accelerate return to play, nor did we find an effect on the one year re-injury rate, the subjective and functional secondary outcome measures, and the extent of oedema on MRI at return to play.

Comparison with existing literature

Previous clinical evidence of the effectiveness of PRP in muscle injuries was limited to one case series[30] and two retrospective case control studies[186,241] with major methodological flaws, including the lack of a proper control group, no blinding and insufficient power. The clinical use of PRP was often supported by animal model results[95,153,222,242], the assumption of a safe autologous therapy and the absence of reported complications and side-effects[90].

One other randomised non-blinded controlled trial examining PRP in acute hamstring injuries have been published. The authors reported a significant reduction in time to return to play in the PRP group compared to the control group[3]. In this study all 28 patients were prescribed a rehabilitation program. The patients in the PRP-group received a single PRP injection within seven days of the injury. The patients in the control group did not receive an injection. The mean time to full recovery was 26.7 (±7.0) days in the PRP-group and 42.5 (±20.6) days in the control group.

This Malaysian study has several methodological flaws. The study is at great risk of bias because neither subjects or treating medical staff were blinded to the intervention. The study failed to assess for re-injury after the completion of treatment. Furthermore, it is remarkable that return to play criteria included a less than 10% side-to-side difference in isokinetic strength testing. This conflicts with existing evidence which indicates that

at return to play after a hamstring injury 67% of the subjects tested had a >10% side-to-side isokinetic strength difference[227].

The time to return to play in our study is within the range of the mean of 22 to 51 days reported in previous high quality randomized controlled trials in hamstring injuries[20,208,213], but longer than in other previously reported case series[216,77,52,231,203,238,63]. There are several factors that may contribute to this discrepancy. Firstly, the inferior study methodology of the majority of previous published series may lead to bias towards a quicker return to play, as methodological quality is often negatively correlated with reported outcome success[50,205]. Secondly, patients with more severe injuries may be more willing to participate in research and receive an injection, which is reflected by the proportion of patients with severe injuries with macroscopic muscle fiber disruption on MRI. Thirdly, the majority of previously published series were performed in professional athletes, compared to our study which had a large number of competitive amateur athletes. It may be that professional athletes are more likely to seek and receive medical care for less severe injuries than amateur athletes, and thus progress faster through rehabilitation.

Strengths and limitations

The methodological strengths of our study include the minimization of bias by the placebo controlled double-blind design, no loss to follow-up for the primary outcome measure and the identical measurements for all patients performed by one physician. To minimize the influence of subjective judgments, all patients performed a pre-defined criteria-based rehabilitation program with strict functional criteria to progress through the program. The nationwide recruitment in three different clinical settings (academic clinic, general clinic and specialized high-level athlete clinic) contributes to the generalizability of the results.

Our study has some limitations. Firstly, there are some uncertainties about the adherence of the patients to the rehabilitation program, and there was no assessment of the adherence of the supervising physiotherapists in following the recommended physiotherapy protocol. As the rate of missing adherence data is comparable in both study groups, and the physiotherapists were blinded, it is unlikely that this introduces a potential bias in the treatment effect.

Generalizability

This study has several features that may limit the generalizability of the findings. In a letter to the editor Anitua et al. suggested that the timing and the dosage of the PRP injections in our study may have rendered the PRP injections ineffective[10]. In a response letter we indicated that there is no evidence that the optimal time window for injections is earlier than we used in present study (median 3 days, interquartile range 2-4 days)

and adjustment for the time between the injury and the injection did not change the treatment effect[195].

There are several autologous platelet-rich blood products commercially available that differ in their preparation procedure and composition of platelets and leucocytes. Although the generalizability to these other products remains unknown, the platelet concentration is comparable to several other separation systems[41]. The population in this study consisted primarily of male competitive athletes who played sport at least 3 times a week. The generalizability to other populations remains unknown.

Many unanswered questions

Our current scientific knowledge about PRP remains at a basic science level and there are many unanswered questions regarding its use in muscle injury[90]. These include some very basic questions, such as what concentrations and ratio of growth factors are required for optimal muscle healing? Which specific growth factors are active? Is timing and number of injections important? Does the injected PRP remain at the injected site? Is the presence of leucocytes in the PRP beneficial or detrimental for muscle healing? In addition to these unanswered basic questions, currently no proven scientific mechanism is available for a therapeutic effect of PRP in muscle injury. Furthermore, no high quality clinical trials exist that justify the use of PRP in acute muscle injury.

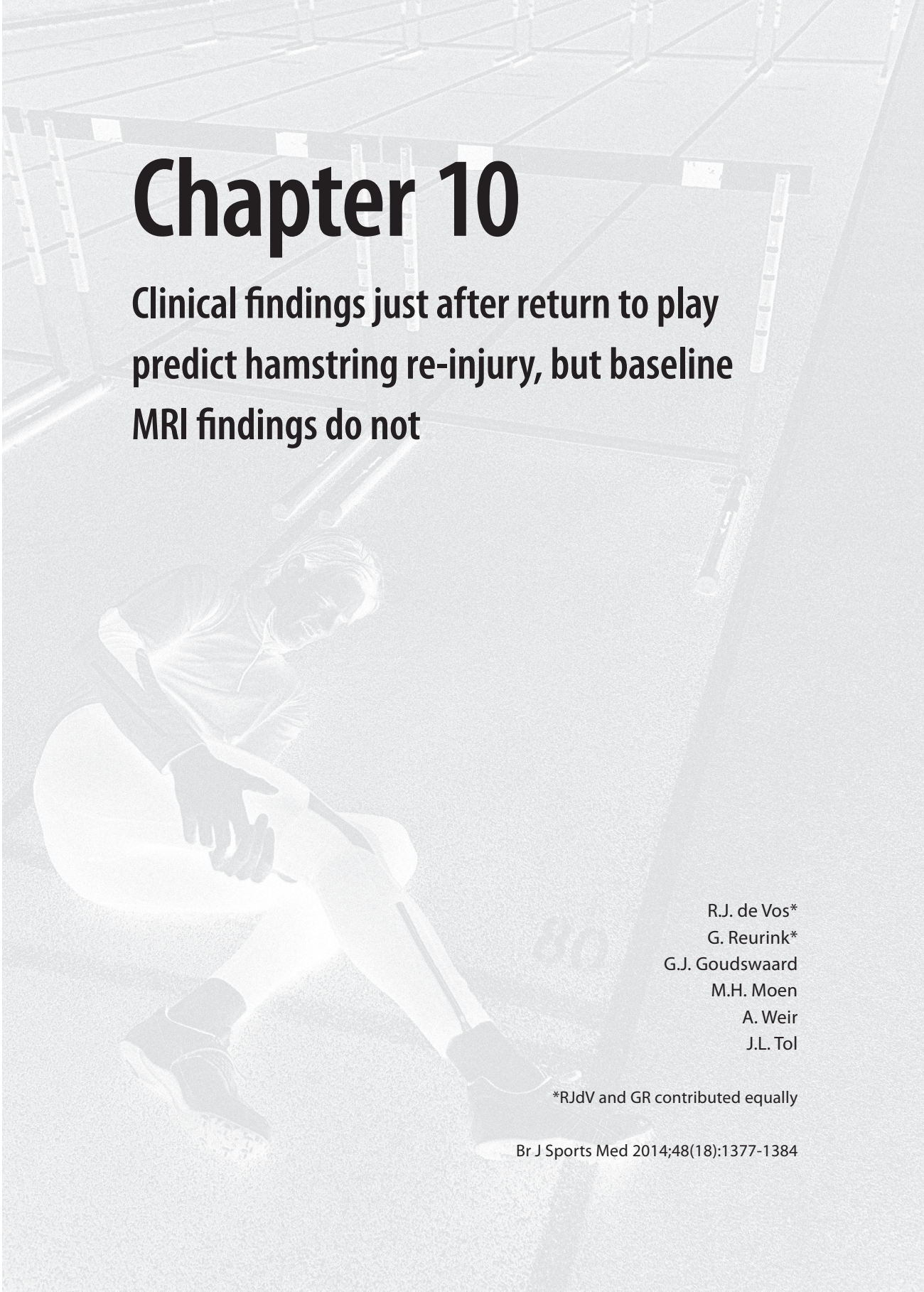
High quality randomised studies on PRP use in other soft tissue injuries, such as tendon and ligament, also failed to find a beneficial effect.[175,236,237]

CONCLUSION

In conclusion, we found no benefit of intramuscular PRP injections compared to placebo injections in patients with acute hamstring injuries in the time to return to play, nor did we find an effect we on the one year re-injury rate or alterations of subjective, clinical and MRI measures.

Chapter 10

Clinical findings just after return to play predict hamstring re-injury, but baseline MRI findings do not



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ABSTRACT

Background – Acute hamstring re-injuries are common and hard to predict. The aim of this study was to investigate the association between clinical and imaging findings and the occurrence of hamstring re-injuries.

Methods – We obtained baseline data (clinical and Magnetic Resonance Imaging (MRI) findings) of athletes who sustained an acute hamstring injury within 5 days of initial injury. We also collected data of standardised clinical tests within 7 days after return to play (RTP). The number of re-injuries was recorded within 12 months. We analysed the association between the possible predictive variables and re-injuries with a multivariate Cox proportional-hazards regression model.

Results – Eighty patients were included at baseline and 64 patients could be included in the final analysis, because data after return to play were not available in 16 cases. There were 17 re-injuries (27%). None of the baseline MRI findings were univariately associated with re-injury. A higher number of previous hamstring injuries (adjusted odds ratio (AOR) 1.33; 95% CI 1.11 to 1.61), more degrees of active knee extension deficit after RTP (AOR 1.13; 95% CI 1.03 to 1.25), isometric knee flexion force deficit at 15° after RTP (AOR 1.04; 95% CI 1.01 to 1.07) and presence of localised discomfort on hamstring palpation after RTP (AOR 3.95; 95% CI 1.38 to 11.37) were significant independent predictors of re-injury. Athletes with localised discomfort on hamstring palpation just after RTP were consequently almost four times more likely to sustain a re-injury.

Conclusion – The number of previous hamstring injuries, active knee extension deficit, isometric knee flexion force deficit at 15° and presence of localised discomfort on palpation just after return to play are associated with a higher hamstring re-injury rate. None of the baseline MRI parameters was a predictor of hamstring re-injury.

INTRODUCTION

High re-injury rates remain a major problem following acute hamstring injuries, despite increasing use of sophisticated imaging techniques, prevention and treatment options[60,61]. Hamstring re-injury rate is 14-63% within two years after the initial injury[234]. Re-injuries require longer rehabilitation[61].

A recent systematic review on risk factors for hamstring *re-injury* has reported limited evidence for an association with (i) a previous ipsilateral ACL reconstruction, (ii) a larger volume measured by Magnetic Resonance Imaging (MRI) and (iii) a grade 1 lesion on MRI of the initial injury as predicting recurrence[234]. Athletes who undertook progressive daily home-based agility and stabilisation exercises were at lower risk for such re-injury[234]. Although there is no evidence for fibrous tissue formation and reduced hamstring strength as re-injury risk factors, they are frequently mentioned as risk factors[210,211]. This is thought to result from inadequate rehabilitation, a premature return to play (RTP) or a combination of both[103,167].

The timing of return to play is challenging and generally based on expert opinion. Currently there is no consensus on RTP decision-making[168]. There is one retrospective study comparing different rehabilitation protocols and RTP strategies[105]. In daily clinical practice an athlete is normally regarded as being fit to RTP if there is a pain free full range of motion and asymptomatic completion of sports specific activities[103,152]. Despite this approach, re-injury rates remain high. Ideally, the results of a subjective assessment in combination with radiological and clinical findings would enable the clinician to predict a safe RTP without a high risk of re-injury. However, findings just after RTP have never been described in association with hamstring re-injury.

The aim of this study, a substudy of the Dutch Hamstring Injection Therapy (HIT) study reported in the New England Journal of Medicine[187], is to describe the association between clinical and imaging findings at baseline (including MRI findings of the initial injury) and standardised clinical tests just after RTP with the occurrence of hamstring re-injuries.

METHODS

Subjects

The patients included in this study were involved in a double blind randomised controlled trial (RCT) on the effect of platelet rich plasma in acute hamstring injuries (ClinicalTrial.gov number NCT01812564)[187]. In brief, the study was performed at three sports medicine departments (a large general district hospital, a university hospital and the medical centre of the national football association). Subjects received either

two injections of 3 ml of either platelet-rich plasma (Autologous Conditioned Plasma, Biocore, Arthrex Inc, Karlsfeld, Germany) or normal saline at the site of the injury. There was no difference in the primary outcome measure (time to return to play) and re-injury rate between these two groups, and therefore it represents a normal cohort[187].

As outlined in our previous publication[187], the eligibility criteria for the present study are an age 18–50 years, a clinical and radiological diagnosis of acute hamstring injury within five days from injury, a Magnetic Resonance Imaging (MRI) grade 1 or 2 hamstring lesion and the availability of a re-assessment within seven days after RTP. The criteria for a clinical diagnosis of a hamstring muscle strain were: acute onset of posterior thigh pain, pain on hamstring stretch and resisted contraction and pain on hamstring muscle palpation. The clinical diagnosis was established by one of the six participating sports medicine physicians. An MRI was performed in each subject within five days from initial injury, using a 1.5-T magnet system (Magnetom Essenza, Siemens) and a body matrix coil. The MRI scans were assessed by a musculoskeletal radiologist, to confirm the diagnosis of a hamstring muscle injury. Patients and the supervising physiotherapist were blinded to the severity of the lesion on MRI. Exclusion criteria were a contraindication for MRI, chronic posterior thigh symptoms, persistent chronic low back pain, posterior thigh injury due to extrinsic trauma, inability to perform active rehabilitation, no desire to return to full sports activity, unwillingness to receive intramuscular injections and previous injection therapy for this injury.

At inclusion, informed consent was acquired from all patients. Approval was obtained from the Medical Ethics Committee Zuidwest Holland, Voorburg, the Netherlands.

Procedure

Baseline patient characteristics at the time of initial injury

At baseline we recorded age, sex, type of sports, sports activity level (recreational or competitive), type of injury (sprinting type or non-sprinting type) and number of prior ipsilateral and contralateral hamstring injuries. Competitive athletes were individuals who played league matches at the highest levels of their club. A sprinting type injury was an injury that occurred during a maximum or near maximum sprint[13]. Injuries that occurred during stretching, deceleration phase of sprinting, high kicking and otherwise not specified were classified as non-sprinting type.

MRI findings at the time of initial injury

We used standardised scoring forms to assess MRIs at baseline[192]. We measured the increased T2 signal intensity on the fluid sensitive sequences (STIR or PD-FS) in cranio-caudal, transverse and anterior-posterior dimensions. We recorded the longitudinal length (cranio-caudal in cm) of the lesion and the distance in cm from the ischial tu-

berosity. The cross sectional area was calculated as a percentage of the total muscle cross sectional area in the transversal plane. The volume of the muscle lesion in cm^3 was measured using the formula for a prolate ellipsoid ([π / 6] × anteroposterior × transverse × cranio-caudal extent)[216]. We recorded the involved muscle(s) and performed grading of the injury[192]: grade 1): increased signal intensity on fluid sensitive sequences without evidence of a macroscopic tear, grade 2): increased signal intensity on fluid sensitive sequences with a partial tear. Good to excellent inter- and intra-observer reliability was found for these MRI findings used in a previous study[93].

Rehabilitation programme

All patients included performed a progressive phased, criteria-based rehabilitation programme which was based on the best available evidence[103,145,208] The rehabilitation program consisted of twice-weekly physiotherapist supervised training sessions combined with daily home-based exercises (Supplementary Table)[187]. The home exercise program consisted of a progressive agility and trunk stabilisation exercise protocol[208]. The number of supervised physiotherapy sessions and daily home-based exercise sessions were logged. Instructional videos of the exercises were supplied on an openly accessible website. The physiotherapists and patients were instructed to progress through the rehabilitation program as fast as possible according to the pre-specified functional progression criteria. With these instructions, we aimed to stimulate early RTP. However, we also emphasized that criteria were symptom-based, as opposed to time-based progressions.

RTP decision

Clearance for RTP was given by the supervising physiotherapist once the patient completed the criteria-based rehabilitation program. According to standardized rehabilitation protocol an athlete was ready to return to play once he or she met the following criteria: symptom-free (e.g. pain and stiffness) during: 1) full range of motion; 2) full speed sprinting; and 3) sport-specific movements (such as jumping and cutting)[103,208]. The final phase of the rehabilitation program consisted of unhindered functional sport specific testing.

The physiotherapist was blinded to the data of the clinical findings collected by the principal investigator. The physiotherapist and the patient were informed that a lesion was present on the baseline MRI and therefore proved the clinical diagnosis, but they were blinded for the grading and extent of the injury. The principal investigator was not involved in the RTP decision and did not advise patients on RTP decision based on the baseline MRI or clinical findings just after RTP.

Questionnaire and recovery score just after RTP

All patients included were invited for a re-assessment within seven days of RTP. The Hamstring Outcome Score (HaOS) was completed[67,68], consisting of five categories (symptoms, muscle soreness, pain, function in sports, and quality of life). The mean score is calculated and displayed between 0% (lowest score) and 100% (maximum score). The HaOS is a screening tool for assessment during normal activities of daily living and sports and used in previous cohorts[67,68]. For our study, the questionnaire was translated into Dutch by a registrar in Sports Medicine who is a native speaker (GR).

Perceived recovery was measured with a 7-point Likert self-rating scale ranging from "completely recovered" (0 points) to "worse than ever" (7 points). Complete recovery was considered as a successful outcome. The time to RTP was measured as the number of days from the initial injury until return to full training or match play in the desired sport.

Clinical assessment just after RTP

The post-return to play clinical evaluation consisted of hamstring flexibility testing, strength testing and muscle palpation. The flexibility of the hamstring muscles was assessed with the active knee extension test[189] and the passive straight leg raise test[68,145,189,208]. Subjects were examined in the supine position and an inclinometer was placed on the anterior tibial border. Both the injured and the uninjured leg were tested. For the active knee extension test, subjects were positioned with the ipsilateral hip in 90° flexion. Subsequently, subjects were asked to extend the knee until experiencing maximal tolerable stretch, with the contralateral leg fixed flat on the examination table. The maximum absolute knee angle was measured.

For the passive knee extension test subjects were instructed to fully relax the leg. Subsequently the leg was lifted by the principal investigator with the hip still in 90° flexion, and the knee in increasing extension until the maximal tolerable stretch was experienced. The contralateral leg remained flat on the examination table. At the endpoint of maximal tolerable stretch, the angle between the leg axis and the horizontal examination table was measured. For both tests the absolute flexibility deficit was calculated by subtracting the established angle of the injured leg from the uninjured leg. Furthermore, subjects were asked whether they experienced normal stretch or localised discomfort in the posterior thigh during the tests.

Isometric knee flexion force was measured using handheld dynamometry[128]. Subjects were tested in prone with a knee flexion angle of 90° and 15°. Each leg was tested three times in both angles. The principal investigator positioned the dynamometer at the subject's heel and applied force to the heel in upward direction, gradually increasing in 3-5 seconds. Subjects were instructed to resist the force applied by the principal investigator (break test). At the point that the subjects were not able to resist the force, the test was terminated and the force level was recorded. For each angle the highest force value was

documented. The relative strength deficit was established as a portion of the maximal force value of the injured leg divided by maximal force value of the uninjured leg.

Palpation of the hamstring muscles was performed with the patient in prone with the leg relaxed and neutral hip and knee position. The entire ipsilateral posterior thigh was carefully palpated from the hamstring origin at the ischial tuberosity to the insertions medial at the pes anserinus and lateral at the head of the fibula. Presence of localised discomfort on palpation was recorded as a dichotomous variable (present or absent).

Outcome measures

The primary outcome measure in this study was the occurrence of a re-injury. A re-injury was defined as acute posterior thigh pain in the index leg within the prospective study follow-up period of 12 months after the initial injury, which caused time loss from training or match play[73]. All patients were instructed to contact the principal investigator in case of a possible re-injury. We confirmed re-injury based on a telephone interview. The principal investigator took a thorough history and instructed the patient to perform stretching and contraction manoeuvres of the hamstring muscles to identify localised pain on stretch and contraction. All patients in the study were also asked about the occurrence of re-injuries at the standard 6- and 12-month follow-ups .

Statistical analysis

We performed statistical analyses with SPSS software (version 20.0; SPSS, Chicago, Illinois). Descriptive statistics were used to analyse baseline patient characteristics. If the data was normally distributed it is presented as a mean with a standard deviation (SD), otherwise a median and inter quartile range (IQR) are used. To aid in data interpretation, a number of variables were categorised.

We analysed the association between the possible predictor variables and re-injuries with a Cox proportional-hazards regression model. In this model the time (days) from return to play to the event (re-injury) or the end of the follow-up is the main variable. All patients who were available for examination shortly after RTP were included in the final analysis. We excluded patients from the analysis if we could not obtain RTP measurements, because cases with missing values are routinely excluded from the multivariate analysis. Subjects that sustained another severe injury (defined as absence from training and matches >28 days[61,83]) during follow-up that was not considered a hamstring re-injury were censored at the time of this injury. Subjects lost to follow-up were censored at the time of their last available follow-up.

We first analysed the association between predictor variables and re-injuries in a univariate model. Variables with a p-value of < 0.1 were analysed in a multivariate stepwise regression. We considered a p-value <0.05 statistical significant.

RESULTS

Participants

One-hundred sixty-one patients were assessed for eligibility and 80 patients were included in the RCT. Finally, 64 patients were available for inclusion in the analysis. In 16 cases (20%) data just after RTP was not available. The number of re-injuries did not differ

Table 10.1 Patient characteristics (n = 80)

	Included (n=64)	**Excluded** (n=16)
Median age (IQR)	28 (23-33)	28 (22-32)
Gender Male / Female	61/3	15/1
Sports		
- Football	45	11
- Futsal (Indoor football)	1	0
- Field hockey	11	1
- Athletics	4	0
- Tennis	1	0
- American football	1	2
- Fitness	1	1
- Cricket	0	1
Level of Sports		
- Competitive	49	10
- Recreational	15	6
Median days (IQR) to initial presentation	3 (2-4)	3 (2-4)
Median number(IQR) of previous hamstring injuries	1 (0-3)	1 (0-3)
Severity of injury on MRI		
- Grade 1	18	5
- Grade 2	46	11
Involved muscles		
- Biceps femoris	56	13
- Semitendinosus/Semimembranosus	8	3
Mean (SD) longitudinal length (cranio-caudal) on MRI	11.4 (5.7)	14.6 (6.9)
Mean (SD) distance from the ischial tuberosity on MRI	15 (7.8)	14.8 (7.7)
Mean (SD) cross sectional area on MRI	37% (28)	33% (21)
Mean (SD) volume of the muscle lesion on MRI (cm^3)	285 (302)	486 (677)
Median (IQR) time to RTP (days)	40 (31-55)	46 (33-67) (n = 11)
Median days (IQR) between RTP and clinical findings	3(2-5)	NA
Number of re-injuries	17 (27%)	4 (36%) (n=11)

Abbreviations: IQR, Interquartile range; SD, Standard Deviation; MRI, magnetic resonance imaging; RTP, return to play; NA Not Applicable. Only 11 patients in the excluded group achieved RTP, therefore some analyses are displayed for these 11 patients (n=11).

significantly between the patients included and excluded from the analysis (p=0.49, see Table 10.1). The progress of patients in the study is displayed in a flow-chart (Figure 1). We performed measurements at a median of 3 days (IQR, 2-5) after the RTP date. The characteristics of the patients included and excluded are presented in Table 10.1.

Descriptive measurements at baseline and just after RTP

The results of the clinical and imaging findings at baseline and just after RTP are displayed in Table 10.2. Twenty-eight percent of the patients sustained a grade 1 injury and 72% a grade 2 injury as graded on MRI. In 88% of the patients a biceps femoris long head injury was present and in 12% a semitendinosis/semimembranosis injury.

Just after RTP 66% of the patients reported a "complete recovery" on the Likert scale. Discomfort during hamstring flexibility, hamstring resistance testing or on localised palpation was present in 25% of cases when the independent principal investigator tested those athletes who had been cleared to RTP.

In total, 50% of the patients kept their daily logs of the rehabilitation program and returned their logbook. The mean percentage adherence for the supervised physiotherapy program was 80%. The mean percentage adherence for the home exercise program was 64%. Because of these missing data, we refrained from including adherence in the Cox proportional-hazards regression model.

Table 10.2 Descriptive statistics of clinical findings just after RTP

Clinical test	Measurement just after RTP
Mean (SD) HaOS (0-100)	88 (12)
Median (IQR) Likert self-rating scale (0-7)	0 (0-1)
Active knee extension test	
- Mean (SD) deficit in angle (degrees)	-2 (5)
- Discomfort (present/absent)	1/63
Passive straight leg raise test	
- Mean (SD) deficit in angle (degrees)	-1 (4)
- Discomfort (present/absent)	1/63
Isometric knee flexion resistance in 90°	
- Mean (SD) force deficit (Newton)	2 (15)
- Discomfort (present/absent)	8/56
Isometric knee flexion resistance in 15°	
- Mean (SD) force deficit (Newton)	1 (16)
- Discomfort (present/absent)	8/56
Localised discomfort on palpation hamstring muscles (present/absent)	16/48

Abbreviations: HaOS, Hamstring Outcome Score; SD, Standard Deviation; IQR, Interquartile Range; RTP, return to play

Prognostic factors for re-injury

None of the 64 patients were lost to follow-up during the 12-month follow-up period. There were 17 (27%) re-injuries. The re-injuries occurred at a median (IQR) of 100 (6-138) days after RTP. There were 7 (11%) re-injuries within the first two months.

The number of previous hamstring injuries (p=0.006), presence of discomfort during isometric knee flexion resistance test at 15° (p=0.008) and localised discomfort on hamstring palpation (p=0.008) were univariately associated with hamstring injury recurrence. For the baseline MRI findings examined we did not find significant univariate associations, as well as for all other measured variables. The results of the univariate analysis are shown in Table 10.3.

Five variables (number of previous hamstring injuries, active knee extension deficit, isometric knee flexion force deficit at 15°, presence of discomfort during isometric knee flexion resistance test at 15° and localised discomfort on posterior thigh palpation) were included in the multivariate model based on a p-value < 0.1 in the univariate analysis (Table 10.4).

The multivariate model showed that athletes with a higher number of previous ipsilateral and/or contralateral hamstring injuries (AOR 1.33; 95% CI 1.11 to 1.61), more degrees of active knee extension deficit (AOR 1.13; 95% CI 1.03 to 1.25), isometric knee flexion force deficit at 15° (AOR 1.04; 95% CI 1.01 to 1.07) and presence of localised discomfort

Table 10.3 Univariate results of the association between the clinical findings just after RTP and event of re-injuries

Variable	n	Hazard ratio (95% CI)	p-value
Patient characteristics			
Categorical variables			
Previous hamstring injury		2.9 (0.8-10.1)	0.094
No (reference)	23		
Yes	41		
Previous ipsilateral hamstring injury		1.8 (0.7-5.0)	0.233
No (reference)	30		
Yes	34		
Previous hamstring injury within 12 months		1.6 (0.6-4.3)	0.309
No (reference)	45		
Yes	19		
Previous ipsilateral hamstring injury within 12 months		1.6 (0.6-4.2)	0.388
No (reference)	47		
Yes	17		
Level of sport		2.5 (0.6-11)	0.218
Recreational (reference)	15		
Competitive	49		

Table 10.3 (continued)

Variable	n	Hazard ratio (95% CI)	p-value
Continuous variables			
Age		1.00 (0.94-1.07)	0.952
Number of previous hamstring injuries		1.26 (1.07-1.48)	0.006
Injury characteristics			
Categorical variables			
Sprinting injury type		1.9 (0.5-6.5)	0.321
No (reference)	17		
Yes	47		
Injured muscle		0.5 (0.1-3.4)	0.440
Biceps femoris (reference)	56		
Semitendinosus/semimembranosus	8		
MRI grade		1.3 (0.4-4.1)	0.624
Grade I (reference)	18		
Grade II	46		
Continuous variables			
Time to RTP		0.98 (0.94-1.01)	0.126
MRI hyperintensity volume		1.00 (1.00-1.00)	0.112
MRI cross sectional area (% of total muscle)		0.95 (0.18-5.11)	0.947
MRI cranio-caudal length		1.00 (0.99-1.01)	0.525
MRI distance to tuber		1.00 (0.98-1.00)	0.978
Characteristics just after RTP			
Categorical variables			
Subjective complete recovery		0.5 (0.2-1.3)	0.136
yes (reference)	22		
no	42		
Localised discomfort on palpation		3.7 (1.4-9.6)	0.008
No (reference)	48		
Yes	16		
Active knee extension discomfort		0.1 (0-303265.6)	0.704
No (reference)			
Yes			
Passive straight leg raise discomfort		2.2 (0.3-16.7)	0.445
No (reference)	62		
Yes	2		
Discomfort on isometric knee flexion resistance in 15°		3.7 (1.4-9.6)	0.008
No (reference)	56		
Yes	8		
Continuous variables			
HaOS		0.98 (0.95-1.01)	0.198
Active knee extension deficit		1.10 (1.00-1.24)	0.059
Passive straight leg raise deficit		0.95 (0.85-1.07)	0.376
Isometric knee flexion force deficit in 15°		1.03 (1.00-1.06)	0.074

Abbreviations: HaOS, Hamstring Outcome Score; MRI, magnetic resonance imaging; RTP, return to play; CI, Confidence interval

on hamstring palpation (AOR 3.95; 95% CI 1.38 to 11.37) were more likely to have a re-injury. The presence of discomfort during isometric knee flexion resistance test at 15° was not a significant independent predictor of re-injury (AOR 2.66; 95% CI 0.83 to 8.55).

Table 10.4 Independent predictors of re-injuries

Clinical test	Adjusted Hazard ratio (95% CI)	p-value
Number of previous hamstring muscle injuries	1.33 (1.11 – 1.61)	0.002
Active knee extension deficit	1.13 (1.03 – 1.25)	0.012
Isometric knee flexion resistance discomfort in 15°	2.66 (0.83 – 8.55)	0.100
Isometric knee flexion force deficit in 15°	1.04 (1.01 – 1.07)	0.020
Localised discomfort on palpation hamstring muscles	3.95 (1.38 – 11.37)	0.011

Abbreviations: CI, Confidence interval

DISCUSSION

Hamstring re-injury[234] may have a different set of risk factors to primary hamstring injury[71]. We evaluated clinical and MRI findings to identify factors associated with re-injury following hamstring injury in competitive and recreational athletes. We evaluated the athletes just after the initial injury and just after return to play, when they successfully completed a criteria-based rehabilitation programme. Some players exhibited a deficit in several functional tests after return to play. Four specific clinical findings that had not fully returned to normal – as compared to the unaffected side – just after return to play appear to be associated with an increased re-injury risk (a higher number of previous hamstring injuries, more degrees of active knee extension deficit, isometric knee flexion force deficit at 15° and the presence of localised discomfort on posterior thigh palpation just after RTP).

Independent predictors of re-injury which can be used in daily clinical practice

Significant independent predictors of hamstring re-injury were a higher number of previous hamstring injuries, more degrees of active knee extension deficit, isometric knee flexion force deficit at 15° and the presence of localised discomfort on posterior thigh palpation just after RTP. These various independent predictors were analysed using a multivariate model. These results provide useful prognostic information for clinicians involved in the treatment of hamstring injuries and who are responsible for the RTP decision.

These findings are important, as acute hamstring injuries frequently result in a recurrence with a prolonged rehabilitation time. With easy to assess clinical evaluation – performed by clinicians or physiotherapists – those subjects with an increased re-injury risk

can be identified. These findings emphasize that it is of major importance to monitor the athlete in the first week after RTP and not only at RTP.

We found that athletes with localised discomfort on hamstring palpation just after the RTP date were almost four times more likely to sustain a re-injury compared to athletes with absence of discomfort on palpation. Also, the continuous variables number of previous hamstring injuries (adjusted odds ratio 1.33, 33% increased risk per number of previous hamstring injury), degrees of active knee extension deficit (adjusted odds ratio 1.13, 13% increased risk per deficit in degree) and isometric knee flexion force deficit at 15° (adjusted odds ratio 1.04, 4% increased risk per deficit in Newton) showed to be of prognostic value. For example, an athlete is at 33% more risk for re-injury if there is one previous hamstring injury and at 77% more risk (hazard ratio increases with 1.33 x 1.33 = 1.77) if there are two previous hamstring injuries, compared to no previous hamstring injury.

MRI findings at baseline is not a predictor of re-injury - comparison with previous studies

Clinical findings just after RTP have not been related to hamstring re-injury rate in previous studies. A recent study from our group described the MRI findings just after RTP[192]. We reported that in 89% of clinically recovered hamstring injuries, increased intramuscular signal intensity on fluid sensitive sequences was observed just after RTP[192]. The presence of increased signal intensity was not discriminative as a predictor for re-injury. The number of re-injuries was too small to draw conclusions on the effect of the presence of fibrous tissue on MRI. These results emphasize that clinical and functional tests seem to be better associated with re-injury rates than findings on MRI just after RTP[152,223].

In a previous study, Warren et al.[238] reported on the value of baseline history and clinical signs measured within 0-3 days in 59 athletes who sustained an acute hamstring injury. They concluded that hamstring injury in the previous medical history predicted re-injury (Relative Risk of 19.5 and 95%CI 1.5 to 261.1). Baseline clinical findings for hamstring flexibility, pain on resistance and palpation at the site of the injury were also included, but were found not to be significant early predictors. A comparable study in 30 athletes with acute hamstring injury did not show an association with re-injury and the baseline clinical findings assessed at 12-18 hours post injury[232]. The lack of association between clinical test in the acute phase and re-injury risk might be explained by the fact that almost all these patients experience pain at the early stages of the injury and therefore the discriminative power of these tests are not yet present in the acute stage. For this reason – and also because it is common in clinical practice – we repeated the assessment of clinical findings just after the RTP moment.

The predictive value of baseline MRI findings of the initial injury for re-injury has been reported in previous studies. One study[77] did not show an association between the size

of the initial injury and re-injury rate. They found, however, that a higher frequency of re-injury was reported in grade 1 hamstring injury at the initial trauma, compared to MRI negative injuries. In a study of 30 Australian Rules Footballers (AFL), Verrall and colleagues[232] found that baseline MRI features were not associated with increased recurrent injury risk within the same playing season. Larger transverse size and volume of injury on MRI was reflected in re-injury risk if the subsequent playing season was also included in the analysis. Koulouris et al.[125] performed a cohort study in 41 Australian Football players and showed a correlation between length of the lesion on MRI and re-injury risk.

Because of the above mentioned study results, it is suggested that a more severe injury on MRI might result a longer expected recovery time and postponed RTP decision. In our study, patients were blinded for the severity of the injury on baseline MRI; only the presence of a lesion was confirmed. The RTP decision was therefore not influenced by the grading of the lesion on MRI. We did not find any of the baseline MRI findings to be associated with re-injury. As 89% of the MRIs still showed abnormalities at RTP[192], MRI at RTP did not provide stronger associations (data not shown). Based on our study – in which blinding of the patients and care-providers was performed – baseline MRI is not a predictor of hamstring re-injury.

Study strengths and limitations

The strength of this study is that one single independent principal investigator performed all clinical tests. He was not involved in the RTP decision and only assessed the clinical findings once the player returned to play. The independent physiotherapist – who made the RTP decision – was blinded to the outcomes of the clinical tests performed by the principal investigator. This allows for the opportunity to study the effects of some of these variables that were tested but not included in the RTP decision making algorithm.

There are also some study limitations. Firstly, the number of patients was relatively low with a subsequent low number of re-injuries. Therefore, the study might be underpowered to provide a definite answer on the effect size of the clinical predictors for re-injury at RTP. A previous article reports that 20-50 cases are needed to detect moderate to strong associations[24]. In our study, 17 re-injuries were found, meaning that only strong associations could probably be detected. The sample size of the original study was based on the primary outcome (days between injury and RTP) of the RCT[187]. Therefore, small associations are less likely to be detected with our study. However, the clinical relevance of finding small associations is also questionable.

Furthermore, not all athletes (n=16, 20%) had clinical examination performed after RTP, which may have resulted in risk of bias. However, the percentage of re-injuries did not differ between the patients included and excluded from the analysis. It was challenging to evaluate all patients shortly after the RTP date and there were athletes who did not achieve RTP due to other injuries. To minimize the risk of bias, these athletes

were excluded from the analysis. Two athletes sustained a re-injury after RTP before we could do a clinical assessment and therefore, there may be bias because the outcome (re-injury) resulted in missing data. Another potential source of bias is the fact that re-injuries were diagnosed with a telephone interview. This might have resulted in an overestimation of the re-injuries since posterior thigh pain after an initial hamstring injury is not always due to a hamstring re-injury. However, the principal investigator aimed to collect as much data as possible to establish the diagnosis of a re-injury.

Not all clinical tests we performed have well examined reliability or validity. The active and passive knee extension tests have good inter-tester reliability[189]. For the other clinical tests these characteristics are unknown. Especially discomfort on palpation is difficult to standardise, as pressure of the palpating fingers might influence the results. To prevent large variability in test results, all clinical examinations were performed by one single trained principal investigator. He was not blinded to the side of the injury during the clinical assessment after RTP, which potentially might have led to bias. As this clinical examination was performed within 5 days after RTP (range 2-5), it remains unknown if recorded abnormalities were present at the moment of RTP decision making or developed within the 2-5 days after RTP.

Lastly the independent treating physiotherapists were advised to use the standardised rehabilitation protocol; however they did not log the actual rehabilitation performed. Variations on the protocol might have been used; although the physiotherapists were instructed to follow the protocol. The amount of bias for daily clinical practice is questionable, as many different protocols and RTP decision criteria are described in literature[53,168]. The observation that the re-injuries occurred at a median (IQR) of 100 (6-138) days after RTP suggest that the re-injuries were not a consequence of poor RTP decision making by the supervising physiotherapists. Furthermore, in our study 27% of the athletes had a re-injury, which is within the normal range of re-injury rate in the scientific literature (14-63%)[234].

Recommendations for future studies

Re-injury prevention could be a focus in future studies. We found that a higher number of previous hamstring injuries, more degrees of active knee extension deficit, isometric knee flexion force deficit at 15° and the presence of localised discomfort on posterior thigh palpation were associated with higher re-injury risk after patients completed a criteria-based rehabilitation programme. These factors might be implemented in criteria-based rehabilitation programmes. The associated factors can also be used to test this clinical prediction rule in a prospective study. If they are found to hold up to this scrutiny then an intervention study could be performed to see if more stringent RTP criteria results in lower recurrence rates.

Re-injury prevention might be another interesting focus in future studies. In future research, rehabilitation programmes could be more focussed on recovery of the clinical findings that are associated with re-injury. If the re-injury rate in these identified high-risk athletes can be reduced with prevention programs, it will potentially have a major influence on the number needed to treat.

CONCLUSION

A higher number of previous hamstring injuries, more degrees of active knee extension deficit, isometric knee flexion force deficit at 15° and the presence of localised discomfort on posterior thigh palpation after return to play were associated with hamstring re-injury in athletes who completed a criteria-based rehabilitation programme. These factors could be taken into account by clinicians when making a RTP decision and monitoring athletes after RTP. Based on this study, none of the baseline MRI parameters was a predictor of hamstring re-injury.

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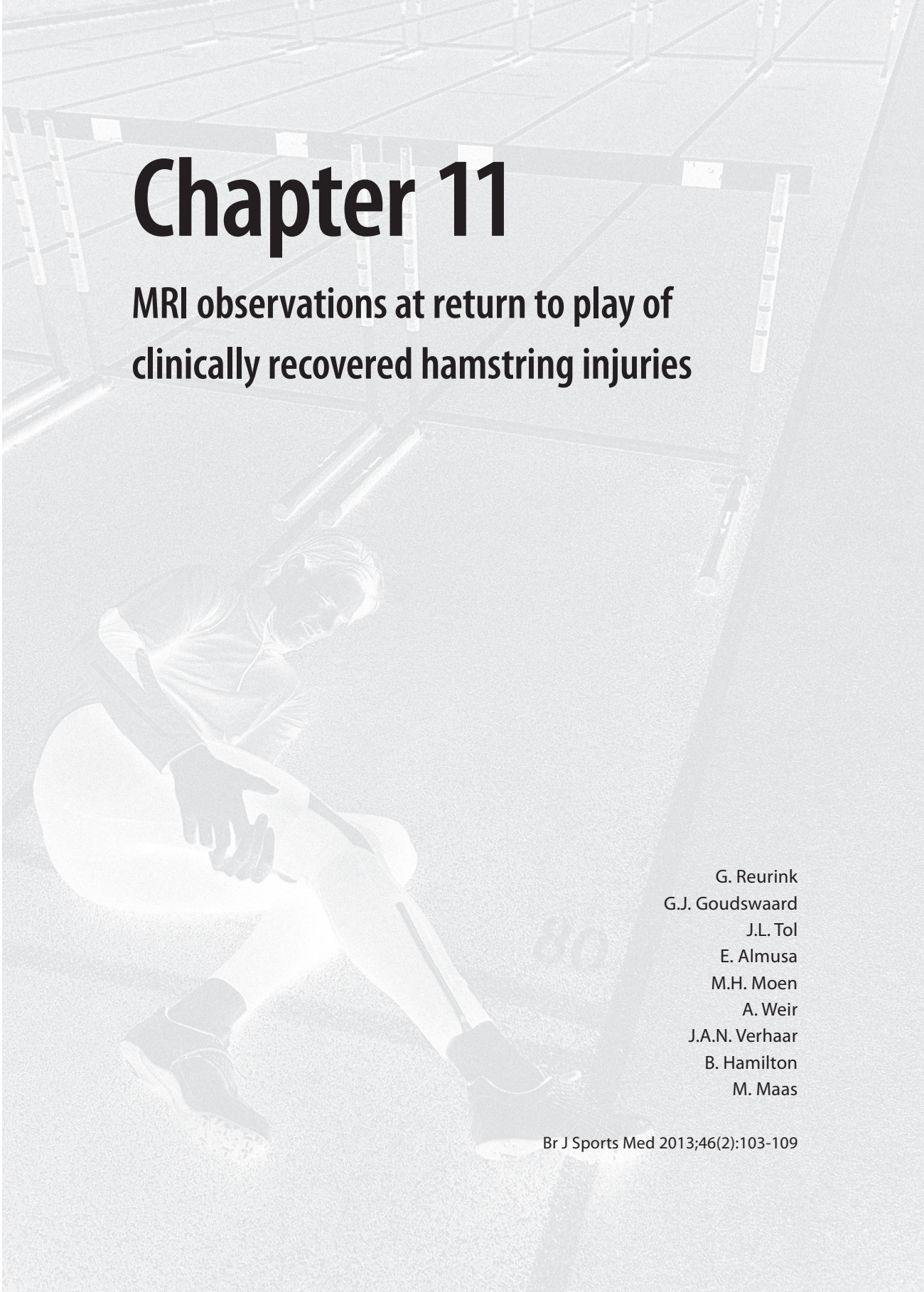
Chapter 11

MRI observations at return to play of clinically recovered hamstring injuries



G. Reurink
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ABSTRACT

Background – Previous studies showed that Magnetic Resonance Imaging (MRI) of fresh hamstring injuries has diagnostic and prognostic value. The clinical relevance of MRI at return to play (RTP) has not been clarified yet. The aim of this study is to describe MRI findings of clinically recovered hamstring injuries in amateur, elite and professional athletes that were cleared for RTP.

Methods – We obtained MR images of 53 consecutive athletes with hamstring injuries within five days of injury and within three days of RTP. We assessed the following parameters: injured muscle, grading of injury, presence and extent of intramuscular signal abnormality. We recorded re-injuries within two months of RTP.

Results – MRIs of the initial injury showed 27 (51%) grade 1 and 26 (49%) grade 2 injuries. Median time to RTP was 28 days (range 12-76). On MRI at RTP 47 athletes (89%) had intramuscular increased signal intensity on fluid sensitive sequences with a mean longitudinal length of 77 mm (± 53) and a median cross sectional area of 8% (range 0-90%) of the total muscle area. In 22 athletes (42%) there was abnormal intramuscular low signal intensity. We recorded five re-injuries.

Conclusion – Eighty-nine percent of the clinically recovered hamstring injuries showed intramuscular increased signal intensity on fluid sensitive sequences on MRI. Normalisation of this increased signal intensity seems not required for a successful RTP. Low-signal intensity suggestive of newly developed fibrous tissue is observed in one third of the clinically recovered hamstring injuries on MRI at RTP, but its clinical relevance and possible association with increased re-injury risk has to be determined.

INTRODUCTION

Magnetic Resonance Imaging (MRI) has been validated for the diagnosis and prognosis of acute hamstring injuries and is frequently used in these common injuries, especially in the elite athlete.[15,51,52,63,77,120,203,216,231] Follow-up MRI has been suggested to monitor recovery after injury and support decisions for return to play (RTP), but has not been validated yet.[120,152] Hamstring injuries are characterized by a high re-injury rate of 14-63% within one year.[61,77,125,139,169,208,232,234] The re-injury is often more severe and associated with a longer absence from play.[61] It has been hypothesised that re-injuries may be related to altered muscle mechanics due to fibrous tissue formation, reduced strength due to disuse atrophy, pain and/or reflex inhibition or to a premature return to play (RTP).[103,139,167,210,211] Although there is no consensus as to when an athlete can safely RTP, in clinical practice an athlete is typically regarded as being ready once full range of motion, full strength and functional sport specific activities (e.g. sprinting, jumping, cutting) can be performed asymptomatically.[103,152,168] Despite this conventional approach, the decision whether an athlete can safely RTP remains challenging.[14,103] This is reflected in the high number of re-injuries that occur shortly after RTP, as it has been reported that 59% occur within the first month after RTP.[35] Obviously, there is a need for assessment tools, which can discriminate between those athletes ready and athletes not ready for RTP.

Imaging modalities may have a role in assisting a safe RTP.[120,152] Little is known about the value of MRI in monitoring recovery and RTP decisions. Connell et al. found that increased signal intensity on fluid sensitive sequences consistent with oedema may persist after resolution of clinical symptoms with 36% (15/42) having persistent abnormal findings on MRI at six weeks after the onset of injury.[52] Similarly, Askling et al. reported increased signal intensity on fluid sensitive sequences on MRI six weeks after the onset of injury in 17 out of 18 athletes.[15] Long-term MRI observations on hamstring injuries have been reported by Silder et al., where 5-23 months after hamstring injury, increased low-signal intensities, suggestive of fibrous tissue, were found in 11 out of 14 subjects.[210] These studies did not relate the MRI observations to RTP.

Two previous studies have reported MRI findings at RTP. Sanfilippo et al. found at RTP in 25 athletes, that on average 20% of the muscles' cross sectional area still showed increased signal intensity on fluid sensitive sequences on MRI.[201] In second study of the same research group Silder et al. reported that none of 21 athletes had complete resolution of the increased signal intensity on MRI after being cleared to RTP and that most subjects showed early signs of scar tissue formation.[213] Detailed information regarding the presence and extent of fibrous tissue at RTP is not reported. If MRI is to be used in facilitating RTP decisions then observations, which can discriminate between a successful and unsuccessful RTP, should be identified.

Our hypothesis is that normalisation of increased signal intensities on fluid sensitive sequences on MRI is not required for a successful RTP and that low-signal intensity suggestive of fibrous tissue may be observed in the majority of clinically recovered hamstring injuries at RTP. The aim of this study is to describe MRI findings of hamstring muscles in athletes, who have clinically recovered from an acute non-contact hamstring injury, and were cleared for RTP.

METHODS

Subjects

At inclusion, informed consent was obtained from all patients. Approval was obtained from the Regional Ethical Committee of South West Holland and the Ethical Committee of Aspetar, Qatar Orthopaedics and Sports Medicine Hospital.

The patients in this study consist of cohorts of two on going double blind randomised controlled trials (RCT) on the effect of platelet rich plasma in hamstring injuries: Dutch trial register number 2771 and ClinicalTrial.gov number NCT01812564. The first multicentre RCT started in February 2011 and was performed at the sports medicine departments of a large general district hospital, a university hospital and the medical centre of the national football association (Dutch cohort). In this study subjects were randomized into an intervention group or a control group. The intervention group received two injections of 3 ml platelet-rich plasma (Autologous Conditioned Plasma, Biocore, Arthrex Inc, Karlsfeld, Germany) and the control group received two injections of 3 ml saline at the site of the injury. The first injection was performed within five days of the injury and the second injection five to seven days later. The other RCT started in November 2009 and was performed in a specialized orthopaedic and sports medicine hospital (Qatar cohort). In this study subjects were randomized into three groups: one group received an injection of 3 ml platelet-rich plasma (Biomet Recover™, USA), one group received an injection of 3 ml platelet-poor plasma and one group received no injection. The injections were performed using a sterile ultrasound guided technique into the region of maximal muscle injury, as determined by the initial MRI. Three separate depots of one ml were injected.[91] All subjects completed a standardized physiotherapy programme, including range of motion exercises, progressive strength exercises, core stability training and agility exercises.

The eligibility criteria for the present study are presented in Table 11.1. In the first cohort the clinical diagnosis of the hamstring injury was made by six registered sports medicine physicians with 3 to 25 years of clinical experience in medical care of professional club and national team athletes in sports where hamstring injuries are common (football, futsal (indoor football), rugby, field hockey and squash). The functional

criteria-based rehabilitation programme was supervised by a sports physiotherapist and clearance was given for RTP once they successfully and asymptomatically completed the physiotherapy programme, including functional sport specific activities. In the second cohort the clinical diagnosis of the hamstring injury and the clearance for RTP was performed by eight registered sports medicine physicians with 7 to 20 years clinical experience, covering medical care of professional club and national team athletes where hamstring injuries are common (predominantly football, rugby, track and field). The guideline criteria to assist RTP decision included: successfully and asymptomatically completing the functional criteria-based 4 staged physiotherapy programme, including a final supervised sport specific (outdoor) training phase and less than 10% side to side difference at isokinetic strength testing. After RTP clearance, athletes were advised to complete five days of team training before participating in partial match play.

Magnetic Resonance Imaging

In each subject, MRI of the injury was performed twice: within five days from initial injury and within three days of RTP. The MRI of the initial injury was performed prior to the injection procedure.

Two comparable MRI protocols were used. The protocol in the first RCT was a modified version of the protocol described by Askling et al.[15] To locate the area of the injury the en-

Table 11.1 Eligibility criteria

Dutch cohort	Qatar cohort
Inclusion criteria	
• Age 18 – 50 years • Clinical diagnosis acute hamstring injury • Presenting and MRI within five days from injury • MRI confirmed grade I or II hamstring lesion • Second MRI available within three days of RTP	• Age 18-50 years • Acute onset of posterior thigh pain • Presenting and MRI within five days from injury • MRI confirmed grade I or II hamstring lesion • Second MRI available within three days of RTP • Gender: Male • Able to perform five sessions physiotherapy a week at the clinic • Available for follow-up
Exclusion criteria	
• Contraindication to MRI • Chronic hamstring injury • Chronic low back pain • Cause of injury is an extrinsic trauma • Not capable of performing rehabilitation • No intention to return to full sports activity • Unwilling to receive the intramuscular injections • Injection therapy received for this injury before	• Contraindication to MRI • Re-injury or chronic hamstring injury • Concurrent other injury inhibiting rehabilitation • Unwilling to comply with follow-up • Needle phobia • Overlying skin infection • Diabetes, immune-compromised state • Medication increasing bleeding risk (e.g. Plavix) • Medical contraindication to injection

Abbreviations: MRI, magnetic resonance imaging; RTP: return to play

tire hamstring of the injured limb was visualised by obtaining coronal and sagittal short tau inversion recovery (STIR) images from the ischial origin of the hamstring muscles to insertion on the fibula and the tibia (repetition time/echo time (TR/TE) of 3500/31 ms, field of view (FOV) of 300 mm and a 256x320 matrix). Subsequently, transversal STIR (repetition time/echo time (TR/TE) of 3500/31 ms, field of view (FOV) of 300 mm and a 205x256 matrix), T1-weighted (TR/TE of 500/12 ms, FOV of 300 mm and a 355x448 matrix) and T2-weighted (TR/TE of 4080/128 ms, FOV of 300 mm and a 355x448 matrix) images were obtained from the injured area. The thickness of the slices for all sequences was 5mm. MR images were obtained with a 1.5-T magnet system (Magnetom Essenza, Siemens) with the use of a body matrix coil.

In the second RCT MR images were obtained of the hamstring muscles with a 1.5-T magnet system (Magnetom Espree, Siemens) with the use of a body matrix coil. First coronal and transversal proton density (PD) weighted images (TR/TE of 3000/30 ms, FOV of 220-240 mm, slice thickness of 5 mm and a 333x512 matrix) were obtained. Subsequently coronal and transversal proton density fat saturation (PD-FS) images (TR/TE of 3000+/30 ms, FOV of 220-320 mm, slice thickness of 3,5 mm, a 326x512 matrix for the coronal images and a 333x512 matrix for the transversal images) were obtained.

Each MRI was assessed by one of two radiologists, each with more than nine years of experience in musculoskeletal radiology (EA and MM). The radiologists were blinded for the information on whether the MRI was of the initial injury or at RTP. For assessment of the MRIs we used standardised scoring forms based on the literature.[52,63,177,210,216] We measured the increased T2 signal intensity for the affected hamstring muscle in cranio-caudal, transverse and anterior-posterior dimensions on the fluid sensitive sequences (STIR or PD-FS). We recorded the longitudinal length (cranio-caudal) and calculated the involved cross sectional area as a percentage of the total muscle cross sectional area in the transversal plane. We measured the extent of low signal on T1 weighted images similarly in the three planes. We recorded the involved muscle(s) and performed grading of the injury using a modification of Peetrons' classification:[63,177] grade 1): increased signal intensity on fluid sensitive sequences without evidence of a macroscopic tear, grade 2): increased signal intensity on fluid sensitive sequences with a partial tear, grade 3): total muscle or tendon rupture. Increased signal intensity was defined as an abnormal intramuscular increased signal compared to the unaffected surrounding muscle tissue. Identically, the low signal intensity was defined as an abnormal intramuscular low signal intensity compared to the surrounding muscle tissue. Good to excellent inter- and intra-observer reliability was found for the used MRI parameters in a previous study.[36]

Re-injury

We recorded acute hamstring injuries that occurred within two months after RTP at the same site as re-injuries.[61]

Statistical analysis

We performed all statistical analysis with SPSS software (version 20.0; SPSS, Chicago, Illinois). We analysed frequencies of the presence of intramuscular signal abnormalities, involved muscles and extent of intramuscular signal abnormalities using descriptive statistics. We tested the normality of the data with the Kolmogorov-Smirnov test: when $p>0.05$ we considered data normally distributed. We analysed differences in the extent of the intramuscular increased signal intensity on fluid sensitive sequences over time using the dependent t-test when normally distributed and the Wilcoxon's signed rank test when there was non-parametric distribution.

Table 11.2 Patient characteristics

Median age (min - max)	27 (18 - 46)
Gender Male / Female	53 / 0
Sports	
- Football	40
- Futsal (Indoor football)	6
- Field hockey	5
- Athletics	1
- Squash	1
Level of Sports	
- Professional	24
- Competitive	19
- Recreational	10

RESULTS

We included fifty-three consecutive patients in the analysis. Patient characteristics are presented in Table 11.2. The median time to RTP was 28 days (range 12 – 76 days). The median time between injury and the first MRI was two days (range 1 – 5 days). The median time between the second MRI and RTP was two days after RTP (range 3 days before – 3 days after RTP). The median time between the last injection and the MRI at RTP was 23 days (range 5 – 71 days).

MRI findings

MRIs of the initial injury showed 27 (51%) grade 1 and 26 (49%) grade 2 injuries. Intramuscular increased signal intensity on fluid-sensitive sequences was present in 89% of the MRIs at RTP (Figures 11.1 and 11.2). The characteristics of intramuscular abnormal increased signal intensity on fluid sensitive MRI sequences of both the initial injury and at RTP are presented in Table 11.3.

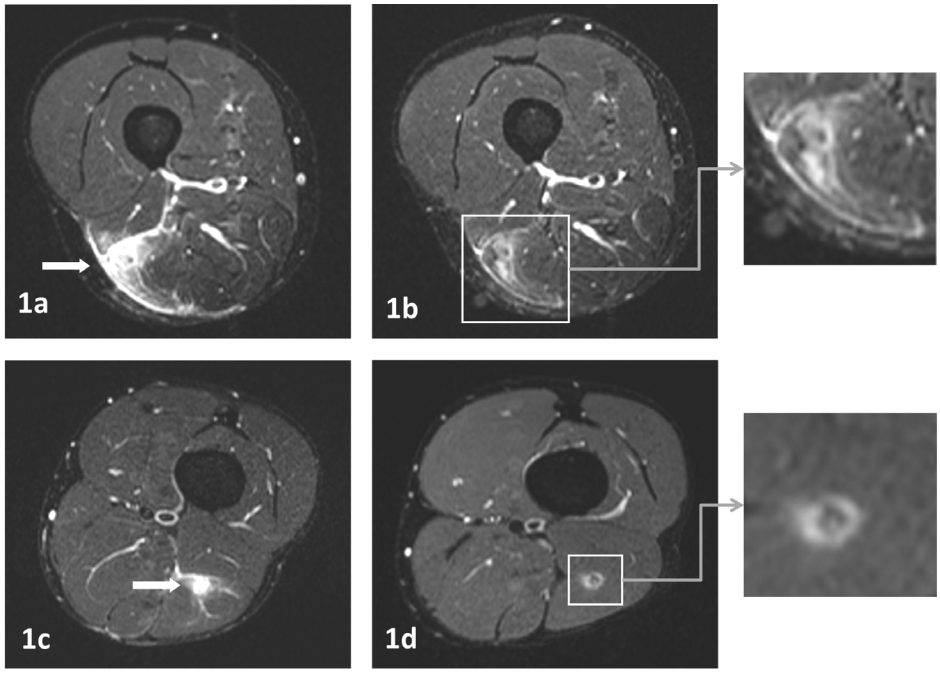

Figure 11.1. (A and C) Short-tau inversion recovery (STIR) images of the initial injuries showing increased signal intensity of the musculus biceps femoris (arrow). (B and D) STIR images at return to play showing increased signal intensity around a centre of low signal at the site of the injury, indicating oedema and fibrous tissues.

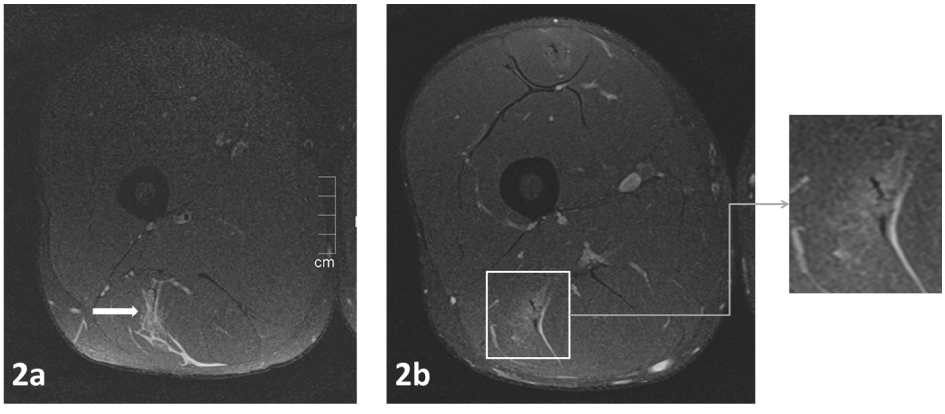

Figure 11.2. (A) Proton density fat saturation (PD-FS) image of the initial injuries showing increased signal intensity of the musculus biceps femoris (arrow). (B) PD-FS image at return to play showing increased signal intensity at the site of the injury.

Table 11.3 Characteristics of intramuscular increased signal intensity on fluid sensitive MRI sequences of initial injury and at RTP

	Initial injury		RTP	
Intramuscular increased signal intensity				
Present	53/53	(100%)	47/53	(89%)
Absent	0/53	(0%)	6/53	(11%)
Involved muscles				
Biceps femoris long head	44/53	(83%)	39/47	(83%)
Biceps femoris short head	0/53	(0%)	0/47	(0%)
Semitendinosus	2/53	(4%)	1/47	(2%)
Semimembranosus	9/53	(17%)	8/47	(17%)
Grade				
Grade 1	27/53	(51%)	37/47	(79%)
Grade 2	26/53	(49%)	10/47	(21%)
Grade 3	0/53	(0%)	0/47	(0%)
Extent of increased signal intensity				
Mean longitudinal length (standard deviation)	132mm	(± 62)	77mm	(± 53)*
Median involved cross sectional muscle area (min - max)	28 %	(1 – 100)	8 %	(0 - 90)*

* Statistical significant difference between initial injury and RTP: p = .000

Intramuscular abnormal low signal intensity was present in 42% of the MRIs at RTP (Figure 11.3). The characteristics of intramuscular abnormal low signal intensity on MRI, measured on T1 weighted images, of both the initial injury and at RTP are presented in Table 11.4. Three subjects (6%) showed no intramuscular signal abnormality on MRI at RTP.

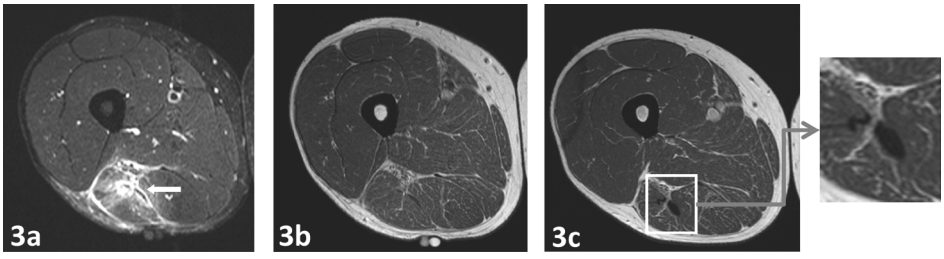

Figure 11.3. (A) Short-tau inversion recovery (STIR) image of the initial injury showing extensive increased signal intensity at the musculotendinous junction of the musculus biceps femoris (arrow). (B) T1-weighted image of the same initial injury showing no abnormality. (C) T1-weighted image at return to play showing an increased area of low-signal intensity at the site of the injury, indicating fibrous tissue formation.

Table 11.4 Characteristics of intramuscular abnormal low signal intensity on MRI (fibrous tissue) of initial injury and at RTP

	Initial injury		**RTP**	
Intramuscular fibrosis				
Present	4/53	(8%)	22/53	(42%)
Absent	49/53	(92%)	31/53	(58%)
Involved muscles				
Biceps femoris long head	3/4	(75%)	20/22	(91%)
Biceps femoris short head	0/4	(0%)	0/22	(0%)
Semitendinosus	0/4	(0%)	3/22	(14%)
Semimembranosus	1/4	(25%)	1/22	(5%)
Extent of fibrosis				
Median longitudinal length (min - max)	78 mm	(72 – 88)	48 mm	(8 – 190)
Median length on axial view (min - max)	9.2 mm	(5.4 – 12.9)	8.5 mm	(2.8 – 22.9)
Median width on axial (min - max)	4.4 mm	(1.3 – 9.0)	4.5 mm	(1.5 – 20.6)

Abbreviations: MRI, magnetic resonance imaging; RTP, return to play

Re-injury

We recorded five (9%) re-injuries within two months after RTP. The re-injuries occurred at two, four, five, seven and 38 days after RTP. The presence and extent of increased signal intensity on fluid sensitive sequences and fibrosis on MRI at RTP of subjects with re-injuries compared to subjects without re-injuries are presented in Table 11.5.

Table 11.5 Intramuscular Increased signal intensity and fibrosis on MRI at RTP of subjects without re-injury compared to subjects with re-injury within 2 months after RTP

	No re-injury (n = 48)		**Re-injury** (n = 5)	
Increased signal intensity present	43/48	(90%)	4/5	(80%)
Extent of increased signal intensity				
Median longitudinal length (min - max)	73 mm	(0 - 220)	65 mm	(0 - 94)
Median involved cross sectional muscle area (min - max)	8 %	(0 - 90)	14 %	(0 - 31)
Intramuscular fibrosis present	18/48	(38%)	4/5	(80%)
Extent of fibrosis				
Median longitudinal length (min - max)	88 mm	(8 - 190)	48 mm	(15 – 130)
Median length on axial view (min - max)	9.4 mm	(3.3 - 20.1)	5.7 mm	(2.8 – 22.9)
Median width on axial (min - max)	4.9 mm	(2.1 - 10.1)	3.1 mm	(1.5 – 20.6)

Abbreviations: MRI, magnetic resonance imaging; RTP, return to play

DISCUSSION

The major finding of this study is that in 89% of clinically recovered grade I and II hamstring injuries we observed intramuscular increased signal intensity on MRI on fluid sensitive sequences at RTP. Low-signal intensity, suggestive of fibrous tissue, was observed in 42% of the clinically recovered grade I and II hamstring injuries on MRI at RTP.

The present study provides a detailed description of the MRI findings at RTP after hamstring injuries and is the largest series currently published on this topic. Two previous published studies found that increased signal intensity is still present on T2 weighted images in athletes cleared for RTP.[201,213] These findings are consistent with the findings of the present study. The present study provides additional information on the presence and extent of both increased signal intensity on fluid sensitive sequences (oedema) and decreased signal intensity (fibrous tissue).

Several published clinical guidelines incorporated follow-up imaging to monitor progression after hamstring injury.[120,152] It is unknown as to what extent intramuscular increased signal on fluid sensitive sequences on MRI, found in 89% of the athletes reflects ongoing muscle damage in recovering muscle. While the extent of the muscle signal intensity alteration on fluid sensitive sequences is decreased at RTP compared to the initial injury, there is an overlap between the extent of the signal intensity alteration found in the initial injury and at RTP. Thus, there are clinically recovered athletes in which the amount of the increased signal intensity on fluid sensitive sequences in the muscle at RTP exceeds that of other athletes at the time of initial injury. This suggests that the extent of the increased signal intensity seen on fluid sensitive sequences does not delineate an injured from a recovered hamstring muscle.

As almost all athletes that are clinically recovered and successfully returned to play showed increased signal intensities on fluid sensitive sequences, some even with extensive signal abnormalities, RTP decisions after hamstring injuries should not depend on MRI features. Schneider-Kolsky et al. reported only moderate correlation between clinical assessment using functional tests and MRI findings and showed that functional testing was more accurate than MRI assessment for predicting time required to RTP in fresh injuries.[203] These studies support that functional performance of the athlete should be leading in rehabilitation and RTP decisions, rather than time dependent related to imaging findings.[152,223] MRI of an acute injury has a role in determining the involved muscle(s) and the location of the injury, but should not be used in RTP decisions.

In the present series five athletes sustained a re-injury, of which four (80%) had increased signal intensity on fluid sensitive sequences observed on MRI at RTP compared to 90% of the subjects that did not sustain a re-injury. The extent of this increased signal intensity reveals a similar pattern in both the re-injured and non-re-injured athletes (table 5). Although there is insufficient statistical power to study the association

between increased signal intensity on fluid sensitive sequences and re-injury risk, the observation that in 90% of the athletes without a re-injury increased signal intensities on fluid sensitive sequences are present on MRI at RTP, suggests that normalisation of this increased signal intensity is not required for a successful RTP.

Increased signal intensity on fluid sensitive sequences on MRI is considered to reflect increased intracellular or extracellular free water (typically "muscle oedema").[147,148] However, there remains limited understanding of the pathophysiological significance of either increased signal intensity on fluid sensitive sequences, or oedema in acute muscle injuries, a point recently highlighted by an experts consensus statement on muscle injuries.[158] Muscle damage is associated with an inflammatory response as well as oedema, both of which can result in increased signal intensity on fluid sensitive sequences.[146] The long term persistence of this increased signal after injury does not seem to fit with the temporal changes of inflammation and oedema.[142] What this increased signal intensity exactly reflects, both at the initial muscle injury and during recovery, is unclear. This should be clarified in future studies. Importantly, our observations suggest that the increased signal intensity seen on fluid sensitive sequences on MRI in clinically recovered hamstring injuries has no relevance for a successful RTP and hence the clinical relevance of increased signal intensity is dubious.

In the present study 42% of the cases had low signal intensity, indicating fibrous tissue, at RTP. Although, as pathological correlation is lacking, the exact nature of this low signal intensity is unknown. In four cases the low signal intensity was present at the initial injury, suggesting a previous injury or other mechanism. Thus, 18 out of 53 (34%) injured athletes developed new low signal intensity at the site of the injury. Clinical studies showed that the low signal intensity of fibrous tissue could persist in the long term on MRI.[52,210] The formation of fibrous tissue alters muscle stiffness and is frequently reported as a risk factor of re-injury,[27,75,210,211] although evidence from clinical studies confirming that fibrosis increases the risk of re-injury is absent. In the present series five subjects sustained a re-injury, of which four (80%) had fibrosis observed on MRI at RTP compared to 38% of the subjects that did not sustained a re-injury. At first sight there seems to be a tendency that the fibrosis at RTP, seen as low signal intensity on MRI, is associated with an increased risk of re-injury. Given its multi-factorial origin, the limited number of re-injuries and insufficient power, it remains however unclear if there is an association between fibrosis on MRI and re-injury risk. Future studies with more participants are needed to examine the prognostic value of fibrosis for re-injuries.

The subjects in the present study were participants of two randomised controlled trials on the effect of platelet-rich plasma. As a part of these double blind placebo controlled studies subjects received either no injection or intramuscular injections with platelet-rich plasma, platelet-poor plasma or normal saline. The effect of these injections on hamstring muscle healing is still unknown. A potential limitation of this

study is that the injections given 5-71 days before the MRI at RTP might influence the findings of the MRI. It could be hypothesised that the needle and/or the injected fluid increase the increased signal intensity on fluid sensitive sequences. However, histological studies in animals show that intramuscular saline injections result in only minimal oedematous changes within the first two days.[220,225] It therefore seems unlikely that the saline injections substantially influence the MRI findings at RTP. Little is known about the effect of platelet-rich plasma injections on muscle oedema. A recent histological study in animals found that healthy muscle tissue injected with platelet-rich plasma showed an inflammatory response with oedema and necrosis followed by fibrosis, similar to the traditional acute healing response in injured muscle.[99] MRI analysis of recovering muscle injuries after PRP injections have been reported previously.[91,241] In a pilot study Wright-Carpenter et al. reported nearly completed regression of the muscle increased signal intensity on fluid sensitive sequences in 18 athletes with muscle injuries treated with PRP injections at 14-16 days after injury.[241] Their treatment regime consisted of a mean of 5.4 injections of 5 ml PRP with two days between the injections. In a case report Hamilton et al. found a resolution of increased signal intensity on fluid sensitive sequences in 17 days after hamstring injury treated with a single 3 ml PRP injection.[91] Although controlled trials comparing MRI analysis after PRP injections with no injections are lacking, the findings in these reports suggest accelerated reduction of the increased signal intensity on fluid sensitive sequences after injection of PRP rather than prolongation. For generalisation to populations without PRP injections the present study might underestimate the amount of increased signal intensity on fluid sensitive sequences found on MRI of clinically recovered hamstring injuries.

Another limitation is that we analysed two different cohorts with some differences in criteria for clearance for RTP in this study. There are however, still no validated criteria to ascertain whether an athlete is recovered from the injury and ready to RTP. This lack of validated criteria is emphasized by the differences of definitions and criteria used in both scientific research and clinical practise.[103,168,193] Our study reflects this common clinical challenge. On the other hand, our data on RTP are comparable with other studies and representative for a prospective cohort of acute hamstring injuries.[52,63,203,216,231] Furthermore, this heterogeneity increases the external validity and generalizability for daily clinical practise where heterogeneous RTP criteria are used.

A second minor limitation of the analysis of two cohorts is that two slightly different MRI protocols were used: STIR and T1-weighted images in the first cohort and PD-FS and PD images in the second cohort. In scientific research and clinical practise however, these sequences are all used in MRI of muscle injuries.[130] This heterogeneity can be considered a minor weakness of present study, although it increases the external validity and generalizability for clinical practice where both protocols are used.

With our cohort we cannot exclude possible gender and age bias. Generalisation of the findings to female athletes and athletes under the 18 years of age should therefore be made with caution.

In summary, we reported the MRI findings of 53 consecutive athletes, after acute non-contact grade I and II hamstring injury, who were cleared for RTP. Eighty-nine percent of the injuries showed intramuscular increased signal intensity on fluid sensitive sequences on MRI at RTP. Normalisation of this increased signal intensity on MRI does not seem required for a successful RTP. Low-signal intensity suggestive of newly developed fibrous tissue at the site of the injury was observed in 34% at RTP. Five re-injuries were recorded. Given this limited number and insufficient power, the possible association of the MRI observations at RTP with increased re-injury risk has yet to be determined.

Acknowledgements

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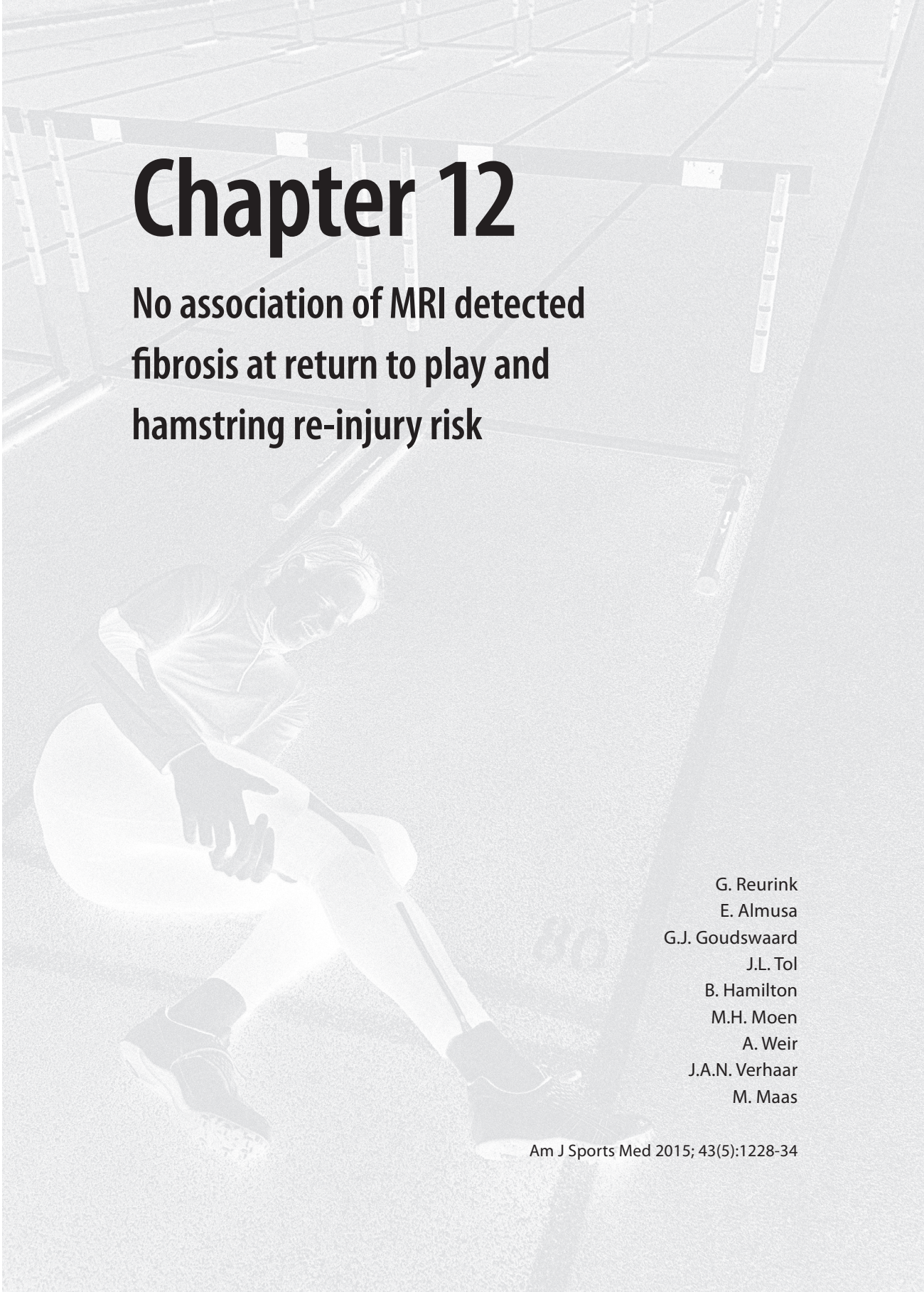
Chapter 12

No association of MRI detected fibrosis at return to play and hamstring re-injury risk



G. Reurink
E. Almusa
G.J. Goudswaard
J.L. Tol
B. Hamilton
M.H. Moen
A. Weir
J.A.N. Verhaar
M. Maas

Am J Sports Med 2015; 43(5):1228-34

ABSTRACT

Background – Connective tissue scar (fibrosis) is a common finding on magnetic resonance imaging after recovery from acute hamstring injuries. Fibrosis has been suggested as a predisposing factor for re-injury, but evidence from clinical studies is lacking.

Hypothesis/Purpose – The aim of this study is to examine the association between the presence of fibrosis on magnetic resonance imaging, at return to play following an acute hamstring injury, and the risk of re-injury. Our hypothesis was that fibrous tissue on MRI was associated with an increased re-injury risk.

Methods – We obtained magnetic resonance images of 108 consecutive athletes with grade 1 or 2 hamstring injuries within five days of injury and within seven days of return to play. We assessed the presence and extent of intramuscular abnormal low signal intensity on MRI on both T1 and T2 weighted images, suggestive of fibrosis. We recorded re-injuries over a one year follow-up. The association between fibrosis and re-injury risk was analyzed with a Cox proportional-hazards model.

Results – Magnetic resonance imaging of the initial injury showed 45 (43%) grade 1 and 63 (57%) grade 2 injuries. Median time to RTP was 30 days (interquartile range 22-42). At return to play, 41 athletes (38%) had fibrosis on magnetic resonance images with a median longitudinal length of 5.8 cm (interquartile range 3.3-12.5) and a median volume of 1.5 cm^3 (interquartile range 1.5-3.9). In athletes with fibrosis, 24% (10 out of 41) sustained a re-injury and in the subjects without fibrosis 24% (16 out of 67) had a re-injury, resulting in a hazard ratio of 0.95 (95% CI, 0.43 to 2.1: p=0.898).

Conclusion – Fibrosis is commonly seen on magnetic resonance imaging at return to play following grade 1 or 2 hamstring injuries, but is not associated with re-injury risk.

INTRODUCTION

Acute hamstring injuries are the most common injuries in sports such as football, track and field and Australian rules football[7,61,169]. They have a high re-injury rate, ranging from 14-63% in the first year after return to play (RTP)[35,172,208,234]. Re-injuries are often more severe than the initial injury and are associated with a longer absence from play[35,61]. A premature RTP[103,168] and scar tissue formation[75,103,152,210,211] are the most frequently suggested predisposing factors for re-injury.

Muscle regeneration after injury follows a fairly constant sequence of degeneration, inflammation and regeneration[75,116]. From two to three days after injury, formation of a connective tissue scar (fibrosis) occurs at the site of the injury. During the following weeks regenerating myofibers begin to penetrate and the fibrous tissue diminishes in size over time[75,116]. While formation of fibrous tissue is an essential component of muscle healing, excessive formation is suggested to impair functional recovery[75,111,116,211]. Persisting fibrosis has been shown to alter muscle contraction mechanics, generating greater tissue strain near the site of prior musculotendinous junction injury of the biceps femoris[211]. While these theoretical arguments suggest that fibrosis may predispose for re-injury, a recent systematic review highlighted that there were no actual clinical studies that have examined the association between fibrosis and hamstring re-injury[234].

Previous studies showed that fibrosis, which has predominately low signal intensity on all sequences on Magnetic Resonance Imaging (MRI), is common in grade 1 and 2 hamstring injuries at RTP[192,213] and can persist in the long-term[201,210]. In a recent observational study it was reported that 42% of hamstring injuries had fibrosis on MRI at RTP[192]. Due to the limited number of re-injuries there was insufficient power to study any association between the presence of fibrous tissue and the risk of re-injury. We therefore conducted the present study with a larger sample size by pooling data from two randomized trials with a prolonged follow-up period.

The aim of this study is to examine the association between MRI determined fibrosis and the risk of re-injury in athletes who have clinically recovered from an acute hamstring injury. Our hypothesis was that fibrous tissue on MRI was associated with an increased re-injury risk.

METHODS

Subjects

The patients in this study were pooled from two double blind randomized controlled trials on the effect of platelet rich plasma in hamstring injuries (Dutch trial register number 2771 and ClinicalTrial.gov number NCT01812564). The first was completed in

November 2013 (Dutch cohort). In this study the intervention group received two ultrasound guided injections of 3 ml platelet-rich plasma (Autologous Conditioned Plasma, Biocore, Arthrex Inc, Karlsfeld, Germany) and the control group received two injections of 3 ml saline at the site of the injury. This study found no difference in time to RTP and re-injury rate between the group that received PRP-injections and the control group that received saline injections[187].

The second randomized controlled trial is an on-going study that started in November 2009 (Qatari cohort). In this study subjects are randomized into three groups: one group received an injection of 3 ml platelet-rich plasma (Biomet Recover™, USA), one group received an injection of 3 ml platelet-poor plasma and one group received no injection. All subjects completed a standardized physiotherapy program, including range of motion exercises, progressive strength exercises, core stability training and agility exercises.

The eligibility criteria for the present study are presented in table 1. In the Dutch cohort the functional criteria-based rehabilitation program was supervised by a sports physiotherapist. Clearance for RTP was given once the athlete successfully completed the physiotherapy program and functional sport specific activities. In the Qatari cohort the guideline criteria to assist RTP decision included: successfully and asymptomatically completing the functional criteria-based physiotherapy program, including a final

Table 12.1 Eligibility criteria

Dutch cohort	**Qatar cohort**
Inclusion criteria	
• Age 18 – 50 years • Clinical diagnosis acute hamstring injury • Presenting and MRI within five days from injury • MRI confirmed grade I or II hamstring lesion • Second MRI available within three days of RTP	• Age 18-50 years • Acute onset of posterior thigh pain • Presenting and MRI within five days from injury • MRI confirmed grade I or II hamstring lesion • Second MRI available within three days of RTP • Gender: Male • Able to perform five sessions physiotherapy a week at the clinic • Available for follow-up
Exclusion criteria	
• Contraindication to MRI • Chronic hamstring injury • Chronic low back pain • Cause of injury is an extrinsic trauma • Not capable of performing rehabilitation • No intention to return to full sports activity • Unwilling to receive the intramuscular injections • Injection therapy received for this injury before	• Contraindication to MRI • Re-injury or chronic hamstring injury • Concurrent other injury inhibiting rehabilitation • Unwilling to comply with follow-up • Needle phobia • Overlying skin infection • Diabetes, immune-compromised state • Medication increasing bleeding risk (e.g. Plavix) • Medical contraindication to injection

Abbreviations: MRI, magnetic resonance imaging; RTP: return to play

supervised sport specific (outdoor) training phase[227]. After RTP clearance, athletes were advised to complete five days of team training before participating in partial match play.

At inclusion, informed consent was obtained from all patients. Approval was obtained from the Regional Ethical Committee of South West Holland and the Ethical Committee of Aspetar, Qatar Orthopaedics and Sports Medicine Hospital.

Magnetic Resonance Imaging

In each subject, MRI of the injury was performed twice: once within five days from the time of initial injury and again within one week of RTP. The MRI of the initial injury was performed prior to any injection procedure.

MRI protocol

Two comparable MRI protocols were used. The protocol in the Dutch cohort was a modified version of the protocol described by Askling et al.[15] To locate the area of the injury the entire hamstring of the injured limb was visualised by obtaining coronal and sagittal short tau inversion recovery (STIR) images from the ischial origin of the hamstring muscles to insertion on the fibula and the tibia (repetition time/echo time (TR/TE) of 3500/31 ms, field of view (FOV) of 300 mm and a 256x320 matrix). Subsequently, transversal STIR (repetition time/echo time (TR/TE) of 3500/31 ms, field of view (FOV) of 300 mm and a 205x256 matrix), T1-weighted (TR/TE of 500/12 ms, FOV of 300 mm and a 355x448 matrix) and T2-weighted (TR/TE of 4080/128 ms, FOV of 300 mm and a 355x448 matrix) images were obtained from the injured area. The slice thickness for all sequences was 5mm. MR images were obtained with a 1.5-T magnet system (Magnetom Essenza, Siemens) with the use of a body matrix coil.

In the Qatari cohort MR images were obtained of the hamstring muscles with a 1.5-T magnet system (Magnetom Espree, Siemens) with the use of a body matrix coil. First coronal and transversal proton density (PD) weighted images (TR/TE of 3000/30 ms, FOV of 220-240 mm, slice thickness of 5 mm and a 333x512 matrix) were obtained. Subsequently coronal and transversal proton density fat saturation (PD-FS) images (TR/TE of 3000+/30 ms, FOV of 220-320 mm, slice thickness of 3,5 mm, a 326x512 matrix for the coronal images and a 333x512 matrix for the transversal images) were obtained.

MRI assessment

Each MRI was assessed by one of two radiologists, each with more than nine years of experience in musculoskeletal radiology (EA and MM). The radiologists were blinded as to whether the MRI was of the initial injury or at RTP. For assessment of the MRIs we used standardised scoring forms based on the literature.[52,63,177,210,216] Increased T2 signal intensity (oedema) for the affected hamstring muscle was measured in the cranio-caudal, transverse and anterior-posterior dimensions on fluid sensitive sequences (STIR

or PD-FS). We recorded the longitudinal length (cranio-caudal) and calculated the involved cross sectional area as a percentage of the total muscle cross sectional area in the transversal plane. We measured the extent of low signal on T1 weighted images similarly in the three planes. We recorded the involved muscle(s) and performed grading of the injury using a modification of Peetrons' classification:[63,177] grade 0) clinical diagnosis of an acute muscle injury without MRI abnormality, grade 1): increased signal intensity on fluid sensitive sequences without evidence of a macroscopic tear, grade 2): increased signal intensity on fluid sensitive sequences with a partial tear, grade 3): total muscle or tendon rupture. Increased signal intensity was defined as an abnormal intramuscular increased signal compared to the unaffected surrounding muscle tissue. The low signal intensity was defined as abnormal intramuscular low signal intensity compared to the surrounding muscle tissue.

Fibrosis

We defined fibrosis as an area of abnormal intramuscular low signal intensity compared to the surrounding muscle tissue on all sequences (T1 weighted, T2 weighted and STIR or PD-FS)[100,130]. We used the T1 weighted images to measure the extent of the low signal intensity. A low signal intensity that presented as a rim around a collection of fluid (high signal on fluid sensitive sequences) was not considered as fibrosis, as this is the typical appearance of a hematoma with a dark rim of hemosiderin deposition[100].

Re-injury

Subjects were followed-up for re-injuries until one year after onset of the initial injury. In the Dutch cohort, players were advised to immediately contact the coordinating researcher in the event of a suspicion of re-injury and re-injury occurrence was monitored at 4, 8, 16, 26 and 52 weeks with phone calls to the subjects. Acute onset of posterior thigh pain that occurred at the same side as the initial injury and caused absence from play were recorded as re-injuries.[61] In the Qatari cohort re-injury occurrence was monitored on a monthly basis with phone calls to the subjects and in the event of a clinical suspicion of re-injury the player was advised to immediately consult the study center. Acute hamstring injuries in the same leg were classified as re-injuries.

Statistical analysis

We performed all statistical analysis with SPSS software (version 20.0; SPSS, Chicago, Illinois). We used descriptive statistics to present the patient and MRI characteristics. If the data was parametric then it is presented as a mean with a standard deviation (SD) and if it was non-parametric then a median and inter quartile range (IQR) are used.

We analyzed the association between the MRI findings at RTP and re-injuries with a Cox proportional-hazards regression model. In this model the time (days) from return

to play to the event (re-injury) or the end of the follow-up is the main variable. Subjects who sustained a severe injury (causing absence from training and matches >28 days[61,83]) during follow-up that was not considered a hamstring re-injury were censored at the time of this injury. Subjects lost to follow-up were censored at the time of their last available follow-up. Subjects completing the one year follow-up were censored at the time of the last follow-up measure. Time-to-re-injury curves were calculated with the Kaplan-Meier method.

We first analyzed the association between presence of fibrous tissue on MRI at RTP and re-injuries in an univariate model. Additionally we performed a multivariate analysis in which we adjust for ipsilateral hamstring injuries in the preceding 12 months and the cohort of the subject (Dutch or Qatari). We decided a priori to adjust for these variables as a history of hamstring injury is previously reported as a predictor for re-injury[235,238] and patients from two different cohorts may potentially lead to bias. We considered a p-value <0.05 statistical significant.

RESULTS

Between November 2009 and July 2014 we included 108 consecutive patients in the analysis. Patient characteristics and MRI findings of the initial injury obtained within 5 days after injury are presented in Table 12.2. The median time to RTP was 30 days (IQR, 22-42). The median time between the second MRI and RTP was 2 days (IQR, 0-4) after RTP. The median time between the initial injury and MRI at RTP was 32 days (IQR, 23-46).

There were no patients lost to follow-up. During follow-up after RTP four patients sustained an injury that was not considered a re-injury but causing absence from training and matches >28 days and were censored in the survival analysis at the time of this injury. Of these four censored patients, there was one contralateral hamstring injury, one knee sprain, one ankle fracture and one hip labral injury.

Findings of fibrosis at MRI at RTP

Intramuscular abnormal low signal intensity, suggestive of fibrosis, was present in 38% of the follow-up MRIs obtained at RTP. Typical examples of fibrosis seen on MR images are showed in Figures 12.1 and 12.2. The characteristics of the low signal intensity findings on MRI are presented in Table 12.3.

Association of fibrosis with re-injury

There were 26 re-injuries during the follow-up, 19 out of 63 (30%) in the Dutch cohort and 7 out of 45 (16%) in the Qatari cohort. Of these 26 re-injuries, 25 (96%) of the initial injuries were located in the biceps femoris and 1 (4%) in the semimembranosus. Six-

teen out of 67 (24%) subjects without fibrosis on MRI and 10 out of 41 (24%) subjects with fibrosis on MRI sustained a re-injury. The cumulative incidences of the re-injuries of subjects with and without fibrosis are presented in Figure 12.3. The univariate Cox regression showed no significant association of MRI detected fibrosis with re-injury, as the hazard ratio was 0.95 (95% CI, 0.43 to 2.1: p=0.898). In the multivariate analysis, the hazard ratio adjusted for ipsilateral injuries in the preceding 12 months and the cohort of the subjects was 1.3 (95% CI, 0.55 to 2.8: p=0.591).

Table 12.2 Patient and injury characteristics (n=108)

	Total study cohort (Dutch + Qatari)	**Dutch cohort** (n=63)	**Qatari cohort** (n=45)
Age, years	28 (±7)	29 (±7)	26 (±6)
Male gender, no.	105 (97%)	60 (95%)	45 (100%)
Sports, no.			
- Football	76 (70%)	45 (71%)	31 (69%)
- Field hockey	12 (11%)	10 (16%)	2 (4%)
- Futsal (Indoor football)	9 (8%)	1 (2%)	8 (18%)
- Athletics	5 (5%)	4 (5%)	1 (2%)
- Other	6 (5%)	3 (5%)	3 (7%)
Level of Sports, no.			
- Professional	44 (41%)	0 (0%)	44 (98%)
- Competitive	48 (44%)	48 (76%)	0 (0%)
- Recreational	16 (15%)	15 (24%)	1 (2%)
Ipsilateral hamstring injury in previous 12 month	22 (20%)	18 (29%)	4 (9%)
MRI characteristics of initial injury			
- Primary injured muscle, no.			
Biceps femoris long head	88 (82%)	56 (89%)	32 (71%)
Biceps femoris short head	0 (0%)	0 (0%)	0 (0%)
Semimembranosus	16 (15%)	5 (8%)	11 (24%)
Semitendinosus	4 (4%)	2 (3%)	2 (4%)
- Grade I / grade II, no.	45 (43%)/63(57%)	18(29%)/45(71%)	45(43%)/63(57%)
- Cross sectional area T2-hyperintesity, % of total muscle	28 (IQR, 10-49)	37 (IQR, 15-53)	18 (IQR, 8-39)
- Longitudinal length T2-hyperintensity, cm	12.9 (IQR, 8.3-17.6)	11.0 (IQR, 6.6-15.4)	15.0 (IQR, 6.6-22.3)
- Intramuscular fibrosis, no.			
Absent	96 (89%)	53 (84%)	43 (96%)
Present	12 (11%)	10 (16%)	2 (4%)

Abbreviations: no., number; IQR, interquartile range

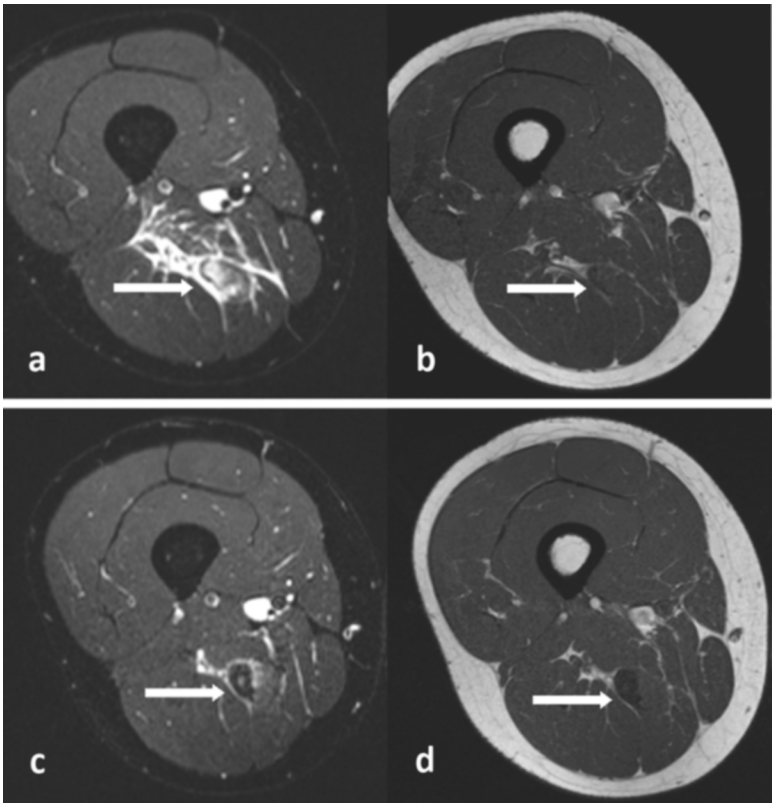


Figure 12.1. a and b) Images of the initial injury. The short- tau inversion recovery (STIR) image (a) shows increased signal intenisty at the musculotendinous juntion of the semimembranosus muscle (arrow). c and d) Images at return to play 50 days after the initial injury. Both STIR (c) and T1-weighted (d)imgage showing an extensive area of low signal intensity, indicating fibrous tissue formation (arrow). The fluid sensitive STIR image (c) shows a halo of increased signal intensity around the area of low signal.

DISCUSSION

We found no association between fibrosis at RTP and re-injury risk, following acute grade 1 and 2 hamstring injury. This is the first clinical study examining the association between MRI detected fibrosis and re-injury risk in acute muscle injury. The finding that fibrosis on MRI at RTP is not associated with re-injury risk is clinically relevant, as it is a common finding at RTP (38% in this study), and fibrosis has historically been considered an important predisposing factor for re-injury[75,103,111,116,210,211] .

Previously, Silder et al. showed that post-injury fibrosis alters muscle contraction mechanics and may therefore theoretically predispose to injury[211]. Using a dynamic MR imaging technique they measured muscle tissue velocities in previously injured subjects with MRI confirmed fibrosis of the proximal musculo-tendinous junction of the biceps

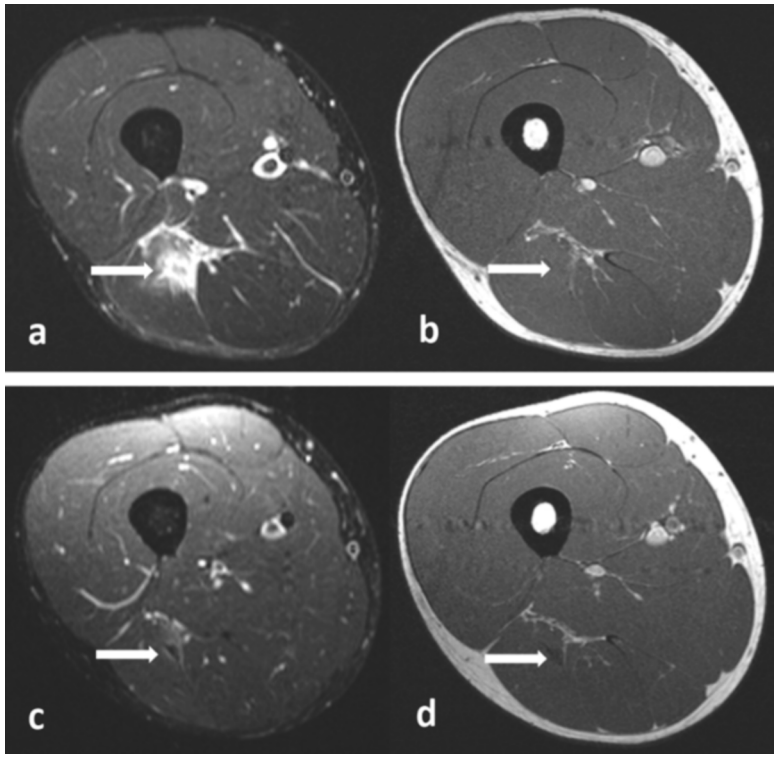


Figure 12.2. a and b) Images of the initial injury. The short- tau inversion recovery (STIR) image (a) shows increased signal intenisty at the musculotendinous juntion of the biceps femoris muscle (arrow). c and d) Images at return to play 34 days after the initial injury. Both STIR (c) and T1-weighted (d)imgages show a small area of low signal intensity, indicating fibrous tissue formation (arrow). The fluid sensitive STIR image (c) shows a halo of increased signal intensity around the area of low signal.

femoris and compared these with healthy controls. The previously injured subjects had significantly greater tissue strain near the proximal musculo-tendinous junction than the controls[211]. In another study, Silder et al. found no correlation between the amount of fibrosis observed on MRI and either strength measures, running kinematics or muscle activation patterns[214]. While to what extent these functional outcome measures are associated with hamstring injury risk remains unknown, these findings together with the results of the current study challenge the role of fibrosis in predisposing to re-injury.

In our study the MRI at RTP was performed at a median of 32 days (IQR, 23-46) after the injury. During the healing process after injury the size of the fibrous tissue changed over time; initially occurring 2-3 days after injury and diminishing in size from around the third week. Scar has been reported to persist up to 12 months after injury[116]. With our MRI observations at RTP it remains unknown to what extent the fibrosis persists in the long-term. We cannot exclude that these observations are just a reflection of normal healing and subsequently disappear. Therefore, whether persisting residual fibrous

Table 12.3 Characteristics of intramuscular abnormal low signal intensity (fibrous tissue) on MRI within 7 days of RTP

	All subjects (n=108)	**Subjects without re-injury** (n=82, 24%)	**Subject with re-injury** (n=26, 24%)
Intramuscular fibrosis, no.			
Absent	67 (62%)	51 (62%)	16 (62%)
Present	41 (38%)	31 (38%)	10 (38%)
Muscle with fibrosis, no.			
Biceps femoris long head	36 (88%)	26 (84%)	10 (100%)
Semimembranosus	5 (12%)	5 (16%)	0 (0%)
Semitendinosus	0 (0%)	0 (0%)	0 (0%)
Extent of fibrosis*			
Longitudinal length, cm	5.8 (IQR, 3.3-12.5)	6.5 (IQR, 4.0-14.5)	3.3 (IQR, 2.5-7.8)
Length on axial view, cm	1.0 (IQR, 0.6-1.3)	1.0 (IQR, 0.7-1.4)	0.7 (IQR, 0.5-1.5)
Width on axial view, cm	0.5 (IQR, 0.3-0.7)	0.5 (IQR, 0.3-0.7)	0.4 (IQR, 0.2-0.6)
Volume, cm^3	1.5 (IQR, 0.5-3.9)	2.0 (IQR, 0.7-3.9)	0.4 (IQR, 0.2-4.2)

Abbreviations: MRI, magnetic resonance imaging; no., number; IQR, interquartile range

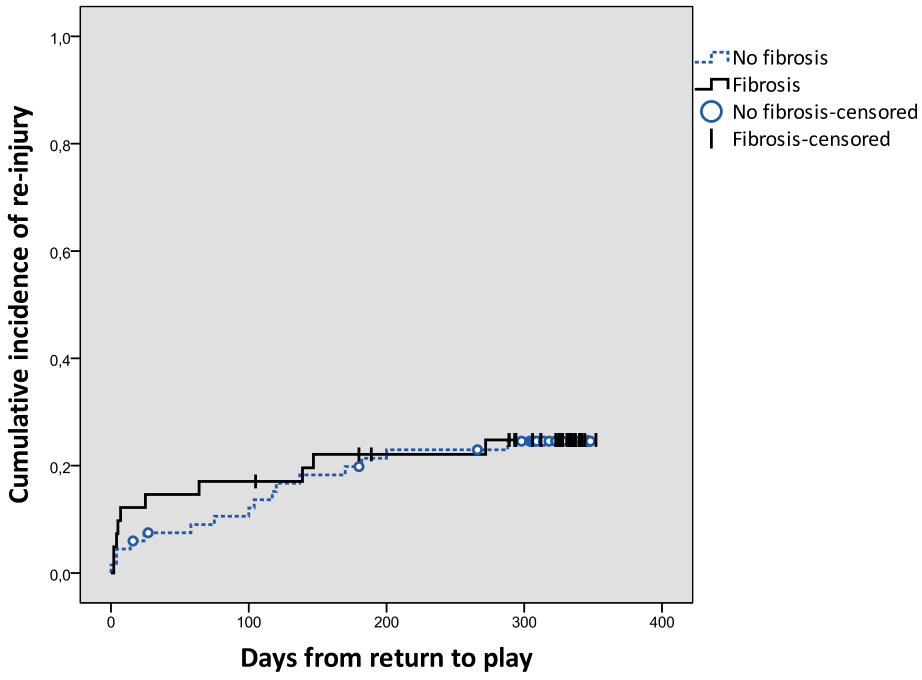


Figure 12.3. Inverse Kaplan-Meier curves showing the cumulative incidence of re-injury for subjects with MRI detected fibrosis (solid line) and subjects without MRI detected fibrosis (dashed line).

tissue predispose to re-injuries remains unknown and should be established in future studies. We recommend studying the time-course of fibrosis in a prospective cohort study with repeated MRI follow-up up to at least one year after injury.

We defined a re-injury as 'an acute onset of posterior thigh pain that occurred at the same side as the initial injury and caused absence from play'. However, the definition of a hamstring re- injury is debatable: should a re-injury involve the same leg, the same muscle and/or the same site within the muscle-tendon complex as the index injury? Can you consider an injury at a different location within the same hamstring muscle group as the index injury as just an 'additional' injury? We argue that the hamstring muscle group acts as one functional anatomic unit and that a re-injury at a different location within the same muscle cannot be considered to be independent of the index injury. We therefore classify each acute hamstring injury that occurs in the same leg as the index injury as a re-injury. This is in accordance with the recommendation on injury definitions in studies of football injuries from the Injury Consensus Group under the auspices of the FIFA (Federation Internationale de Football Association) Medical Assessment and Research Centre[73] and is applied in the current literature on hamstring injuries[61,63,178,187,192,213,235]. Additionally, this definition reflects what is experienced by the athlete and the medical staff: an injury to the same hamstring that keeps the player out of play.

As we did not perform MRI of the re-injury it remains unknown to what extent the re-injuries occur at the same site within the hamstring muscle group as the index injury. This could be assessed in future research.

Strength and limitations

The methodological strengths of our study include the prospective study design, the minimization of bias by blinding of the radiologists, the relatively long term follow-up of one year and the use of multivariate analysis to correct for potential confounding of previous injury and confounding of the use of two different cohorts.

Our study also has some limitations. Firstly, the subjects were participants of two randomized controlled trials on the effect of platelet-rich plasma injections in grade 1 and 2 injuries. The effect of these injections on muscle healing is still unknown. Some suggest a potential fibrotic effect of TGF-β1, one of the platelet derived growth factors[27,75].

Secondly, we analyzed two cohorts with some differences in MRI protocols and in criteria for clearance for RTP. This can be considered a limitation of the study, although it actually increases the external validity and generalizability for clinical practice where heterogeneous RTP criteria and MRI protocols are used. Adjusting for the cohort of the subjects in the analysis did not significantly change the outcome (hazard ratio).

Thirdly, although intramuscular low signal intensity on MRI is generally considered to reflect fibrous tissue[124,130,210,211], the exact nature of this low signal intensity is unknown, as correlation with histopathology is lacking.

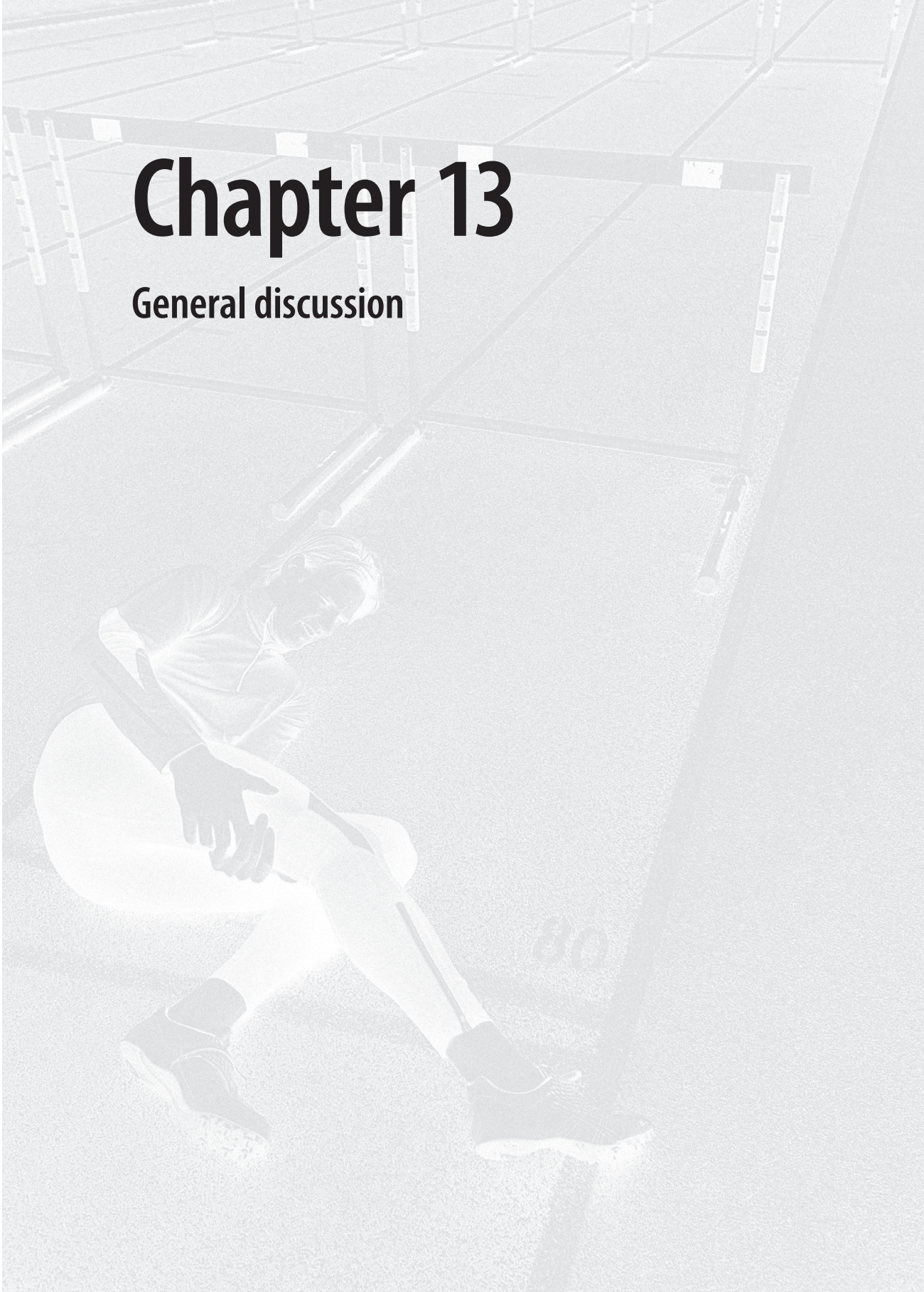
Fourthly, there is currently no data available on the reliability of assessing low signal intensities (fibrosis) on MRI. Measures of increased signal intensity (edema) on MRI have excellent inter-observer and intra-observer reliability[93], but the extent to which this can be generalized to the assessment of low signal intensities remains unknown.

Finally, although the number of subjects and re-injuries is relatively large compared to previously published series on hamstring injuries[20,193,213,231,238], with 26 re-injuries only a moderate to strong association between fibrosis and re-injury could be detected[24]. To detect a weaker association, a larger sample size is required. To show a small to moderate association 200 re-injuries would be needed[24]. Considering the re-injury rate in current study of 24%, this would require over 800 subjects. However, large sample sizes can lead to statistical significant, but clinical irrelevant weak associations.

In conclusion, fibrosis on MRI at RTP following grade 1 or 2 hamstring injuries is not associated with re-injury risk.

Chapter 13

General discussion



Hamstring injuries are among the most prevalent sports injuries, but we are still faced with a lack of scientific knowledge on this topic. Despite the growing number of publications over the past three decades, our current knowledge on aetiology, prognosis, and therapy is still based on less than 2000 published hamstring injuries. The advances in knowledge made over the last 30 years do not seem to have improved outcome, and treatment has changed little over time[2,25,58–60,64,219]. With our work on the prognosis, treatment, and return to play decision making in this thesis we aimed to enhance scientific knowledge on the management of acute hamstring injuries and improve patient outcome.

In this discussion we reflect on the main findings of this thesis, as well on the limitations of the studies and provide advice for future research and clinical practise.

Outcome measures in hamstring research

Return to play

Return to play (RTP) is generally accepted as the most clinically relevant outcome in athletes with acute muscle injuries and therefore used as the primary outcome measure in almost all clinical trials on hamstring injuries. Despite it is being widely used, there are some difficulties with RTP as an outcome measure that need consideration.

Firstly, definitions for RTP differ between studies; return to competition[51,52,203,216,231], return to full team training[77], full training participation and availability for match selection[20,63], performing at a pre-injury level[15,17], completion of rehabilitation[141,213] and fulfilment of pre-defined RTP criteria[3,208] . Heterogenious definitions make comparison between studies difficult.

Secondly, there are still no validated objective criteria to guide progression through rehabilitation protocols and assess readiness for RTP. Consequently, there is currently no consensus and a variety of both protocols and criteria are used. For a valid interpretation of study results we advocate that clear and well-defined criteria for progression through rehabilitation and RTP are used and also reported.

Thirdly, decision-making for progression through rehabilitation protocols and clearance for RTP are substantially affected by subjective judgements of the athletes and medical staff involved. This subjectivity emphasizes that a double blind design is obligatory to prevent bias of results when using time to RTP as an outcome measure.

"A double blind design is obligatory to prevent bias when using time to RTP as an outcome measure"

Re-injuries

Alongside the time to RTP, we feel it is essential to monitor for re-injuries after RTP whenever evaluating a treatment. An intervention may seem to be successful when athletes can return to play earlier. However, if the risk of re-injury increases, the success of the intervention is questionable.

A generally used practical definition for re-injuries in football research is provided by the UEFA injury studies[73]: "An injury of the same type and at the same site as an index injury and which occurs after a player's return to full participation from the index injury". The re-injuries are subsequently classified according to the time of occurrence: within two months of a player's return to full participation is referred to as an "early recurrence", 2–12 months after a player's return to full participation as a "late recurrence", and more than 12 months after a player's return to full participation as a "delayed recurrence".

When we apply this definition for hamstring injuries there is currently no consensus on what should be considered the same site as the index injury: should a re-injury involve the same leg, the same muscle and/or the same site within the muscle-tendon complex as the index injury? As the hamstring muscle group acts as one functional anatomic unit, we suggest classifying each acute hamstring injury that occurs in the same leg as the index injury as a re-injury.

"We suggest classifying each acute hamstring injury that occurs in the same leg as the index injury as a re-injury"

A complete assessment of re-injuries in a research setting can be challenging, especially in the non-elite sporting population. In our studies players were advised to contact the coordinating researcher immediately if the players suspected a re-injury. Re-injury occurrence was also monitored at set time intervals using phone calls. Ideally all re-injuries should be clinically evaluated in the same way as the initial injury. However, in practice not all the re-injured players were available for additional clinical evaluation and some did not contact the coordinating researcher shortly after re-injury. Although not supported by actual data, we feel that the diagnosis of a (re)injury seemed to be made quite adequately using a history taking on the phone, as subjects are unfortunately already familiar with hamstring injuries. Assessing the severity was more complicated and probably not reliable.

Advice for future research: The time to RTP and re-injury rates are the most relevant clinical outcome measures in the management of hamstring injuries. Well-defined crite-

ria for progression during rehabilitation and RTP, and a double blind design are obligatory to prevent bias. We suggest classifying each acute hamstring injury that occurs in the same leg as the index injury as a re-injury. A complete assessment of a re-injury is preferred, but monitoring by phone might be a practical and feasible alternative.

Return to play prognosis

The prognostic value of clinical examination has not often been reported in the literature. Previous research has mainly focused on the prognostic value of magnetic resonance imaging (MRI). In a systematic review of the literature we found that there is currently no strong evidence for any MRI finding for the prognosis for the time to RTP. There was considerable risk of bias in most of the studies on this topic (**chapter 4**). The major methodological flaw is the lack of blinding of the subjects and managing clinicians to the MRI findings being studied.

No study analysed both clinical and MRI findings, so it was unknown how MRI findings provide prognostic information that would be complementary to predictors already obtained with clinical evaluation. This limits the generalizability to clinical practise in which the diagnostic work-up always consists of history, physical examination and possibly additional imaging. In **chapter 5** we examined the predictive value of both clinical and MRI parameters for the time to RTP in a double blind study design with a multivariate analysis. The clinical parameters; self-predicted time to RTP and passive straight leg raise deficit were significantly associated with the time to RTP, while none of the MRI parameters were. As this study was performed in MRI positive hamstring injuries without a complete rupture we do not know to what extent this applies to MRI negative injuries and complete ruptures. Thus, time to RTP estimations can be based on these clinical parameters. Clinicians should be aware that MRI in these cases provides no additional information.

Can we provide a prognosis in clinical practice?

After being injured one of the first questions of the athlete, coaching staff and press is: when can he/she return to play? Although our knowledge has improved at a group level, the current available research does not satisfactorily answer this question for the individual athlete. We will illustrate this with two examples.

The prognostic parameters found in our study in **chapter 5** (self-estimated time to RTP and deficit in passive straight leg raise) explained only 20% of the total variance of the time to RTP. The mean time to RTP was 44±18 days, indicating that approximately 95% of the athletes returned to play between 8 and 80 days (mean ± double the standard deviation). With the self-predicted and passive straight leg raise deficit we could only narrow the range down slightly. For an athlete, with a self-estimated time to RTP of 42

days and a passive straight leg raise deficit of 10°, the 95% confidence interval for the estimated time to RTP by the model is 16–83 days, instead of 8–80 days.

In the largest series on the prognostic value of MRI, Ekstrand et al. found that in professional football players MRI grading was significantly correlated with injury time[87]. This study found, for each injury grade (in days ± standard deviation): grade I, 18±19; grade II, 24±13; grade III, 60±57. By applying these results to an individual professional football player with a grade II hamstring injury, we can estimate that there is a 95% chance that he returns to play within 0 to 50 days (mean 24 days +/- two times the standard deviation of 13 days).

The athlete, coaching staff and press will correctly argue that these estimations of the injury time are far from being satisfactory. Currently we are still far away from the answer to the athlete's most important and simple question.

Advice for future research: A challenge for future research is to provide tools to give a more accurate prediction of the time to RTP. The first step is to identify the relevant prognostic factors. We advocate focusing on clinical parameters, as these are underrepresented in the current literature. In clinical practice recovery of injury is usually monitored over time with repeated assessments. Future research should identify whether such repeated assessments can provide relevant prognostic information.

Hamstring injuries are complex and multifactorial, and only if we combine multiple prognostic factors in multivariate models we will be able to provide accurate predictions for the individual athlete. Designing and validating an ultimate prognostic model requires the standardized documentation of a large number of hamstring injuries.

Future studies should consider the common methodological flaws in current prognostic studies, such as insufficient numbers of participants to show clinically relevant associations, the lack of blinding of subjects and outcome assessors, insufficient handling of potential confounders, lack of information on the reliability of the measures used, and the use of simple univariate statistical analysis.

Advice for clinical practice: Clinicians should be aware that clinical parameters are most valuable for predicting the time to RTP. MRI does not seem to provide additional information on time to RTP prognosis in grade I and II injuries. The passive straight leg raise test and self-predicted time to RTP can be used to guide the prognosis, but even then the individual prognosis remains inaccurate. Providing such a prognosis should be done with caution, as it may lead to unrealistic expectations.

"Clinicians should be aware that clinical parameters are most valuable for predicting the time to RTP"

Treatment: Intramuscular injections

Despite the growing number of recent publications, the current treatment of hamstring injuries is still mainly based on expert practice. If we restrict ourselves to randomised controlled trials, there are less than 550 hamstring injuries examined in the entire field[3,19,20,48,141,187,196,208,213]. Although there is general consensus among experts that a progressive rehabilitation program is the cornerstone of the treatment of acute muscle injuries, intramuscular injection of drugs to assist recovery and help players return to play more quickly are being used increasingly[88,131,132,171].

There is growing interest in sports medicine and athletic communities for "regenerative medicine" using endogenous growth factors directly into the injury site to facilitate healing after injury[156,209]. The most popular is the injection of platelet rich plasma (PRP)[156,209]. Platelets release various growth factors upon activation that are assumed to provide regenerative benefits. Basic science studies have shown that myoblasts can be proliferated by growth factors like platelet derived growth factor (PDGF), insulin-like growth factor (IGF-1), basic fibroblast growth factor (bFGF-2) and nerve growth factor (NGF)[94,153,242]. In deliberately injured animal muscles these growth factors increase regeneration[94,153,242].

Despite the promising results from basic research, and apparent widespread clinical use, there was a lack of high-level evidence from randomized clinical trials assessing the efficacy of PRP in treating muscle injuries[156,209]. We therefore performed a double-blind randomized controlled trial to assess the efficacy of PRP in hamstring injuries and found no benefit on the time to RTP, re-injury rate or any of the other secondary outcome measures (**Chapter 9**).

In a another recently published randomized controlled trial of Hamid et al. a significant reduction in time to RTP in the PRP group was found compared to the control group[3]. However, this study has some serious methodological flaws. The subjects were not blinded to the treatment they received. The lack of blinding is an important source of bias in the study. The study also failed to assess for possible re-injury after the completion of treatment meaning that we do not know if the significantly faster RTP resulted in more reccurence

The PRP preparation procedure and composition of platelets and leucocytes differ between our study and the study of Hamid et al. There is currently no known 'optimal' PRP content, nor is there a generally accepted protocol for PRP use with regard to volume, number and timing of injections. It is unknown whether these factors will affect clinical outcome, as it has never been examined and compared. This requires further investigation in high quality clinical trials.

A criticism of our randomised trial might be the limited generalizability to an elite athlete setting (in which PRP is most likely to be applied), as it was performed in a non-elite athletic population, we used a limited physiotherapy program (two sessions a week),

incomplete compliance, and the time to RTP is longer than previously described in elite athletes[87,88]. Although in our study the best estimate is that there is no effect at all, the 95% confidence interval still allows for a 8% chance that there could be a potential clinically relevant difference between the groups. This difference could be in favour of, but also against PRP. Based on the 95% confidence interval for the difference between median return to play, the probability that the actual difference exceeds 20% (8 days) in favor of the intervention group is 7%. However, the same can be said for the probability that the actual return to play exceeds 8 days in favor of the placebo group.

Finally we would emphasize that all interventions have a risk of side effects that should be considered. In **chapter 8** we evaluated the possible myotoxic effects of commonly used intramuscular injection preparations in a systematic review and we found evidence for myotoxicity of local anaesthetics, non-steroidal anti-inflammatory drugs and corticosteroids. For PRP there was conflicting evidence. Histological changes of inflammatory cell infiltration, oedema and necrosis followed by fibrosis are reported following intramuscular PRP injection. With the paucity of high-level evidence that intramuscular injected preparations are efficacious in acute muscle injury, clinicians should consider the "Primum non nocere" ("first do no harm") dogma of Hippocrates before using treatments.

Advice for future research: High quality clinical trials are required to assess efficacy of medical treatment modalities in acute muscle injuries. A double blind study design is obligatory to prevent bias when evaluating time to RTP as an outcome measure. Whether different PRP preparations affect clinical outcome requires further investigation, but our study did not show any effect.

Advice for clinical practice: An active progressive rehabilitation program is the cornerstone of the treatment of acute muscle injuries. Additional medical treatment modalities are not recommended.

"Additional medical treatment modalities are not recommended."

Return to play decision making and re-injuries

It is a major challenge to decide whether an athlete can safely return to play. The high re-injury rate reflects this challenge[234]. The re-injuries have been reported predominantly to occur in the first weeks after RTP[35,234]. Although there is no consensus, in clinical practice an athlete is typically regarded as being ready once full range of motion, full strength and functional sport specific activities (e.g. sprinting, jumping, cutting, shooting) can be performed asymptomatically[103]. Despite this conventional approach, assessing functional, physiological and psychological readiness remains challenging.

The ultimate test whether an athlete is ready to RTP is to mimic the use and loading of the injured muscle as required during (match) play itself. This means that failing this test results in the athlete suffering a re-injury. Less rigorous tests will reduce the risk of re-injury during testing, but will always leave uncertainty on the athlete's actual readiness for RTP. Basic science shows that injury healing is incomplete at the time when clinical tests indicate recovery, and that the majority of athletes can return to play successfully prior to complete tissue healing[167,168,201]. After successfully returned to play the majority of athletes (89%)still have signal abnormalities on MRI (**chapters 11**). A conservative approach by waiting for complete tissue healing would probably decrease the re-injury rate, but would extend the RTP.

Orchard et al. stated that RTP management strategies should not aim at re-injury risk elimination, but at re-injury risk evaluation to support RTP decisions[167,168]. The practical decision-based RTP model of Creighton et al.[53] uses 3 steps. In step 1, medical factors, such as age, injury history, psychological state, outcome of clinical tests and imaging are evaluated. In step 2, sport-specific risk modifiers, such as type, level of sport, and player position is evaluated. Finally in step 3, decision modifiers, such as timing in season, importance of a match, external pressure, and financial conflicts of interest are considered.

In **chapter 10** we examined medical factors assessed with clinical examination and MRI, and sport-specific risk modifiers and their association with re-injury risk. Several medical factors assessed with clinical examination shortly after RTP were associated with the re-injury risk (the number of previous hamstring injuries, active knee extension deficit, isometric knee flexion force deficit at 15° and the presence of localized discomfort on palpation). With these medical factors athletes at higher risk for re-injuries can be identified. As both remaining oedema and fibrosis formation on MRI at RTP were not associated with re-injury risk (**chapter 11 & 12**), RTP decisions should not be guided by MRI findings.

"RTP decisions should not be guided by MRI findings."

Advice for future research: Future research should aim at further validation of the medical factors and sport risk modifiers to provide models to accurately predict re-injury risk to guide RTP decision making after hamstring injury. For example, based on multiple factors, such as patient characteristics (e.g. age, sex, previous injuries), injury characteristics (e.g. mechanism, injured muscle), clinical tests (e.g. palpation, flexibility, strength, functional field testing), the ultimate model estimates that a player has a 6% risk of being re-injured when participating in the upcoming match and 2% in the second game. The decision to RTP in the upcoming match will differ based on whether it is a world cup final or a pre-season friendly game. Although such a model does not provide definitive

RTP criteria, it provides an evidence-based risk estimation that fits into a decision-based RTP approach.

Advice for clinical practice: After RTP athletes at risk for re-injuries can be identified with the following clinical findings: the number of previous hamstring injuries, active knee extension deficit, isometric knee flexion force deficit at 15° and presence of localized discomfort on palpation. In the absence of validated RTP criteria, although not based on available evidence, the following practical criteria can guide RTP decisions:

1. Absence of localized discomfort on palpation and isometric strength testing.
2. A pain free complete range of motion compared to the uninjured leg using the active knee extension test.
3. Pain free repeated maximal sprinting efforts (applicable for return to sports that include sprinting).
4. Successful progression through a progressive rehabilitation program, including sport-specific exercises (e.g. shooting, cutting, jumping).
5. Symptom free (group)training before resumption of match play.
6. MRI is not recommended in RTP decision-making.

FUTURE PROSPECTS:

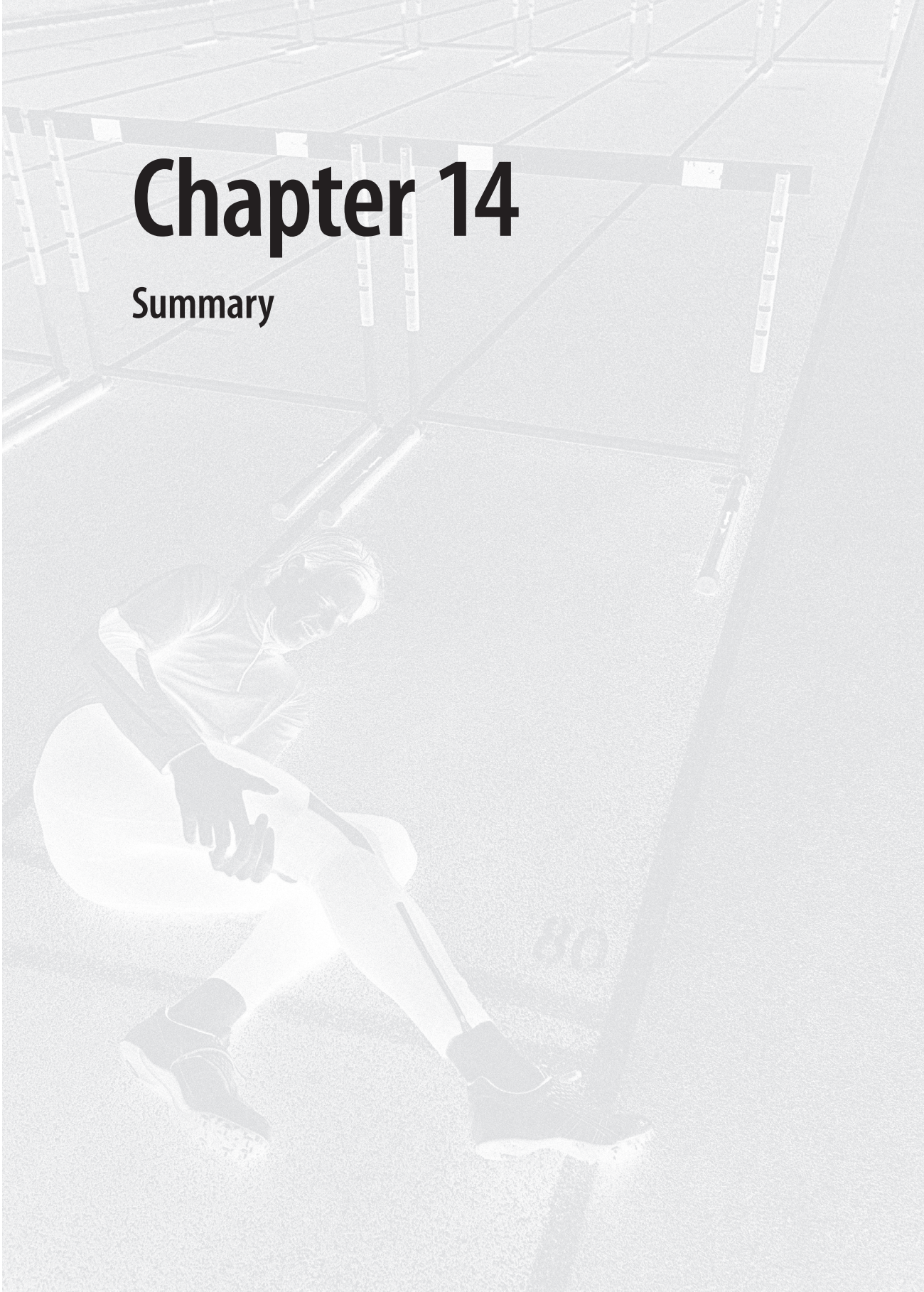
With the experience gained in working on the studies in this thesis we recommend that future hamstring research should focus on the following topics:

1. Aetiology and injury mechanisms. We are still using simple terms (sprinting and stretching types of injury) and our understanding of the aetiology and injury mechanisms is still limited. The increased availability of high quality, high speed camera recordings in elite sports might offer an opportunity to study large numbers of injury situations and correlate these with clinical and imaging features.
2. Time to RTP is the most clinically relevant outcome in athletes with hamstring muscle injuries. Validated criteria to assess readiness to RTP are needed, both for research purposes as for clinical practice. A multivariate assessment tool including functional, physiological and psychological readiness should be designed and validated.
3. Prognostic factors for the time to RTP. Research has shown that a single assessment of the initial injury cannot provide an accurate estimation of the time to RTP. Future research should identify whether repeated assessments during recovery can provide more accurate prognostic information. Hamstring injuries are complex and multifactorial. Only by combining multiple prognostic factors for time to RTP in multivariate models we can hope to provide accurate predictions for the individual athlete. Designing and validating a prognostic model requires a large number of standardized documented hamstring injuries.

4. The efficacy of different rehabilitation protocols studied in high quality randomised controlled trials to optimise rehabilitation after injury.
5. Risk factors for hamstring injury and re-injury to be able to identify those players at risk and to quantify the risk.
6. (Secondary) preventative measures, especially aimed at those players at risk for injury and re-injury. For example should eccentric training be continued after RTP to prevent re-injuries?
7. New imaging techniques, such as dynamic MRI and diffuse tensor imaging (DTI). DTI is an advanced MRI-technique that images detailed muscle fiber structure and has potential for quantifying muscle damage and monitoring tissue healing.

Chapter 14

Summary



Acute hamstring injuries are one of the most common sports injuries. Surprisingly we have remarkable little evidence from clinical studies on their management. This thesis examined the diagnostics, treatment and return to play (RTP) decision-making in acute hamstring injuries.

In **chapter 1** an introduction to the work of this thesis is given, consisting of a brief overview of the current knowledge of the functional anatomy, injury mechanism, diagnosis, prognosis, treatment and return to play decision-making in acute hamstring injuries.

In **chapter 2** we examined the intertester reliability of measuring hamstring flexibility with the active (AKET) and passive knee extension test (PKET). These tests were already proven to be reliable in healthy subjects. In injured hamstrings, flexibility testing is often limited by pain, which raises concerns about its reliability.

We included 50 consecutive athletes with acute hamstring injuries confirmed with magnetic resonance imaging (MRI). For each subject two testers performed the AKET and the PKET within five days of injury. We determined intraclass correlation coefficients, standard error of measurements and minimal detectable differences. Good intertester reliability was found for the AKET and PKET in injured hamstrings. We concluded that both tests can be used to reliably assess flexibility in injured hamstrings.

In **chapter 3** we assessed the interrater reliability and the prognostic value of handheld dynamometry (HHD) strength measurement in acute hamstring injuries. Hamstring strength is impaired after an acute injury, but it was unknown whether a strength deficit has prognostic value for the time needed to return to play (RTP). HHD is a commonly used method of measuring muscle strength, but its reliability had not been determined in athletes with acute hamstring injuries.

We measured knee flexion strength with HHD in 60 athletes at two visits: at baseline within five days of hamstring injury and at follow-up five to seven days after the baseline measurement. We assessed isometric hamstrings strength in 15°and 90° of knee flexion. We recorded the time needed to RTP. Reliability analysis testing was performed by two testers independently at the follow-up visit.

The intraclass correlations of the strength measurements in injured hamstring were between 0.75 and 0.83. There was a statistical significant but weak correlation for the baseline strength deficit at 15° of knee flexion and time to RTP (Spearman's r =0.27, p=0.048). None of the other strength variables were significantly correlated with time to RTP.

We concluded that hamstring strength can be reliably measured with HHD in athletes with acute hamstring injuries. The prognostic value of strength measurements is limited, as there is only a weak association between the time to RTP and hamstrings strength

deficit 15° of knee flexion after acute injury. Seven percent of the variance in time to RTP is explained by this strength deficit.

As sports physicians and radiologists are increasingly requested to perform MRI of acute hamstring injuries and to provide a prognosis of the time to return to play (RTP) based on their findings, we systematically reviewed the literature on the prognostic value of MRI findings for the time to RTP in **chapter 4**. We searched multiple electronic databases for studies evaluating MRI as a prognostic tool for determining time to RTP in athletes with acute hamstring injuries. We assessed the risk of bias using criteria for quality appraisal of prognosis studies and used a best evidence synthesis to determine the level of evidence.

Of the 12 studies included, 11 had a high risk of bias. There is moderate evidence that injuries without hyperintensity on fluid sensitive images are associated with a shorter time to RTP and injuries involving the proximal free tendon with a longer time to RTP. Limited evidence was found for an association of central tendon disruption, injury not affecting the musculotendinous junction and a total rupture with a longer time to RTP. The other MRI findings studied showed either no association or there was conflicting evidence.

We concluded that there is currently no strong evidence for any MRI finding to provide a prognosis on the time to RTP after an acute hamstring injury, due to considerable risks of bias in the studies on this topic.

In **chapter 5** we examined the prognostic value of 28 clinical and MRI parameters for the time to RTP in a prognostic follow-up study in 80 athletes with MRI positive hamstring injuries undergoing a standardised rehabilitation programme. The association between the possible prognostic parameters and time to RTP was assessed in a multivariate linear regression model.

The clinical parameters self-predicted time to RTP and passive straight leg raise deficit were independently associated with the time to RTP. MRI parameters in grade 1 and 2 hamstring injuries, as described in the literature, were not associated with the time to RTP. We concluded that prognosis of the time to RTP in these injuries can best be estimated using these clinical parameters. Performing an MRI to estimate the time to RTP may not be advised in these injuries.

It is common practice to examine injured muscles using palpation to assess mechanical properties like stiffness and tone. The effect of acute muscle injury on these muscle properties had never been examined. In **chapter 6** we examined the time course of changes in muscle mechanical properties after acute hamstrings injury using a muscle myometer.

In a prospective cohort study we included 25 athletes with acute injuries to the biceps femoris muscle. They were examined by a single observer who measured the muscle mechanical properties: stiffness, tension and elasticity using a myometer. Athletes were examined at inclusion, after one week, at RTP and after 26 weeks.

We found that at initial examination the muscle stiffness and tension were significantly reduced in the injured leg and this normalized at return to play and remained so at 26 weeks. The muscle elasticity was not found to be different at any time. Future studies may investigate if these altered muscle mechanical properties can be used to predict re-injury or guide return to play decision-making.

In **chapter 7** we systematically reviewed the literature on the effectiveness of therapeutic interventions for acute hamstring injuries. We searched several electronic databases on prospective studies comparing the effect of an intervention with another intervention or a control group without intervention. We assessed the risk of bias with the Physiotherapy Evidence Database score and used a best evidence synthesis to determine the level of evidence.

We included six studies and found that there was limited evidence for a positive effect of stretching, agility and trunk stability exercises, intramuscular Actovegin injections and slump stretching in the management of acute hamstring injuries. There was limited evidence that there is no effect for non-steroidal anti-inflammatory drugs or manipulation of the sacroiliac joint. We concluded that there was lack of high quality studies on the treatment of acute hamstring injuries and that further research is needed using an appropriate control group, randomisation and blinding.

Injection therapies are widely used for muscle injuries, but there is only a limited evidence for their efficacy. Clinicians should be aware of the potential harmful effects of these injected preparations. We systematically reviewed the literature on the myotoxic effects of commonly used intramuscular injection preparations for acute muscle injuries in **chapter 8**.

Studies reporting histological evaluation or creatine kinase activity after intramuscular injection with local anesthetics, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), platelet-rich plasma (PRP), Traumeel and Actovegin, or combination preparations were eligible for inclusion. We assessed the risk of bias and used a best evidence synthesis was to determine the level of evidence.

We included 49 studies. There is strong to moderate evidence that intramuscular injected local anesthetics and NSAIDs are myotoxic, and conflicting evidence on the myotoxicity of PRP. There is limited evidence that single corticosteroids injections are not myotoxic, but have a synergistic myotoxic effect together with local anesthetics. There is no information to assess whether Actovegin and Traumeel are myotoxic.

We concluded that local anesthetics and NSAIDs injections are not recommended for the treatment of muscle injuries in athletes, as they are myotoxic. The possible myotoxic effects of corticosteroids, PRP, Traumeel and Actovegin should be assessed in future research.

In **chapter 9** we present the results of a multicenter, randomized, double-blind, placebo-controlled trial on the efficacy of PRP injections in acute hamstring injuries. In this trial we randomly assigned 80 competitive and recreational athletes with acute hamstring muscle injuries to PRP (intervention group) or isotonic saline placebo injections (control group) with both groups performed a standardized criteria-based rehabilitation program. The primary outcome measure was the time needed to RTP. Treatment differences were analysed with a Cox proportional-hazards model. Re-injury rate was assessed as a secondary outcome measure.

The median time to return to play was 42 days (interquartile range, 30 to 58) in the PRP-group and 42 days (interquartile range, 37 to 56) in the placebo-group (hazard ratio, 0.96; 95% CI, 0.61 to 1.51: p=0.66). The re-injury rate was 16% in the PRP-group and 14% in the placebo-group (Odds ratio 1.17; 95% CI, 0.33 to 4.18: p=0.81). There were no serious adverse events. In conclusion, we found no benefit of intramuscular PRP injections compared to placebo injections in athletes with acute hamstring injuries.

Acute hamstring re-injuries are common but hard to predict. We therefore examined the association between clinical and imaging findings and the occurrence of hamstring re-injuries in **chapter 10**. In a prospective follow-up study we obtained baseline data (clinical and MRI findings) of athletes who sustained an acute hamstring injury within five days of initial injury and collected data of standardised clinical tests within seven days of RTP. We recorded the re-injuries within 12 months follow-up. We analysed the association between the possible predictive variables and re-injuries with a multivariate Cox proportional-hazards model.

We included 64 patients in the final analysis. There were 17 re-injuries (27%). We found a higher number of previous hamstring injuries (adjusted odds ratio 1.33; 95% CI 1.11 to 1.61), more degrees of active knee extension deficit after RTP (adjusted odds ratio 1.13; 95% CI 1.03 to 1.25), isometric knee flexion strength deficit at 15° after RTP (adjusted odds ratio 1.04; 95% CI 1.01 to 1.07) and the presence of localised discomfort on hamstring palpation after RTP (adjusted odds ratio 3.95; 95% CI 1.38 to 11.37) to be significant independent predictors of re-injury. None of the MRI findings were associated with re-injury.

Little is known about the value of MRI in monitoring recovery and RTP decisions. In **chapter 11** we describe MRI findings of hamstring muscles in athletes, who have clinically recovered from an acute hamstring injury, and were cleared for RTP.

We obtained MRI of 53 athletes within five days of injury and within three days of RTP. On MRI at RTP 47 athletes (89%) had intramuscular increased signal intensity on fluid sensitive sequences with a mean longitudinal length of 77 mm (± 53) and a median cross sectional area of 8% (range 0-90%) of the total muscle area. In 22 athletes (42%) there was abnormal intramuscular low signal intensity, suggestive of fibrosis. Five re-injuries (9%) occurred within two months after RTP.

We concluded that normalisation of this increased signal intensity is not required for successful RTP. Low-signal intensity suggestive of fibrosis is a common finding on MRI at RTP, but its clinical relevance and possible association with increased re-injury risk needed to be examined in a larger study.

To assess the possible association between fibrosis on MRI at RTP and re-injuries, we conducted a supplementary study with a larger sample size, by pooling data from two randomised trials, and using a prolonged follow-up period in **chapter 12**.

We obtained MRI of 108 athletes with hamstring injuries within five days of injury and within seven days of RTP. We assessed the presence and extent of intramuscular abnormal low signal intensity on MRI, suggestive for fibrosis. We recorded re-injuries within one-year follow-up. The association between the presence of fibrosis and the re-injury risk was analysed with a Cox proportional-hazards model.

At RTP, 41 athletes (38%) showed presence of fibrosis with a median longitudinal length of 5.8 cm (interquartile range 3.3-12.5) and a median volume of 1.5 cm^3 (interquartile range 1.5-3.9). In the group of athletes with fibrosis 24% (10 out of 41) sustained a re-injury and in the subjects without fibrosis 24% (16 out of 67) had a re-injury, resulting in a hazard ratio of 0.95 (95% CI, 0.43 to 2.1: p=0.898). This means that fibrosis on MRI following hamstring injuries is common at RTP, but is not associated with a higher re-injury risk.

In **chapter 13** we reflect on the main findings of this thesis, as well on the limitations of the studies and provide advice for future research and clinical practise.

The prognosis on the time to RTP remains inaccurate and should only be done with caution, as it may lead to unrealistic expectations. An active progressive rehabilitation program is the cornerstone of the treatment of acute hamstring injuries. Additional medical treatment modalities are not recommended. In the absence of validated RTP criteria, several practical criteria that can guide RTP decisions are provided. MRI is not recommended in RTP decision-making.

Finally recommendations for directions in future research are made.

Nederlandse samenvatting

(ABSTRACT IN DUTCH)

Acute hamstringblessures behoren tot de meest voorkomende sportblessures. Opvallende genoeg is er weinig bewijs uit klinische onderzoeken voor de huidige toegepaste diagnostiek en behandeling van deze blessures. Dit proefschrift bestudeert de diagnostiek, behandeling en beslissingen voor sporthervatting bij acute hamstring blessures.

In **hoofdstuk 1** wordt een introductie op het werk van dit proefschrift gegeven die bestaat uit een bondig overzicht van de huidige kennis over de functionele anatomie, blessuremechanismen, diagnostiek, prognose, behandeling en sporthervatting beslissingen bij acute hamstringblessures.

In **hoofdstuk 2** onderzochten we de interbeoordelaars betrouwbaarheid bij het meten van hamstring flexibiliteit met de actieve- (AKET) en passieve knie extensie test (PKET). Deze testen zijn eerder betrouwbaar gebleken bij gezonde proefpersonen. Bij acute hamstringblessures wordt het testen van flexibiliteit vaak beperkt door pijn, waardoor de betrouwbaarheid van de testen in twijfel wordt getrokken.

Wij onderzochten 50 sporters met een op magnetic resonance imaging (MRI) bevestigde acute hamstringblessure. Bij elke proefpersoon voerden twee onderzoekers de AKET en de PKET binnen vijf dagen na de blessure uit. Wij bepaalden de intraclass correlatie coëfficiënten, standardmeetfouten en minimaal detecteerbare verschillen.

De interbeoordelaars betrouwbaarheid voor de AKET en de PKET was goed. We concludeerden dat beide testen betrouwbaar de flexibiliteit kunnen meten in geblesseerde hamstrings.

In **hoofdstuk 3** bepaalden we de interbeoordelaars betrouwbaarheid en de prognostische waarde van krachtmetingen met handheld dynamometrie (HHD) bij acute hamstringblessures. Hamstringkracht is afgenomen na een blessure, maar het was onbekend of het krachtsverlies prognostische waarde heeft voor de tijd die nodig is voor sporthervatting. HHD is een veelgebruikte methode om spierkracht te meten, maar de betrouwbaarheid bij sporters met een hamstringblessure is nooit eerder bepaald.

We hebben de knieflexie kracht gemeten met HHD in 60 sporters bij twee poliklinische consulten: bij baseline binnen vijf dagen na een hamstringblessure en bij follow-up vijf tot zeven dagen later. We maten isometrische hamstringkracht in 15°en 90° knieflexie en noteerden de tijd tot sporthervatting. Testen voor de betrouwbaarheidsanalyse werden uitgevoerd door twee onderzoekers onafhankelijk van elkaar bij de follow-up visite.

De intraclass correlatie coëfficiënten voor de krachtmetingen in de geblesseerde hamstrings lagen tussen de 0,75 en 0,83. Er was een statistisch significante, maar zwakke correlatie voor de baseline krachtmeting in 15° knieflexie en de tijd tot sporthervatting (Spearman's r =0,27, p=0,048). Geen van de andere krachtmetingen was significant geassocieerd met de tijd tot sporthervatting.

We concludeerden dat hamstringkracht betrouwbaar gemeten kan worden met HHD in sporters met een acute hamstringblessure. De prognostische waarde van de krachtmetingen is beperkt, aangezien er slechts een zwakke associatie is met de tijd tot sporthervatting en hamstringkrachtsverlies gemeten in 15° knieflexie na een blessure. Zeven procent van de variantie in de tijd tot sporthervatting wordt verklaard door dit krachtsverlies.

Omdat sportartsen en radiologen in toenemende mate worden gevraagd om MRI van acute hamstringblessures te vervaardigen en op basis van hun bevindingen een uitspraak te doen over de verwachtte tijd tot sporthervatting, hebben we in **hoofdstuk 4** een systematische literatuuronderzoek uitgevoerd naar de prognostische waarde van MRI voor de tijd tot sporthervatting.

We doorzochten meerdere elektronische databases naar onderzoeken die MRI als een prognostisch instrument voor het bepalen van de tijd tot sporthervatting bij sporters met een acute hamstringblessure onderzochten. We gebruikten kwaliteitscriteria voor prognostische studies om het risico op bias te beoordelen en bepaalden het niveau van bewijsvoering met een 'best evidence' synthese.

Van de 12 geïncludeerde studies hadden er 11 een hoog risico op bias. Er is redelijk bewijs dat blessures zonder hyperintensiteit op vochtgevoelige opnames geassocieerd zijn met een kortere tijd tot sporthervatting en blessures met betrokkenheid van de proximale vrije pees met een langere tijd tot sporthervatting. Beperkt bewijs werd gevonden voor een associatie van een ruptuur van de centrale pees, blessures die niet die spierpeesovergang betroffen en totale spierrupturen met een langere tijd tot sporthervatting. De andere bestudeerde MRI bevindingen hadden geen associatie met de tijd tot sporthervatting of er was conflicterend bewijs.

We concludeerden dat er geen of slechts zwak bewijs is dat MRI variabelen prognostische waarde hebben voor de tijd tot sporthervatting na een hamstringblessure, als gevolg van substantiële risico's op bias in de studies op dit onderwerp.

In **hoofdstuk 5** onderzochten we de prognostische waarde van 28 klinische en MRI parameters voor de tijd tot sporthervatting in 80 sporters met MRI positieve hamstringblessures die een gestandaardiseerd revalidatie programma volgden. De associatie tussen de mogelijke prognostische parameters en de tijd tot sporthervatting werd geanalyseerd in een multivariaat lineair regressiemodel.

De klinische parameters zelf-voorspelde tijd tot sporthervatting en het flexibiliteitsverlies gemeten met de passieve gestrekt heffen test waren onafhankelijk geassocieerd met de tijd tot sporthervatting. MRI parameters in graad 1 en 2 hamstringblessures, zoals beschreven in de literatuur, waren niet geassocieerd met de tijd tot sporthervatting. We concludeerden dat de prognose van de tijd tot sporthervatting het best ingeschat kan worden met deze klinische parameters. Een MRI vervaardigen voor het bepalen van de tijd tot sporthervatting wordt niet geadviseerd in deze blessures.

In de praktijk is het gebruikelijk bij onderzoek van spierblessures middels palpatie de mechanische eigenschappen als stijfheid en tonus te beoordelen. Het effect van acute spierblessures op deze mechanische eigenschappen is nooit eerder onderzocht. In **hoofdstuk 6** onderzochten we de veranderingen van mechanische eigenschappen van de hamstrings over de tijd na een acute blessure met een myometer.

In een prospectieve cohort studie includeerden we 25 sporters met een acute blessure van de biceps femoris spier. Eén beoordelaar bepaalde de volgende mechanische eigenschappen van de spier met de myometer: stijfheid, spanning en elasticiteit. De metingen werden bij inclusie, na één week, bij sporthervatting en na 26 weken uitgevoerd.

We vonden dat bij de eerste meting de spierstijfheid en –spanning significant afgenomen was in het geblesseerde been en dat dit normaliseerde bij sporthervatting en dit zo bleef na 26 weken. Bij geen van de metingen was er een verschil in spierelasticiteit. Toekomstige studies kunnen onderzoeker of deze veranderende mechanische spiereigenschappen gebruikt kunnen worden voor sporthervatting beslissingen of om het risico op recidiefblessures in te schatten.

In **hoofdstuk 7** hebben we systematisch de literatuur doorzocht naar de effectiviteit van therapeutische interventies bij acute hamstringblessures. We doorzochten meerdere elektronische databases naar prospectieve onderzoeken die het effect van een behandeling met een andere behandeling of controlegroep zonder behandeling vergeleken. We beoordeelden het risico op bias met de Physiotherapy Evidence Database score en bepaalden het niveau van bewijsvoering met een 'best evidence' synthese.

We includeerden zes onderzoeken en vonden dat er slechts beperkt bewijs was voor een positief effect van rekken, behendigheids- en rompstabiliteitsoefeningen, intramusculaire Actovegin injecties en 'slump stretching' bij de behandeling van acute hamstringblessures. Er is beperkt bewijs dat er geen effect is van niet-steroïde anti-inflammatoire medicatie en manipulatie van het sacro-iliacale gewricht. We concludeerden dat er een gebrek aan hoge kwaliteit studies bestaat en dat toekomstig onderzoek nodig is dat gebruik maakt van een geschikte controlegroep, randomisatie en blindering.

Injectie therapieën worden wijdverbreid toegepast bij spierblessures, maar er is slechts beperkt bewijs voor de hun effectiviteit. Artsen moeten zich bewust zijn van de poten-

tiele schadelijke effecten van de injectiepreparaten. In **hoofdstuk 8** voerden we een systematisch literatuuronderzoek uit naar de myotoxische effecten van veelgebruikte injectiepreparaten voor de behandeling van acute spierblessures.

Onderzoeken die een histologische evaluatie doen of meting van creatine kinase activiteit na het intramusculair injecteren van lokale anesthetica, corticosteroïden, niet-steroide anti-inflammatoire drugs (NSAIDs), plaatjes-rijk plasma (PRP), Traumeel en Actovegin, of combinatie preparaten, werden geïncludeerd. We beoordeelden het risico of bias en bepaalden het niveau van bewijsvoering met een 'best evidence' synthese.

We includeerden 49 onderzoeken. Er is sterk tot redelijk bewijs dat intramusculaire injecties met lokale anesthetica en NSAIDs myotoxisch zijn, en conflicterend bewijs voor myotoxiciteit van PRP. Er is beperkt bewijs dat injecties met alleen een corticosteroïd niet myotoxisch is, maar wel een synergetisch myotoxisch effect heeft in combinatie met een lokaal anestheticum. Er is geen informatie beschikbaar om de mogelijke myotoxiciteit van Traumeel en Actovegin te beoordelen.

We concludeerden dat lokale anesthetica- en NSAIDs injecties niet kunnen worden aanbevolen bij de behandeling van spierblessures, omdat deze myotoxisch zijn. De mogelijke myotoxische effecten van corticosteroïden, Traumeel en Actovegin dienen in toekomstig onderzoek verder beoordeeld te worden.

In **hoofdstuk 9** presenteren we de resultaten van een multicenter, gerandomiseerd, dubbel-blind, placebo-gecontroleerd onderzoek naar de werkzaamheid van PRP injecties bij acute hamstringblessures. In dit onderzoek randomiseerden we 80 sporters voor PRP- (interventiegroep) of fysiologisch zout placebo injecties (controlegroep). Beide groepen voerden een gestandaardiseerd revalidatieprogramma uit. De primaire uitkomstmaat was de tijd tot sporthervatting. Verschillen tussen de behandelgroepen analyseerden we met een Cox proportionele-hazards model. Het aantal recidiefblessures werd beoordeeld als een secundaire uitkomstmaat.

De mediane tijd tot sporthervatting was 42 dagen (interkwartielafstand, 30 tot 58) in de PRP-groep en 42 dagen (interkwartielafstand, 37 tot 56) in de placebogroep (hazard ratio 0,96; 95% betrouwbaarheidsinterval 0,61 tot 1,51: p=0,66). Het aantal recidiefblessures was 16% in de PRP-griep en 14% in de placebogroep (Odds ratio 1,17; 95% betrouwbaarheidsinterval 0,33 tot 4,18: p=0,81). Er waren geen serieuze ongewenste gebeurtenissen met schade. Concluderend vonden we geen voordeel van intramusculaire PRP injecties in vergelijking met placebo injecties bij sporters met acute hamstringblessures.

Recidief hamstringblessures komen veel voor, maar zijn moeilijk te voorspellen. Daarom onderzochten we de associatie tussen bevindingen bij klinisch- en beeldvormend onderzoek en het ontstaan van recidief hamstringblessures in **hoofdstuk 10**. In een

prospectieve follow-up studie verrichtten we op baseline klinisch- en beeldvormend onderzoek van sporters met een acute hamstringblessure binnen 5 dagen na de blessure en verzamelden data van gestandaardiseerde klinische testen binnen 7 dagen na sporthervatting. We registreerden de recidiefblessures in een 12 maanden follow-up periode. We analyseerden de associatie tussen de mogelijk voorspellende variabelen en recidiefblessures met een multivariaat Cox proportionele-hazards model.

We includeerden 64 patiënten in de uiteindelijke analyse. Er waren 17 (27%) recidiefblessures. We vonden dat een hoger aantal eerdere hamstringblessures (geadjusteerde odds ratio 1,33; 95% BI 1,11 tot 1,61), meer actieve knie extensie deficit na sporthervatting (geadjusteerde odds ratio 1,13; 95% BI 1,03 tot 1,25), isometrische knieflexie krachtsdeficit in 15° na sporthervatting (geadjusteerde odds ratio 1,04; 95% BI 1,01 tot 1.,07) en de aanwezigheid van gelokaliseerde gevoeligheid bij palpatie van de hamstrings na sporthervatting (geadjusteerde odds ratio 3,95; 95% BI 1,38 tot 11,37) significante onafhankelijke voorspellers zijn van recidiefblessures. Geen van de MRI bevindingen was geassocieerd met recidiefblessures.

Er is weinig bekend over de waarde van MRI voor het monitoren van herstel en sporthervatting beslissingen bij acute hamstringblessures. In **hoofdstuk 11** beschrijven we MRI bevindingen bij sporters die klinisch hersteld waren van een acute hamstringblessure en vrijgegeven voor sporthervatting.

We vervaardigden MRI bij 53 sporters binnen vijf dagen na de blessure en binnen drie dagen van sporthervatting. Op MRI bij sporthervatting hadden 47 sporters (89%) intramusculaire verhoogde signaal intensiteit op vochtgevoelige opnames met een gemiddelde longitudinale lengte van 77 mm (± 53) en een mediane cross-sectioneel oppervlakte van 8% (range 0-90%) van het totale spieroppervlak. Bij 22 sporters (42%) was er een afwijkend intramusculair laag signaal intensiteit, suggestief voor fibrose. Er waren vijf recidiefblessures binnen twee maanden na sporthervatting.

We concludeerden dat normalisatie van de verhoogde signaal intensiteit niet vereist is voor een succesvolle sporthervatting. Laag signaal intensiteit suggestief voor fibrose is een gangbare bevinding bij sporthervatting, maar de klinische relevantie hiervan en de mogelijke associatie met een verhoogd recidiefblessure risico moet nader onderzocht worden in een grotere studie.

Om de mogelijke associatie tussen fibrose op MRI bij sporthervatting en recidiefblessures te bepalen voerden we een aanvullende studie uit in **hoofdstuk 12** met een grotere steekproefomvang, voegden de we data van twee gerandomiseerde trials samen en gebruikten we een langere follow-up periode.

We vervaardigden een MRI bij 108 sporters binnen vijf dagen na een hamstringblessure en binnen zeven dagen van sporthervatting. We beoordeelden de aanwezigheid

en de afmeting van intramusculair afwijkend laag signaal intensiteit op MRI, suggestief voor fibrose. We noteerden de recidiefblessures in één jaar follow-up. De associatie tussen de aanwezigheid van fibrose en het recidiefblessurerisico analyseerden we met een Cox proportionele-hazards model.

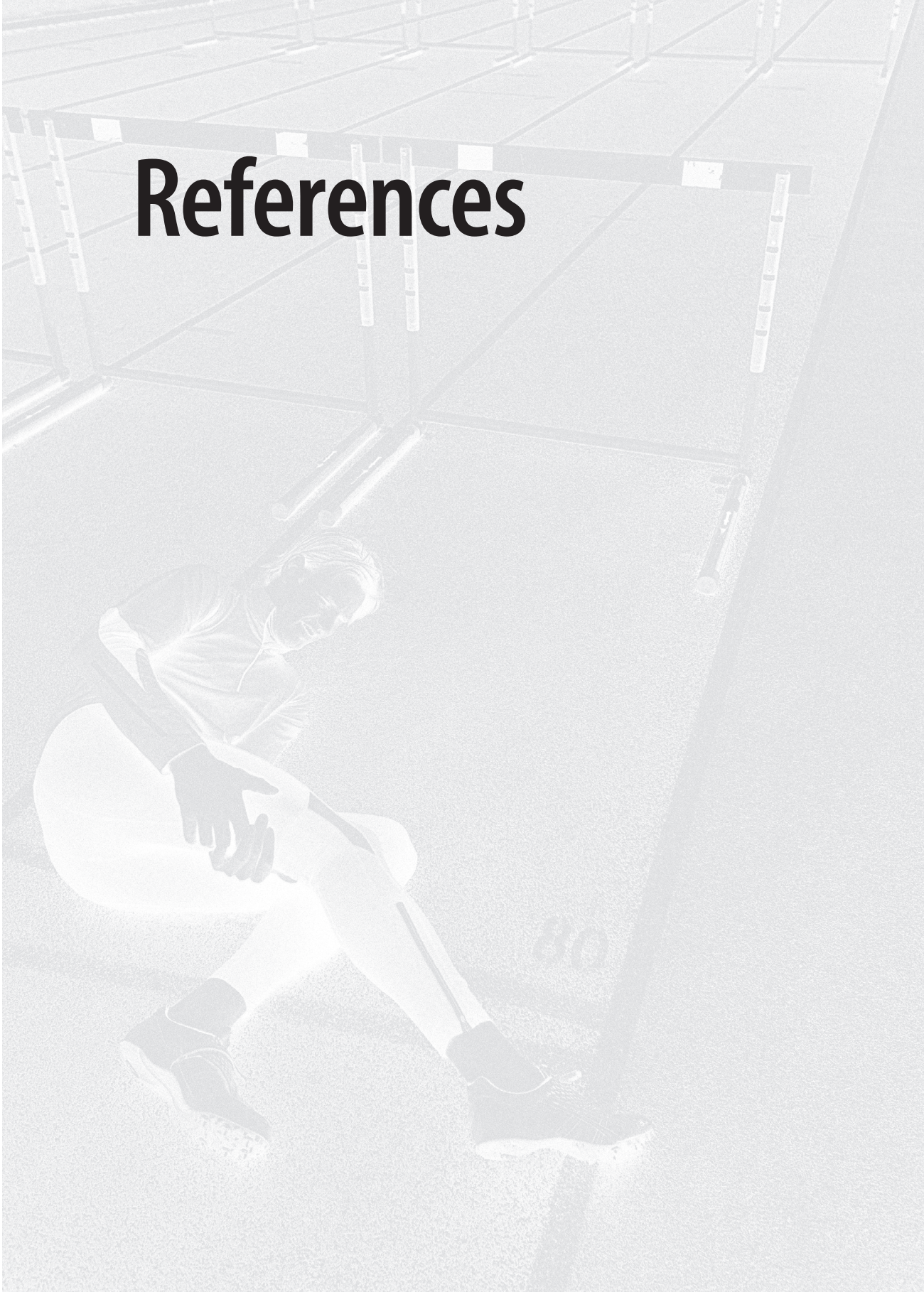
Bij sporthervatting hadden 41 sporters (38%) fibrose met een mediane longitudinale lengte van 5,8 cm (interkwartielafstand 3,3-12,5) en een mediaan volume van 1,5 cm^3 (interkwartielafstand 1,5-3,9). In de groep sporters met fibrose liep 24% (10 van de 41) een recidiefblessure op en in de groep zonder fibrose 24% (16 van de 67). Dit resulteerde in een hazards ratio van 0,95 (95% BI, 0,43 to 2,1: p=0,898). Concluderend, fibrose op MRI bij sporthervatting na een hamstringblessure is gangbaar, maar is niet geassocieerd met een hoger recidiefblessurerisico.

In **hoofdstuk 13** bespreken we zowel de belangrijkste bevindingen als de beperkingen van de studies van dit proefschrift en geven we adviezen voor toekomstig onderzoek en de klinische praktijk.

Een inschatting van de tijd tot sporthervatting blijft inaccuraat. Voorzichtigheid is daarom geboden bij het maken van een inschatting, omdat dit tot onterechte verwachtingen kan leiden. Een actief opbouwend revalidatieprogramma is de hoeksteen van de behandeling van acute hamstringblessures. Aanvullende medische behandelmodaliteiten worden niet geadviseerd. In de afwezigheid van gevalideerde criteria voor sporthervatting geven we enkele praktische criteria die sporthervatting beslissingen kunnen ondersteunen. MRI wordt niet geadviseerd voor sporthervatting beslissingen.

Afsluitend geven we aanbevelingen voor onderwerpen voor toekomstig onderzoek.

References



1. Abe, J., Y. Fujii, Y. Kuwamura, and K. Hizawa. Fiber type differentiation and myosin expression in regenerating rat muscles. Acta Pathol. Jpn. 37:1537–1547, 1987.
2. Agre, J. C. Hamstring injuries. Proposed aetiological factors, prevention, and treatment. Sports Med. Auckl. NZ 2:21–33, 1985.
3. A Hamid, M. S., M. R. Mohamed Ali, A. Yusof, J. George, and L. P. C. Lee. Platelet-Rich Plasma Injections for the Treatment of Hamstring Injuries: A Randomized Controlled Trial. Am. J. Sports Med., 2014. doi:10.1177/0363546514541540
4. Aird, L., D. Samuel, and M. Stokes. Quadriceps muscle tone, elasticity and stiffness in older males: reliability and symmetry using the MyotonPRO. Arch. Gerontol. Geriatr. 55:e31–39, 2012.
5. Akiyama, C., S. Kobayashi, and I. Nonaka. Comparison of behavior in muscle fiber regeneration after bupivacaine hydrochloride- and acid anhydride-induced myonecrosis. Acta Neuropathol. (Berl.) 83:584–589, 1992.
6. Almekinders, L. C. Anti-inflammatory treatment of muscular injuries in sport. An update of recent studies. Sports Med. Auckl. NZ 28:383–388, 1999.
7. Alonso, J.-M., P. Edouard, G. Fischetto, B. Adams, F. Depiesse, and M. Mountjoy. Determination of future prevention strategies in elite track and field: analysis of Daegu 2011 IAAF Championships injuries and illnesses surveillance. Br. J. Sports Med. 46:505–514, 2012.
8. Alonso, J.-M., P. Edouard, G. Fischetto, B. Adams, F. Depiesse, and M. Mountjoy. Determination of future prevention strategies in elite track and field: analysis of Daegu 2011 IAAF Championships injuries and illnesses surveillance. Br. J. Sports Med. 46:505–514, 2012.
9. Andia, I., M. Sánchez, and N. Maffulli. Platelet rich plasma therapies for sports muscle injuries: any evidence behind clinical practice? Expert Opin. Biol. Ther. 11:509–518, 2011.
10. Anitua, E., M. Sánchez, and S. Padilla. More on platelet-rich plasma injections in acute muscle injury. N. Engl. J. Med. 371:1264, 2014.
11. Arthur C. Rettig, Susan Meyers, Patrick A. Kersey, Greg P. Ballard, Kathy Oneacre, and Patti Hunker. Categorization of hamstring strain injuries by MRI and playing time lost in professional football players. NATA News 29–32, 2008.
12. Askling, C. Askling internet bestand.
13. Askling, C. M., N. Malliaropoulos, and J. Karlsson. High-speed running type or stretching-type of hamstring injuries makes a difference to treatment and prognosis. Br. J. Sports Med. 46:86–87, 2012.
14. Askling, C. M., J. Nilsson, and A. Thorstensson. A new hamstring test to complement the common clinical examination before return to sport after injury. Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA 18:1798–1803, 2010.
15. Askling, C. M., M. Tengvar, T. Saartok, and A. Thorstensson. Acute first-time hamstring strains during high-speed running: a longitudinal study including clinical and magnetic resonance imaging findings. Am. J. Sports Med. 35:197–206, 2007.
16. Askling, C. M., M. Tengvar, T. Saartok, and A. Thorstensson. Acute first-time hamstring strains during high-speed running: a longitudinal study including clinical and magnetic resonance imaging findings. Am. J. Sports Med. 35:197–206, 2007.
17. Askling, C. M., M. Tengvar, T. Saartok, and A. Thorstensson. Acute first-time hamstring strains during slow-speed stretching: clinical, magnetic resonance imaging, and recovery characteristics. Am. J. Sports Med. 35:1716–1724, 2007.
18. Askling, C. M., M. Tengvar, T. Saartok, and A. Thorstensson. Proximal hamstring strains of stretching type in different sports: injury situations, clinical and magnetic resonance imaging characteristics, and return to sport. Am. J. Sports Med. 36:1799–1804, 2008.

19. Askling, C. M., M. Tengvar, O. Tarassova, and A. Thorstensson. Acute hamstring injuries in Swedish elite sprinters and jumpers: a prospective randomised controlled clinical trial comparing two rehabilitation protocols. Br. J. Sports Med. 48:532–539, 2014.
20. Askling, C. M., M. Tengvar, and A. Thorstensson. Acute hamstring injuries in Swedish elite football: a prospective randomised controlled clinical trial comparing two rehabilitation protocols. Br. J. Sports Med., 2013.doi:10.1136/bjsports-2013-092165
21. Askling, C., T. Saartok, and A. Thorstensson. Type of acute hamstring strain affects flexibility, strength, and time to return to pre-injury level. Br. J. Sports Med. 40:40–44, 2006.
22. Askling, C., T. Saartok, and A. Thorstensson. Type of acute hamstring strain affects flexibility, strength, and time to return to pre-injury level. Br. J. Sports Med. 40:40–44, 2006.
23. Askling, C., M. Tengvar, T. Saartok, and A. Thorstensson. Sports related hamstring strains--two cases with different etiologies and injury sites. Scand. J. Med. Sci. Sports 10:304–307, 2000.
24. Bahr, R., and I. Holme. Risk factors for sports injuries--a methodological approach. Br. J. Sports Med. 37:384–392, 2003.
25. Baker, B. E. Current concepts in the diagnosis and treatment of musculotendinous injuries. Med. Sci. Sports Exerc. 16:323–327, 1984.
26. Basson, M. D., and B. M. Carlson. Myotoxicity of single and repeated injections of mepivacaine (Carbocaine) in the rat. Anesth. Analg. 59:275–282, 1980.
27. Bedair, H. S., T. Karthikeyan, A. Quintero, Y. Li, and J. Huard. Angiotensin II receptor blockade administered after injury improves muscle regeneration and decreases fibrosis in normal skeletal muscle. Am. J. Sports Med. 36:1548–1554, 2008.
28. Van Beijsterveldt, A.-M., K. Steffen, J. H. Stubbe, J. E. Frederiks, I. G. L. van de Port, and F. J. G. Backx. Soccer Injuries and Recovery In Dutch Male Amateur Soccer Players: Results of a Prospective Cohort Study. Clin. J. Sport Med. Off. J. Can. Acad. Sport Med., 2013.doi:10.1097/JSM.0000000000000028
29. Beitzel, F., P. Gregorevic, J. G. Ryall, D. R. Plant, M. N. Sillence, and G. S. Lynch. Beta2-adrenoceptor agonist fenoterol enhances functional repair of regenerating rat skeletal muscle after injury. J. Appl. Physiol. Bethesda Md 1985 96:1385–1392, 2004.
30. Bernuzzi, G., F. Petraglia, M. F. Pedrini, M. De Filippo, F. Pogliacomi, M. A. Verdano, and C. Costantino. Use of platelet-rich plasma in the care of sports injuries: our experience with ultrasound-guided injection. Blood Transfus. Trasfus. Sangue 1–6, 2013.doi:10.2450/2013.0293-12
31. Bizzini, M., and A. F. Mannion. Reliability of a new, hand-held device for assessing skeletal muscle stiffness. Clin. Biomech. Bristol Avon 18:459–461, 2003.
32. Blom, L., and F. Rasmussen. Tissue damage at the infection site after intramuscular injection of drugs in hens. Br. Poult. Sci. 17:1–4, 1976.
33. Brazeau, G. A., and H. L. Fung. An in vitro model to evaluate muscle damage following intramuscular injections. Pharm. Res. 6:167–170, 1989.
34. Brazeau, G., S. L. Sauberan, L. Gatlin, P. Wisniecki, and J. Shah. Effect of particle size of parenteral suspensions on in vitro muscle damage. Pharm. Dev. Technol. 16:591–598, 2011.
35. Brooks, J. H. M., C. W. Fuller, S. P. T. Kemp, and D. B. Reddin. Incidence, risk, and prevention of hamstring muscle injuries in professional rugby union. Am. J. Sports Med. 34:1297–1306, 2006.
36. Bruce Hamilton, Rod Whiteley, Emad Almusa, Bernard Roger, Celeste Geertsema, and Johannes L Tol. Excellent reliability for MRI grading and prognostic parameters in acute hamstring injuries
37. Brukner, P., and K. M. Khan. Clinical Sports Medicine. McGraw Hill, 2012.
38. Cacchio, A., J. D. Rompe, J. P. Furia, P. Susi, V. Santilli, and F. De Paulis. Shockwave therapy for the treatment of chronic proximal hamstring tendinopathy in professional athletes. Am. J. Sports Med. 39:146–153, 2011.

39. Campbell, R. S. D., and A. J. Dunn. Radiological interventions for soft tissue injuries in sport. Br. J. Radiol. 85:1186–1193, 2012.
40. Carlson, B. M., B. Shepard, and T. E. Komorowski. A histological study of local anesthetic-induced muscle degeneration and regeneration in the monkey. J. Orthop. Res. Off. Publ. Orthop. Res. Soc. 8:485–494, 1990.
41. Castillo, T. N., M. A. Pouliot, H. J. Kim, and J. L. Dragoo. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. Am. J. Sports Med. 39:266–271, 2011.
42. Cereda, C. M. S., G. R. Tofoli, L. G. Maturana, A. Pierucci, L. A. S. Nunes, M. Franz-Montan, A. L. R. de Oliveira, S. Arana, D. R. de Araujo, and E. de Paula. Local neurotoxicity and myotoxicity evaluation of cyclodextrin complexes of bupivacaine and ropivacaine. Anesth. Analg. 115:1234–1241, 2012.
43. Chellman, G. J., G. F. Faurot, L. O. Lollini, and T. E. McCullough. Rat paw-lick/muscle irritation model for evaluating parenteral formulations for pain-on-injection and muscle damage. Fundam. Appl. Toxicol. Off. J. Soc. Toxicol. 15:697–709, 1990.
44. Chellman, G. J., L. O. Lollini, A. E. Dorr, and L. R. DePass. Comparison of ketorolac tromethamine with other injectable nonsteroidal anti-inflammatory drugs for pain-on-injection and muscle damage in the rat. Hum. Exp. Toxicol. 13:111–117, 1994.
45. Cherng, C.-H., C.-S. Wong, C.-T. Wu, and C.-C. Yeh. Intramuscular bupivacaine injection dose-dependently increases glutamate release and muscle injury in rats. Acta Anaesthesiol. Taiwanica Off. J. Taiwan Soc. Anesthesiol. 48:8–14, 2010.
46. Chumanov, E. S., B. C. Heiderscheit, and D. G. Thelen. The effect of speed and influence of individual muscles on hamstring mechanics during the swing phase of sprinting. J. Biomech. 40:3555–3562, 2007.
47. Chumanov, E. S., B. C. Heiderscheit, and D. G. Thelen. Hamstring musculotendon dynamics during stance and swing phases of high-speed running. Med. Sci. Sports Exerc. 43:525–532, 2011.
48. Cibulka, M. T., S. J. Rose, A. Delitto, and D. R. Sinacore. Hamstring muscle strain treated by mobilizing the sacroiliac joint. Phys. Ther. 66:1220–1223, 1986.
49. Cohen, S., and J. Bradley. Acute proximal hamstring rupture. J. Am. Acad. Orthop. Surg. 15:350–355, 2007.
50. Coleman, B. D., K. M. Khan, N. Maffulli, J. L. Cook, and J. D. Wark. Studies of surgical outcome after patellar tendinopathy: clinical significance of methodological deficiencies and guidelines for future studies. Victorian Institute of Sport Tendon Study Group. Scand. J. Med. Sci. Sports 10:2–11, 2000.
51. Comin, J., P. Malliaras, P. Baquie, T. Barbour, and D. Connell. Return to competitive play after hamstring injuries involving disruption of the central tendon. Am. J. Sports Med. 41:111–115, 2013.
52. Connell, D. A., M. E. Schneider-Kolsky, J. L. Hoving, F. Malara, R. Buchbinder, G. Koulouris, F. Burke, and C. Bass. Longitudinal study comparing sonographic and MRI assessments of acute and healing hamstring injuries. AJR Am. J. Roentgenol. 183:975–984, 2004.
53. Creighton, D. W., I. Shrier, R. Shultz, W. H. Meeuwisse, and G. O. Matheson. Return-to-play in sport: a decision-based model. Clin. J. Sport Med. Off. J. Can. Acad. Sport Med. 20:379–385, 2010.
54. Dhillon, R. S., E. M. Schwarz, and M. D. Maloney. Platelet-rich plasma therapy - future or trend? Arthritis Res. Ther. 14:219, 2012.
55. Dietzel, D. P., and E. C. Hedlund. Injections and return to play. Curr. Pain Headache Rep. 9:11–16, 2005.
56. Diness, V. Local tissue damage after intramuscular injections in rabbits and pigs: quantitation by determination of creatine kinase activity at injection sites. Acta Pharmacol. Toxicol. (Copenh.) 56:410–415, 1985.

57. Duguez, S., L. Féasson, C. Denis, and D. Freyssenet. Mitochondrial biogenesis during skeletal muscle regeneration. Am. J. Physiol. Endocrinol. Metab. 282:E802–809, 2002.
58. Ekstrand, J., and J. Gillquist. The frequency of muscle tightness and injuries in soccer players. Am. J. Sports Med. 10:75–78, 1982.
59. Ekstrand, J., and J. Gillquist. Soccer injuries and their mechanisms: a prospective study. Med. Sci. Sports Exerc. 15:267–270, 1983.
60. Ekstrand, J., M. Hägglund, K. Kristenson, H. Magnusson, and M. Waldén. Fewer ligament injuries but no preventive effect on muscle injuries and severe injuries: an 11-year follow-up of the UEFA Champions League injury study. Br. J. Sports Med. 47:732–737, 2013.
61. Ekstrand, J., M. Hägglund, and M. Waldén. Epidemiology of muscle injuries in professional football (soccer). Am. J. Sports Med. 39:1226–1232, 2011.
62. Ekstrand, J., M. Hägglund, and M. Waldén. Epidemiology of muscle injuries in professional football (soccer). Am. J. Sports Med. 39:1226–1232, 2011.
63. Ekstrand, J., J. C. Healy, M. Waldén, J. C. Lee, B. English, and M. Hägglund. Hamstring muscle injuries in professional football: the correlation of MRI findings with return to play. Br. J. Sports Med. 46:112–117, 2012.
64. Ekstrand, J., H. Roos, and H. Tropp. Normal course of events amongst Swedish soccer players: an 8-year follow-up study. Br. J. Sports Med. 24:117–119, 1990.
65. Elkins, M. R., R. D. Herbert, A. M. Moseley, C. Sherrington, and C. Maher. Rating the quality of trials in systematic reviews of physical therapy interventions. Cardiopulm. Phys. Ther. J. 21:20–26, 2010.
66. Elliott, M. C. C. W., B. Zarins, J. W. Powell, and C. D. Kenyon. Hamstring muscle strains in professional football players: a 10-year review. Am. J. Sports Med. 39:843–850, 2011.
67. Engebretsen, A. H., G. Myklebust, I. Holme, L. Engebretsen, and R. Bahr. Prevention of Injuries Among Male Soccer Players: A Prospective, Randomized Intervention Study Targeting Players With Previous Injuries or Reduced Function. Am. J. Sports Med. 36:1052–1060, 2008.
68. Engebretsen, A. H., G. Myklebust, I. Holme, L. Engebretsen, and R. Bahr. Intrinsic risk factors for hamstring injuries among male soccer players: a prospective cohort study. Am. J. Sports Med. 38:1147–1153, 2010.
69. Feeley, B. T., S. Kennelly, R. P. Barnes, M. S. Muller, B. T. Kelly, S. A. Rodeo, and R. F. Warren. Epidemiology of National Football League training camp injuries from 1998 to 2007. Am. J. Sports Med. 36:1597–1603, 2008.
70. Foster, A. H., and B. M. Carlson. Myotoxicity of local anesthetics and regeneration of the damaged muscle fibers. Anesth. Analg. 59:727–736, 1980.
71. Freckleton, G., and T. Pizzari. Risk factors for hamstring muscle strain injury in sport: a systematic review and meta-analysis. Br. J. Sports Med. 47:351–358, 2013.
72. Fujikake, T., R. Hart, and K. Nosaka. Changes in B-mode ultrasound echo intensity following injection of bupivacaine hydrochloride to rat hind limb muscles in relation to histologic changes. Ultrasound Med. Biol. 35:687–696, 2009.
73. Fuller, C. W., J. Ekstrand, A. Junge, T. E. Andersen, R. Bahr, J. Dvorak, M. Hägglund, P. McCrory, and W. H. Meeuwisse. Consensus statement on injury definitions and data collection procedures in studies of football (soccer) injuries. Br. J. Sports Med. 40:193–201, 2006.
74. Gavronski, G., A. Veraksits, E. Vasar, and J. Maaroos. Evaluation of viscoelastic parameters of the skeletal muscles in junior triathletes. Physiol. Meas. 28:625–637, 2007.
75. Gharaibeh, B., Y. Chun-Lansinger, T. Hagen, S. J. M. Ingham, V. Wright, F. Fu, and J. Huard. Biological approaches to improve skeletal muscle healing after injury and disease. Birth Defects Res. Part C Embryo Today Rev. 96:82–94, 2012.

76. Ghozlan, P. R., M. Bernhardt, P. Vélicitat, and E. Bluhmki. Tolerability of multiple administration of intramuscular meloxicam: a comparison with intramuscular piroxicam in patients with rheumatoid arthritis or osteoarthritis. Br. J. Rheumatol. 35 Suppl 1:51–55, 1996.
77. Gibbs, N. J., T. M. Cross, M. Cameron, and M. T. Houang. The accuracy of MRI in predicting recovery and recurrence of acute grade one hamstring muscle strains within the same season in Australian Rules football players. J. Sci. Med. Sport Sports Med. Aust. 7:248–258, 2004.
78. Giraudeau, B., and J. Y. Mary. Planning a reproducibility study: how many subjects and how many replicates per subject for an expected width of the 95 per cent confidence interval of the intraclass correlation coefficient. Stat. Med. 20:3205–3214, 2001.
79. GlobalData. Platelet Rich Plasma: A Market Snapshotat <http://www.docstoc.com/docs/47503668/Platelet-Rich-Plasma-A-Market-Snapshot>
80. Grim, M., L. Rerábková, and B. M. Carlson. A test for muscle lesions and their regeneration following intramuscular drug application. Toxicol. Pathol. 16:432–442, 1988.
81. Guterres, S. S., H. Fessi, G. Barratt, F. Puisieux, and J. P. Devissaguet. Poly(rac-lactide) nanocapsules containing diclofenac: protection against muscular damage in rats. J. Biomater. Sci. Polym. Ed. 11:1347–1355, 2000.
82. Guttu, R. L., D. G. Page, and D. M. Laskin. Delayed healing of muscle after injection of bupivicaine and steroid. Ann. Dent. 49:5–8, 1990.
83. Hägglund, M., M. Waldén, and J. Ekstrand. Previous injury as a risk factor for injury in elite football: a prospective study over two consecutive seasons. Br. J. Sports Med. 40:767–772, 2006.
84. Hägglund, M., M. Waldén, and J. Ekstrand. Injuries among male and female elite football players. Scand. J. Med. Sci. Sports 19:819–827, 2009.
85. Hall-Craggs, E. C. Rapid degeneration and regeneration of a whole skeletal muscle following treatment with bupivacaine (Marcain). Exp. Neurol. 43:349–358, 1974.
86. Hallén, A., and J. Ekstrand. Return to play following muscle injuries in professional footballers. J. Sports Sci. 1–8, 2014.doi:10.1080/02640414.2014.905695
87. Hallén, A., and J. Ekstrand. Return to play following muscle injuries in professional footballers. J. Sports Sci. 32:1229–1236, 2014.
88. Hamilton, B. Medical management of hamstring muscle injury: strained evidence for platelet rich plasma. Br. J. Sports Med., 2014.doi:10.1136/bjsports-2014-094009
89. Hamilton, B., P. Fowler, H. Galloway, and N. Popovic. Nicolau syndrome in an athlete following intramuscular diclofenac injection. Acta Orthop. Belg. 74:860–864, 2008.
90. Hamilton, B. H., and T. M. Best. Platelet-enriched plasma and muscle strain injuries: challenges imposed by the burden of proof. Clin. J. Sport Med. Off. J. Can. Acad. Sport Med. 21:31–36, 2011.
91. Hamilton, B., W. Knez, C. Eirale, and H. Chalabi. Platelet enriched plasma for acute muscle injury. Acta Orthop. Belg. 76:443–448, 2010.
92. Hamilton, B., R. Whiteley, E. Almusa, B. Roger, C. Geertsema, and J. L. Tol. Excellent reliability for MRI grading and prognostic parameters in acute hamstring injuries. Br. J. Sports Med., 2013.doi:10.1136/bjsports-2013-092564
93. Hamilton, B., R. Whiteley, E. Almusa, B. Roger, C. Geertsema, and J. L. Tol. Excellent reliability for MRI grading and prognostic parameters in acute hamstring injuries. Br. J. Sports Med., 2013.doi:10.1136/bjsports-2013-092564
94. Hammond, J. W., R. Y. Hinton, L. A. Curl, J. M. Muriel, and R. M. Lovering. Use of autologous platelet-rich plasma to treat muscle strain injuries. Am. J. Sports Med. 37:1135–1142, 2009.
95. Hammond, J. W., R. Y. Hinton, L. A. Curl, J. M. Muriel, and R. M. Lovering. Use of autologous platelet-rich plasma to treat muscle strain injuries. Am. J. Sports Med. 37:1135–1142, 2009.

96. Hancock, C. R., T. G. Sanders, M. B. Zlatkin, P. D. Clifford, and D. Pevsner. Flexor femoris muscle complex: grading systems used to describe the complete spectrum of injury. Clin. Imaging 33:130–135, 2009.
97. Harris, J. D., M. J. Griesser, T. M. Best, and T. J. Ellis. Treatment of proximal hamstring ruptures - a systematic review. Int. J. Sports Med. 32:490–495, 2011.
98. Harris, N. L., W. E. Huffer, E. von Stade, A. I. Larson, S. Phinney, and M. L. Purnell. The effect of platelet-rich plasma on normal soft tissues in the rabbit. J. Bone Joint Surg. Am. 94:786–793, 2012.
99. Harris, N. L., W. E. Huffer, E. von Stade, A. I. Larson, S. Phinney, and M. L. Purnell. The effect of platelet-rich plasma on normal soft tissues in the rabbit. J. Bone Joint Surg. Am. 94:786–793, 2012.
100. Hayashi, D., B. Hamilton, A. Guermazi, R. de Villiers, M. D. Crema, and F. W. Roemer. Traumatic injuries of thigh and calf muscles in athletes: role and clinical relevance of MR imaging and ultrasound. Insights Imaging 3:591–601, 2012.
101. Hayden, J. A., P. Côté, and C. Bombardier. Evaluation of the quality of prognosis studies in systematic reviews. Ann. Intern. Med. 144:427–437, 2006.
102. Heiderscheit, B. C., D. M. Hoerth, E. S. Chumanov, S. C. Swanson, B. J. Thelen, and D. G. Thelen. Identifying the time of occurrence of a hamstring strain injury during treadmill running: a case study. Clin. Biomech. Bristol Avon 20:1072–1078, 2005.
103. Heiderscheit, B. C., M. A. Sherry, A. Silder, E. S. Chumanov, and D. G. Thelen. Hamstring strain injuries: recommendations for diagnosis, rehabilitation, and injury prevention. J. Orthop. Sports Phys. Ther. 40:67–81, 2010.
104. Heiderscheit, B. C., M. A. Sherry, A. Silder, E. S. Chumanov, and D. G. Thelen. Hamstring strain injuries: recommendations for diagnosis, rehabilitation, and injury prevention. J. Orthop. Sports Phys. Ther. 40:67–81, 2010.
105. Heiser, T. M., J. Weber, G. Sullivan, P. Clare, and R. R. Jacobs. Prophylaxis and management of hamstring muscle injuries in intercollegiate football players. Am. J. Sports Med. 12:368–370, 1984.
106. Horiguchi, T., M.-A. Shibata, Y. Ito, N. A. S. Eid, M. Abe, and Y. Otsuki. Macrophage apoptosis in rat skeletal muscle treated with bupivacaine hydrochloride: possible role of MCP-1. Muscle Nerve 26:79–86, 2002.
107. Hoskins, W. T., and H. P. Pollard. Successful management of hamstring injuries in Australian Rules footballers: two case reports. Chiropr. Osteopat. 13:4, 2005.
108. Huard, J., Y. Li, and F. H. Fu. Muscle injuries and repair: current trends in research. J. Bone Jt. Surg. 84:822–832, 2002.
109. Ishiura, S., I. Nonaka, T. Fujita, and H. Sugita. Effect of cycloheximide administration on bupivacaine-induced acute muscle degradation. J. Biochem. (Tokyo) 94:1631–1636, 1983.
110. Ishiura, S., I. Nonaka, and H. Sugita. Biochemical aspects of bupivacaine-induced acute muscle degradation. J. Cell Sci. 83:197–212, 1986.
111. Järvinen, T. A. H., T. L. N. Järvinen, M. Kääriäinen, V. Aärimaa, S. Vaittinen, H. Kalimo, and M. Järvinen. Muscle injuries: optimising recovery. Best Pract. Res. Clin. Rheumatol. 21:317–331, 2007.
112. Jiménez-Díaz, F., I. Jimena, E. Luque, S. Mendizábal, A. Bouffard, L. Jiménez-Reina, and J. Peña. Experimental muscle injury: correlation between ultrasound and histological findings. Muscle Nerve 45:705–712, 2012.
113. Jones, G. H. Protein synthesis in bupivacaine (marcaine)-treated, regenerating skeletal muscle. Muscle Nerve 5:281–290, 1982.
114. De Jonge, S., R. J. de Vos, A. Weir, H. T. M. van Schie, S. M. A. Bierma-Zeinstra, J. A. N. Verhaar, H. Weinans, and J. L. Tol. One-Year Follow-up of Platelet-Rich Plasma Treatment in Chronic Achilles Ten-

dinopathy: A Double-Blind Randomized Placebo-Controlled Trial. Am. J. Sports Med. 39:1623–1629, 2011.

115. Jordan, J. L., M. A. Holden, E. E. Mason, and N. E. Foster. Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. Cochrane Database Syst. Rev. CD005956, 2010. doi:10.1002/14651858.CD005956.pub2
116. Kääriäinen, M., T. Järvinen, M. Järvinen, J. Rantanen, and H. Kalimo. Relation between myofibers and connective tissue during muscle injury repair. Scand. J. Med. Sci. Sports 10:332–337, 2000.
117. Karanicolas, P. J., M. Bhandari, H. Kreder, A. Moroni, M. Richardson, S. D. Walter, G. R. Norman, G. H. Guyatt, and Collaboration for Outcome Assessment in Surgical Trials (COAST) Musculoskeletal Group. Evaluating agreement: conducting a reliability study. J. Bone Joint Surg. Am. 91 Suppl 3:99–106, 2009.
118. Kelln, B. M., P. O. McKeon, L. M. Gontkof, and J. Hertel. Hand-held dynamometry: reliability of lower extremity muscle testing in healthy, physically active,young adults. J. Sport Rehabil. 17:160–170, 2008.
119. Kendall, F. P., E. K. McCreary, P. G. Provance, M. M. Rodgers, and W. A. Romani. Muscles testing and function with posture and pain. In: Muscles, testing and function with posture and pain. Baltimore: Lippincott Willians and Wilkins, 2005, p. 17.
120. Kerkhoffs, G. M. M. J., N. van Es, T. Wieldraaijer, I. N. Sierevelt, J. Ekstrand, and C. N. van Dijk. Diagnosis and prognosis of acute hamstring injuries in athletes. Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA 21:500–509, 2013.
121. Kerkhoffs, G. M. M. J., N. van Es, T. Wieldraaijer, I. N. Sierevelt, J. Ekstrand, and C. N. van Dijk. Diagnosis and prognosis of acute hamstring injuries in athletes. Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA 21:500–509, 2013.
122. Komorowski, T. E., B. Shepard, S. Okland, and B. M. Carlson. An electron microscopic study of local anesthetic-induced skeletal muscle fiber degeneration and regeneration in the monkey. J. Orthop. Res. Off. Publ. Orthop. Res. Soc. 8:495–503, 1990.
123. Kornberg, C., and P. Lew. The effect of stretching neural structures on grade one hamstring injuries. J. Orthop. Sports Phys. Ther. 10:481–487, 1989.
124. Koulouris, G., and D. Connell. Hamstring muscle complex: an imaging review. Radiogr. Rev. Publ. Radiol. Soc. N. Am. Inc 25:571–586, 2005.
125. Koulouris, G., D. A. Connell, P. Brukner, and M. Schneider-Kolsky. Magnetic resonance imaging parameters for assessing risk of recurrent hamstring injuries in elite athletes. Am. J. Sports Med. 35:1500–1506, 2007.
126. Kusma, M., R. Seil, and D. Kohn. Isolated avulsion of the biceps femoris insertion-injury patterns and treatment options: a case report and literature review. Arch. Orthop. Trauma Surg. 127:777–780, 2007.
127. Lagrota-Candido, J., I. Canella, D. F. Pinheiro, L. P. Santos-Silva, R. S. Ferreira, F. J. Guimarães-Joca, J. Lannes-Vieira, and T. Quirico-Santos. Characteristic pattern of skeletal muscle remodelling in different mouse strains. Int. J. Exp. Pathol. 91:522–529, 2010.
128. Landes, S., J. Nyland, B. Elmlinger, E. Tillett, and D. Caborn. Knee flexor strength after ACL reconstruction: comparison between hamstring autograft, tibialis anterior allograft, and non-injured controls. Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA 18:317–324, 2010.
129. Landes, S., J. Nyland, B. Elmlinger, E. Tillett, and D. Caborn. Knee flexor strength after ACL reconstruction: comparison between hamstring autograft, tibialis anterior allograft, and non-injured controls. Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA 18:317–324, 2010.

130. Lee, J. C., A. W. M. Mitchell, and J. C. Healy. Imaging of muscle injury in the elite athlete. Br. J. Radiol. 85:1173–1185, 2012.
131. Lee, P., A. Rattenberry, S. Connelly, and L. Nokes. Our experience on Actovegin, is it cutting edge? Int. J. Sports Med. 32:237–241, 2011.
132. Levine, W. N., J. A. Bergfeld, W. Tessendorf, and C. T. Moorman 3rd. Intramuscular corticosteroid injection for hamstring injuries. A 13-year experience in the National Football League. Am. J. Sports Med. 28:297–300, 2000.
133. Lima, E. M., and A. G. Oliveira. Tissue tolerance of diclofenac sodium encapsulated in liposomes after intramuscular administration. Drug Dev. Ind. Pharm. 28:673–680, 2002.
134. Linklater, J. M., B. Hamilton, J. Carmichael, J. Orchard, and D. G. Wood. Hamstring injuries: anatomy, imaging, and intervention. Semin. Musculoskelet. Radiol. 14:131–161, 2010.
135. Louboutin, J. P., V. Fichter-Gagnepain, and J. Noireaud. External calcium dependence of extensor digitorum longus muscle contractility during bupivacaine-induced regeneration. Muscle Nerve 19:994–1002, 1996.
136. Lu, T.-W., H.-C. Hsu, L.-Y. Chang, and H.-L. Chen. Enhancing the examiner's resisting force improves the reliability of manual muscle strength measurements: comparison of a new device with handheld dynamometry. J. Rehabil. Med. Off. J. UEMS Eur. Board Phys. Rehabil. Med. 39:679–684, 2007.
137. Lu, Y.-M., J.-H. Lin, S.-F. Hsiao, M.-F. Liu, S.-M. Chen, and Y.-J. Lue. The Relative and Absolute Reliability of Leg Muscle Strength Testing by a Handheld Dynamometer: J. Strength Cond. Res. 25:1065–1071, 2011.
138. Maher, C. G., C. Sherrington, R. D. Herbert, A. M. Moseley, and M. Elkins. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys. Ther. 83:713–721, 2003.
139. Malliaropoulos, N., T. Isinkaye, K. Tsitas, and N. Maffulli. Reinjury after acute posterior thigh muscle injuries in elite track and field athletes. Am. J. Sports Med. 39:304–310, 2011.
140. Malliaropoulos, N., E. Papacostas, O. Kiritsi, A. Papalada, N. Gougoulias, and N. Maffulli. Posterior thigh muscle injuries in elite track and field athletes. Am. J. Sports Med. 38:1813–1819, 2010.
141. Malliaropoulos, N., S. Papalexandris, A. Papalada, and E. Papacostas. The role of stretching in rehabilitation of hamstring injuries: 80 athletes follow-up. Med. Sci. Sports Exerc. 36:756–759, 2004.
142. Marqueste, T., B. Giannesini, Y. L. Fur, P. J. Cozzone, and D. Bendahan. Comparative MRI analysis of T2 changes associated with single and repeated bouts of downhill running leading to eccentric-induced muscle damage. J. Appl. Physiol. Bethesda Md 1985 105:299–307, 2008.
143. Mason, D. L., V. A. Dickens, and A. Vail. Rehabilitation for hamstring injuries. Cochrane Database Syst. Rev. 12:CD004575, 2012.
144. Mason, D. L., V. A. Dickens, and A. Vail. Rehabilitation for hamstring injuries. Cochrane Database Syst. Rev. 12:CD004575, 2012.
145. Mason, D. L., V. Dickens, and A. Vail. Rehabilitation for hamstring injuries. Cochrane Database Syst. Rev. CD004575, 2007.doi:10.1002/14651858.CD004575.pub2
146. Mathur, S., R. S. Vohra, S. A. Germain, S. Forbes, N. D. Bryant, K. Vandenborne, and G. A. Walter. Changes in muscle T2 and tissue damage after downhill running in mdx mice. Muscle Nerve 43:878–886, 2011.
147. May, D. A., D. G. Disler, E. A. Jones, A. A. Balkissoon, and B. J. Manaster. Abnormal signal intensity in skeletal muscle at MR imaging: patterns, pearls, and pitfalls. Radiogr. Rev. Publ. Radiol. Soc. N. Am. Inc 20 Spec No:S295–315, 2000.
148. McMahon, C. J., J. S. Wu, and R. L. Eisenberg. Muscle edema. AJR Am. J. Roentgenol. 194:W284–292, 2010.

149. McNeill Ingham, S. J., A. de Castro Pochini, D. A. de Oliveira, B. C. Garcia Lisboa, A. Beutel, V. B. Valero-Lapchik, A. M. Ferreira, R. J. Abdalla, M. Cohen, and S. W. Han. Bupivacaine injection leads to muscle force reduction and histologic changes in a murine model. PM R 3:1106–1109, 2011.
150. Mehallo, C. J., J. A. Drezner, and J. R. Bytomski. Practical management: nonsteroidal antiinflammatory drug (NSAID) use in athletic injuries. Clin. J. Sport Med. Off. J. Can. Acad. Sport Med. 16:170–174, 2006.
151. Mendiguchia, J., E. Alentorn-Geli, and M. Brughelli. Hamstring strain injuries: are we heading in the right direction? Br. J. Sports Med. 46:81–85, 2012.
152. Mendiguchia, J., and M. Brughelli. A return-to-sport algorithm for acute hamstring injuries. Phys. Ther. Sport 12:2–14, 2011.
153. Menetrey, J., C. Kasemkijwattana, C. S. Day, P. Bosch, M. Vogt, F. H. Fu, M. S. Moreland, and J. Huard. Growth factors improve muscle healing in vivo. J. Bone Joint Surg. Br. 82:131–137, 2000.
154. Miike, T., I. Nonaka, Y. Ohtani, H. Tamari, and T. Ishitsu. Behavior of sarcotubular system formation in experimentally induced regeneration of muscle fibers. J. Neurol. Sci. 65:193–200, 1984.
155. Mikkelsen, U. R., H. Langberg, I. C. Helmark, D. Skovgaard, L. L. Andersen, M. Kjaer, and A. L. Mackey. Local NSAID infusion inhibits satellite cell proliferation in human skeletal muscle after eccentric exercise. J. Appl. Physiol. Bethesda Md 1985 107:1600–1611, 2009.
156. Moraes, V. Y., M. Lenza, M. J. Tamaoki, F. Faloppa, and J. C. Belloti. Platelet-rich therapies for musculoskeletal soft tissue injuries. In: Cochrane Database of Systematic Reviews, edited by The Cochrane Collaboration.
157. De Morton, N. A. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust. J. Physiother. 55:129–133, 2009.
158. Mueller-Wohlfahrt, H.-W., L. Haensel, K. Mithoefer, J. Ekstrand, B. English, S. McNally, J. Orchard, C. N. van Dijk, G. M. Kerkhoffs, P. Schamasch, D. Blottner, L. Swaerd, E. Goedhart, and P. Ueblacker. Terminology and classification of muscle injuries in sport: the Munich consensus statement. Br. J. Sports Med. 47:342–350, 2013.
159. Mustalampi, S., J. Ylinen, H. Kautiainen, A. Weir, and A. Häkkinen. Acute effects of cold pack on mechanical properties of the quadriceps muscle in healthy subjects. Phys. Ther. Sport 13:265–269, 2012.
160. Narjes, H., D. Türck, U. Busch, G. Heinzel, and G. Nehmiz. Pharmacokinetics and tolerability of meloxicam after i.m. administration. Br. J. Clin. Pharmacol. 41:135–139, 1996.
161. Nepomnyashchikh, L. M., M. A. Bakarev, and V. G. Tsimmerman. Reparative reactions of the skeletal muscles in early aging OXYS rats with toxic metabolic injuries caused by bupivacaine. Bull. Exp. Biol. Med. 144:370–375, 2007.
162. Nonaka, I., A. Takagi, S. Ishiura, H. Nakase, and H. Sugita. Pathophysiology of muscle fiber necrosis induced by bupivacaine hydrochloride (Marcaine). Acta Neuropathol. (Berl.) 60:167–174, 1983.
163. Nosaka, K. Changes in serum enzyme activities after injection of bupivacaine into rat tibialis anterior. J. Appl. Physiol. Bethesda Md 1985 81:876–884, 1996.
164. Nosaka, K., and K. Sakamoto. Changes in plasma enzyme activity after intramuscular injection of bupivacaine into the human biceps brachii. Acta Physiol. Scand. 167:259–265, 1999.
165. Nosaka, K., and K. Sakamoto. Changes in plasma enzyme activity after intramuscular injection of bupivacaine into the human biceps brachii. Acta Physiol. Scand. 167:259–265, 1999.
166. Nyska, A., M. Skolnick, G. Ziv, and A. Gulkarov. Correlation of injection site damage and serum creatine kinase activity in turkeys following intramuscular and subcutaneous administration of norfloxacin nicotinate. Avian Pathol. J. WVPA 23:671–682, 1994.

167. Orchard, J., and T. M. Best. The management of muscle strain injuries: an early return versus the risk of recurrence. Clin. J. Sport Med. Off. J. Can. Acad. Sport Med. 12:3–5, 2002.
168. Orchard, J., T. M. Best, and G. M. Verrall. Return to play following muscle strains. Clin. J. Sport Med. Off. J. Can. Acad. Sport Med. 15:436–441, 2005.
169. Orchard, J., and H. Seward. Epidemiology of injuries in the Australian Football League, seasons 1997-2000. Br. J. Sports Med. 36:39–44, 2002.
170. Orchard, J., and H. Seward. Epidemiology of injuries in the Australian Football League, seasons 1997-2000. Br. J. Sports Med. 36:39–44, 2002.
171. Orchard, J. W., T. M. Best, H.-W. Mueller-Wohlfahrt, G. Hunter, B. H. Hamilton, N. Webborn, R. Jaques, D. Kenneally, R. Budgett, N. Phillips, C. Becker, and P. Glasgow. The early management of muscle strains in the elite athlete: best practice in a world with a limited evidence basis. Br. J. Sports Med. 42:158–159, 2008.
172. Orchard, J. W., H. Seward, and J. J. Orchard. Results of 2 decades of injury surveillance and public release of data in the Australian Football League. Am. J. Sports Med. 41:734–741, 2013.
173. Orimo, S., E. Hiyamuta, K. Arahata, and H. Sugita. Analysis of inflammatory cells and complement C3 in bupivacaine-induced myonecrosis. Muscle Nerve 14:515–520, 1991.
174. Osawa, K., N. Maeda, M. Kumegawa, and T. Masuda. Long-term observations of the masseter muscle following single or repeated injections of lidocaine hydrochloride into developing mice. Shika Kiso Igakkai Zasshi 31:198–210, 1989.
175. Paoloni, J., R. J. De Vos, B. Hamilton, G. A. C. Murrell, and J. Orchard. Platelet-rich plasma treatment for ligament and tendon injuries. Clin. J. Sport Med. Off. J. Can. Acad. Sport Med. 21:37–45, 2011.
176. Peer, K. S., J. E. Barkley, and D. M. Knapp. The acute effects of local vibration therapy on ankle sprain and hamstring strain injuries. Phys. Sportsmed. 37:31–38, 2009.
177. Peetrons, P. Ultrasound of muscles. Eur. Radiol. 12:35–43, 2002.
178. Petersen, J., K. Thorborg, M. B. Nielsen, E. Budtz-Jørgensen, and P. Hölmich. Preventive effect of eccentric training on acute hamstring injuries in men's soccer: a cluster-randomized controlled trial. Am. J. Sports Med. 39:2296–2303, 2011.
179. Pfister, A., and W. Koller. [Treatment of fresh muscle injury]. Sportverletz. Sportschaden Organ Ges. Für Orthop.-Traumatol. Sportmed. 4:41–44, 1990.
180. Plant, D. R., F. E. Colarossi, and G. S. Lynch. Notexin causes greater myotoxic damage and slower functional repair in mouse skeletal muscles than bupivacaine. Muscle Nerve 34:577–585, 2006.
181. Politi, P. K., S. Havaki, P. Manta, and G. Lyritis. Bupivacaine-induced regeneration of rat soleus muscle: ultrastructural and immunohistochemical aspects. Ultrastruct. Pathol. 30:461–469, 2006.
182. Portney, L. G., and M. P. Watkins. Foundations of clinical research: applications to practice. Upper Saddle River, N.J.: Pearson/Prentice Hall, 2009.
183. Pyörälä, S., T. Laurila, S. Lehtonen, S. Leppä, and L. Kaartinen. Local tissue damage in cows after intramuscular administration of preparations containing phenylbutazone, flunixin, ketoprofen and metamizole. Acta Vet. Scand. 40:145–150, 1999.
184. Rasmussen, F. Tissue damage at the injection site after intramuscular injection of drugs. Vet. Sci. Commun. 2:173–182, 1978.
185. Rasmussen, F., and O. Svendsen. Tissue damage and concentration at the injection site after intramuscular injection of chemotherapeutics and vehicles in pigs. Res. Vet. Sci. 20:55–60, 1976.
186. Rettig, A. C., S. Meyer, and A. K. Bhadra. Platelet-Rich Plasma in Addition to Rehabilitation for Acute Hamstring Injuries in NFL Players Clinical Effects and Time to Return to Play. Orthop. J. Sports Med. 1:, 2013.

187. Reurink, G., G. J. Goudswaard, M. H. Moen, A. Weir, J. A. N. Verhaar, S. M. A. Bierma-Zeinstra, M. Maas, J. L. Tol, and Dutch Hamstring Injection Therapy (HIT) Study Investigators. Platelet-rich plasma injections in acute muscle injury. N. Engl. J. Med. 370:2546–2547, 2014.
188. Reurink, G., G. J. Goudswaard, M. H. Moen, A. Weir, J. A. N. Verhaar, S. M. A. Bierma-Zeinstra, M. Maas, J. L. Tol, and Dutch Hamstring Injection Therapy (HIT) Study Investigators. Platelet-rich plasma injections in acute muscle injury. N. Engl. J. Med. 370:2546–2547, 2014.
189. Reurink, G., G. J. Goudswaard, H. G. Oomen, M. H. Moen, J. L. Tol, J. A. N. Verhaar, and A. Weir. Reliability of the Active and Passive Knee Extension Test in Acute Hamstring Injuries. Am. J. Sports Med., 2013.doi:10.1177/0363546513490650
190. Reurink, G., G. J. Goudswaard, H. G. Oomen, M. H. Moen, J. L. Tol, J. A. N. Verhaar, and A. Weir. Reliability of the Active and Passive Knee Extension Test in Acute Hamstring Injuries. Am. J. Sports Med., 2013.doi:10.1177/0363546513490650
191. Reurink, G., G. J. Goudswaard, J. L. Tol, E. Almusa, M. H. Moen, A. Weir, J. A. N. Verhaar, B. Hamilton, and M. Maas. MRI observations at return to play of clinically recovered hamstring injuries. Br. J. Sports Med., 2013.doi:10.1136/bjsports-2013-092450
192. Reurink, G., G. J. Goudswaard, J. L. Tol, E. Almusa, M. H. Moen, A. Weir, J. A. N. Verhaar, B. Hamilton, and M. Maas. MRI observations at return to play of clinically recovered hamstring injuries. Br. J. Sports Med., 2013.doi:10.1136/bjsports-2013-092450
193. Reurink, G., G. J. Goudswaard, J. L. Tol, J. A. N. Verhaar, A. Weir, and M. H. Moen. Therapeutic interventions for acute hamstring injuries: a systematic review. Br. J. Sports Med. 46:103–109, 2012.
194. Reurink, G., G. J. Goudswaard, J. L. Tol, J. A. N. Verhaar, A. Weir, and M. H. Moen. Therapeutic interventions for acute hamstring injuries: a systematic review. Br. J. Sports Med. 46:103–109, 2012.
195. Reurink, G., J. A. N. Verhaar, and J. L. Tol. More on platelet-rich plasma injections in acute muscle injury. N. Engl. J. Med. 371:1264–1265, 2014.
196. Reynolds, J. F., T. D. Noakes, M. P. Schwellnus, A. Windt, and P. Bowerbank. Non-steroidal anti-inflammatory drugs fail to enhance healing of acute hamstring injuries treated with physiotherapy. South Afr. Med. J. Suid-Afr. Tydskr. Vir Geneeskd. 85:517–522, 1995.
197. Rochcongar, P., H. de Labareyre, J. de Lecluse, A. Monroche, and E. Polard. L'utilisation et la prescription des corticoïdes en médecine du sport. Sci. Sports 19:145–154, 2004.
198. Rosenblatt, J. D., and R. I. Woods. Hypertrophy of rat extensor digitorum longus muscle injected with bupivacaine. A sequential histochemical, immunohistochemical, histological and morphometric study. J. Anat. 181 (Pt 1):11–27, 1992.
199. Sadeh, M., K. Czyewski, and L. Z. Stern. Chronic myopathy induced by repeated bupivacaine injections. J. Neurol. Sci. 67:229–238, 1985.
200. Sadeh, M., L. Z. Stern, K. Czyzewski, P. R. Finley, and D. H. Russell. Alterations in creatine kinase, ornithine decarboxylase, and transglutaminase during muscle regeneration. Life Sci. 34:483–488, 1984.
201. Sanfilippo, J. L., A. Silder, M. A. Sherry, M. J. Tuite, and B. C. Heiderscheit. Hamstring strength and morphology progression after return to sport from injury. Med. Sci. Sports Exerc. 45:448–454, 2013.
202. Sauerwein, H. P., T. Brouwer, and A. J. Dunning. [Creatine phosphokinase, myocardial infarction and intramuscular injection]. Ned. Tijdschr. Geneeskd. 119:1399–1402, 1975.
203. Schneider-Kolsky, M. E., J. L. Hoving, P. Warren, and D. A. Connell. A comparison between clinical assessment and magnetic resonance imaging of acute hamstring injuries. Am. J. Sports Med. 34:1008–1015, 2006.
204. Seibel, H. R., M. F. Dolwick, F. M. Bush, and S. S. Craig. Electron-microscopic study of the rat masseter muscle following injection of lidocaine. Acta Anat. (Basel) 100:354–364, 1978.

205. Serner, A., C. H. van Eijck, B. R. Beumer, P. Hölmich, A. Weir, and R.-J. de Vos. Study quality on groin injury management remains low: a systematic review on treatment of groin pain in athletes. Br. J. Sports Med., 2015.doi:10.1136/bjsports-2014-094256
206. Shankar, P. R., S. K. Fields, C. L. Collins, R. W. Dick, and R. D. Comstock. Epidemiology of high school and collegiate football injuries in the United States, 2005-2006. Am. J. Sports Med. 35:1295–1303, 2007.
207. Shen, W., Y. Li, Y. Tang, J. Cummins, and J. Huard. NS-398, a cyclooxygenase-2-specific inhibitor, delays skeletal muscle healing by decreasing regeneration and promoting fibrosis. Am. J. Pathol. 167:1105–1117, 2005.
208. Sherry, M. A., and T. M. Best. A comparison of 2 rehabilitation programs in the treatment of acute hamstring strains. J. Orthop. Sports Phys. Ther. 34:116–125, 2004.
209. Sheth, U., N. Simunovic, G. Klein, F. Fu, T. A. Einhorn, E. Schemitsch, O. R. Ayeni, and M. Bhandari. Efficacy of autologous platelet-rich plasma use for orthopaedic indications: a meta-analysis. J. Bone Joint Surg. Am. 94:298–307, 2012.
210. Silder, A., B. C. Heiderscheit, D. G. Thelen, T. Enright, and M. J. Tuite. MR observations of long-term musculotendon remodeling following a hamstring strain injury. Skeletal Radiol. 37:1101–1109, 2008.
211. Silder, A., S. B. Reeder, and D. G. Thelen. The influence of prior hamstring injury on lengthening muscle tissue mechanics. J. Biomech. 43:2254–2260, 2010.
212. Silder, A., M. A. Sherry, J. Sanfilippo, M. J. Tuite, S. J. Hetzel, and B. C. Heiderscheit. Clinical and morphological changes following 2 rehabilitation programs for acute hamstring strain injuries: a randomized clinical trial. J. Orthop. Sports Phys. Ther. 43:284–299, 2013.
213. Silder, A., M. A. Sherry, J. Sanfilippo, M. J. Tuite, S. J. Hetzel, and B. C. Heiderscheit. Clinical and morphological changes following 2 rehabilitation programs for acute hamstring strain injuries: a randomized clinical trial. J. Orthop. Sports Phys. Ther. 43:284–299, 2013.
214. Silder, A., D. G. Thelen, and B. C. Heiderscheit. Effects of prior hamstring strain injury on strength, flexibility, and running mechanics. Clin. Biomech. Bristol Avon 25:681–686, 2010.
215. Slavin, R. E. Best evidence synthesis: an intelligent alternative to meta-analysis. J. Clin. Epidemiol. 48:9–18, 1995.
216. Slavotinek, J. P., G. M. Verrall, and G. T. Fon. Hamstring injury in athletes: using MR imaging measurements to compare extent of muscle injury with amount of time lost from competition. AJR Am. J. Roentgenol. 179:1621–1628, 2002.
217. Steiness, E., F. Rasmussen, O. Svendsen, and P. Nielsen. A comparative study of serum creatine phosphokinase (CPK) activity in rabbits, pigs and humans after intramuscular injection of local damaging drugs. Acta Pharmacol. Toxicol. (Copenh.) 42:357–364, 1978.
218. Stevens, K. J., J. M. Crain, K. H. Akizuki, and C. F. Beaulieu. Imaging and ultrasound-guided steroid injection of internal oblique muscle strains in baseball pitchers. Am. J. Sports Med. 38:581–585, 2010.
219. Sutton, G. Hamstrung by hamstring strains: a review of the literature*. J. Orthop. Sports Phys. Ther. 5:184–195, 1984.
220. Sutton, S. C., L. A. Evans, M. T. Rinaldi, and K. A. Norton. Predicting injection site muscle damage. I: Evaluation of immediate release parenteral formulations in animal models. Pharm. Res. 13:1507–1513, 1996.
221. Tamaki, T., A. Akatsuka, S. Uchiyama, Y. Uchiyama, and T. Shiraishi. Appearance of complex branched muscle fibers is associated with a shift to slow muscle characteristics. Acta Anat. (Basel) 159:108–113, 1997.

222. Terada, S., S. Ota, M. Kobayashi, T. Kobayashi, Y. Mifune, K. Takayama, M. Witt, G. Vadalà, N. Oyster, T. Otsuka, F. H. Fu, and J. Huard. Use of an antifibrotic agent improves the effect of platelet-rich plasma on muscle healing after injury. J. Bone Joint Surg. Am. 95:980–988, 2013.
223. Thorborg, K. Why hamstring eccentrics are hamstring essentials. Br. J. Sports Med. 46:463–465, 2012.
224. Thorsson, O., B. Lilja, P. Nilsson, and N. Westlin. Immediate external compression in the management of an acute muscle injury. Scand. J. Med. Sci. Sports 7:182–190, 1997.
225. Thuilliez, C., L. Dorso, P. Howroyd, S. Gould, F. Chanut, and R. Burnett. Histopathological lesions following intramuscular administration of saline in laboratory rodents and rabbits. Exp. Toxicol. Pathol. Off. J. Ges. Für Toxikol. Pathol. 61:13–21, 2009.
226. Titford, M. The long history of hematoxylin. Biotech. Histochem. Off. Publ. Biol. Stain Comm. 80:73–78, 2005.
227. Tol, J. L., B. Hamilton, C. Eirale, P. Muxart, P. Jacobsen, and R. Whiteley. At return to play following hamstring injury the majority of professional football players have residual isokinetic deficits. Br. J. Sports Med., 2014.doi:10.1136/bjsports-2013-093016
228. Tomas i Ferré, J., R. Fenoll i Brunet, M. Santafé, and E. Mayayo. Changes in motor nerve terminals during bupivacaine-induced postsynaptic deprivation. J. Anat. 162:225–234, 1989.
229. Van Tulder, M., A. Furlan, C. Bombardier, L. Bouter, and Editorial Board of the Cochrane Collaboration Back Review Group. Updated method guidelines for systematic reviews in the cochrane collaboration back review group. Spine 28:1290–1299, 2003.
230. Verhagen, A. P., H. C. de Vet, R. A. de Bie, A. G. Kessels, M. Boers, L. M. Bouter, and P. G. Knipschild. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J. Clin. Epidemiol. 51:1235–1241, 1998.
231. Verrall, G. M., J. P. Slavotinek, P. G. Barnes, and G. T. Fon. Diagnostic and prognostic value of clinical findings in 83 athletes with posterior thigh injury: comparison of clinical findings with magnetic resonance imaging documentation of hamstring muscle strain. Am. J. Sports Med. 31:969–973, 2003.
232. Verrall, G. M., J. P. Slavotinek, P. G. Barnes, G. T. Fon, and A. Esterman. Assessment of physical examination and magnetic resonance imaging findings of hamstring injury as predictors for recurrent injury. J. Orthop. Sports Phys. Ther. 36:215–224, 2006.
233. Verrall, G. M., J. P. Slavotinek, P. G. Barnes, G. T. Fon, and A. J. Spriggins. Clinical risk factors for hamstring muscle strain injury: a prospective study with correlation of injury by magnetic resonance imaging. Br. J. Sports Med. 35:435–439; discussion 440, 2001.
234. De Visser, H. M., M. Reijman, M. P. Heijboer, and P. K. Bos. Risk factors of recurrent hamstring injuries: a systematic review. Br. J. Sports Med. 46:124–130, 2012.
235. De Vos, R.-J., G. Reurink, G.-J. Goudswaard, M. H. Moen, A. Weir, and J. L. Tol. Clinical findings just after return to play predict hamstring re-injury, but baseline MRI findings do not. Br. J. Sports Med., 2014. doi:10.1136/bjsports-2014-093737
236. De Vos, R. J., A. Weir, H. T. van Schie, S. M. Bierma-Zeinstra, J. A. Verhaar, H. Weinans, and J. L. Tol. Platelet-rich plasma injection for chronic Achilles tendinopathy. JAMA J. Am. Med. Assoc. 303:144–149, 2010.
237. De Vos, R.-J., J. Windt, and A. Weir. Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review. Br. J. Sports Med. 48:952–956, 2014.
238. Warren, P., B. J. Gabbe, M. Schneider-Kolsky, and K. L. Bennell. Clinical predictors of time to return to competition and of recurrence following hamstring strain in elite Australian footballers. Br. J. Sports Med. 44:415–419, 2010.

239. White, J. P., K. A. Baltgalvis, S. Sato, L. B. Wilson, and J. A. Carson. Effect of nandrolone decanoate administration on recovery from bupivacaine-induced muscle injury. J. Appl. Physiol. Bethesda Md 1985 107:1420–1430, 2009.
240. Woods, C., R. D. Hawkins, S. Maltby, M. Hulse, A. Thomas, A. Hodson, and Football Association Medical Research Programme. The Football Association Medical Research Programme: an audit of injuries in professional football--analysis of hamstring injuries. Br. J. Sports Med. 38:36–41, 2004.
241. Wright-Carpenter, T., P. Klein, P. Schäferhoff, H. J. Appell, L. M. Mir, and P. Wehling. Treatment of muscle injuries by local administration of autologous conditioned serum: a pilot study on sportsmen with muscle strains. Int. J. Sports Med. 25:588–593, 2004.
242. Wright-Carpenter, T., P. Opolon, H. J. Appell, H. Meijer, P. Wehling, and L. M. Mir. Treatment of muscle injuries by local administration of autologous conditioned serum: animal experiments using a muscle contusion model. Int. J. Sports Med. 25:582–587, 2004.
243. Yildiz, K., S. N. Efesoy, S. Ozdamar, A. Yay, C. Bicer, R. Aksu, and E. Kilic. Myotoxic effects of levobupivacaine, bupivacaine and ropivacaine in a rat model. Clin. Investig. Med. Médecine Clin. Exp. 34:E273, 2011.
244. Ziltener, J.-L., S. Leal, and P.-E. Fournier. Non-steroidal anti-inflammatory drugs for athletes: an update. Ann. Phys. Rehabil. Med. 53:278–282, 282–288, 2010.
245. Zink, W., and B. M. Graf. Local anesthetic myotoxicity. Reg. Anesth. Pain Med. 29:333–340, 2004.
246. Consumer Safety Institute. Factsheet Sportblessures (in dutch). [Factsheet sports injuries] Amsterdam 2011

Appendices

Dankwoord

Curriculum Vitae

PhD Portfolio Summary

List of Publications

Dutch HIT-study Rehabilitation Program

DANKWOORD

Bij een multicenter onderzoek zoals de HIT-studie zijn altijd zeer veel mensen betrokken, die allen een bijdrage geleverd hebben aan het succes van het project. Omdat het onmogelijk is iedereen persoonlijk te noemen wil ik hierbij alle betrokken collega's van het Erasmus MC, MC Haaglanden, UMC Utrecht, de KNVB en het AMC bedanken. Een aantal mensen wil ik in het bijzonder bedanken.

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Al het werk in dit proefschrift is het resultaat van teamwork: **het HIT-studie team**. Veel dank gaat dan ook uit naar de kern van dit team, bestaande uit: Hans Tol, Maarten Moen, Gert Jan Goudswaard en Adam Weir. Ik heb altijd met veel plezier gewerkt in dit topteam. Ik hoop dat we op eenzelfde wijze in de toekomst doorgaan met het wetenschappelijke onderbouwen van ons specialisme Sportgeneeskunde.

Dr. J.L. Tol, co-promotor, Hans. Jij bent zonder twijfel de drijvende kracht achter dit promotietraject geweest. De Lionel Messi van het HIT-studie team: zonder Hans zouden we een goed team zijn, maar met Hans wereldtop. Je bent de architect van het onderzoek en altijd bereikbaar, snel en scherp. Elk document, van artikel tot nieuwsbrief, is vormgegeven door jouw kritische blik. In een gesprek dat ik met een hoogleraar had werd je een *fenomeen* genoemd: naar mijn bescheiden mening is dit volledig waar. Je hebt ook gezorgd dat ik een half jaar in Aspetar als onderzoeker heb kunnen werken tussen de internationale Sportgeneeskundige wereldtop. Een fantastische ervaring, waar ik je zeer dankbaar voor ben.

Dr. M.H. Moen, co-promotor, Maarten. Ik ben jou veel dank verschuldigd: jij staat aan de basis van mijn (nog prille) Sportgeneeskunde carrière. Toen ik begon aan mijn coschap bij jou op de afdeling in Leiderdorp twijfelde ik erg: door een hevige blessure was mijn voetbalcarrière net geëindigd en had ik het even helemaal gehad met sport. Maar jouw enthousiasme voor het vak en de wetenschap was zo aanstekelijk dat ik er snel uit was: dat wilde ik ook. Daarna heb jij me de mogelijkheid geboden om aan het hamstringonderzoek mee te werken: een droomstart. De avondjes bier drinken in Amsterdamse kroegen waar wetenschap en alledaagse zaken de revue passeren moeten we wat mij betreft in stand houden. Veel dank voor de super leuke samenwerking en ik hoop op nog veel van hetzelfde in de toekomst.

Dr. A. Weir, co-promotor, Adam. Je bent de meest vrolijke en aardige dokter die ik ooit heb meegemaakt: een ongekende eigenschap die op iedereen met wie je samenwerkt uitstraalt. Je bent een top teamspeler en een fantastische wetenschapper: ik ben erg blij

dat we je voor het HIT-team hebben weten te strikken. De gastvrijheid van jou, Marja en de kinderen in Qatar was super. Het was een erg leuke tijd op Alfardan's Garden: BBT'en, tennissen, Dune-bashen (met jou meestal Dune-crashen): onvergetelijk!

Gert Jan Goudswaard. De *medicus practicus* van het HIT-team. Jouw uitgebreide praktijk ervaring in het professionele voetbal zijn van zeer grote waarde geweest voor het onderzoek. Voor mij als jonge onderzoeker met beperkte praktijk ervaring is de brug tussen de wetenschap en de (top)sportpraktijk vaak lastig: veel dank voor jou adviezen en bijsturing hierin.

Prof. dr. M. Maas, Mario. Veel dank voor de vele (vrije) uren die je besteed hebt aan het beoordelen van de MRIs van het hamstringonderzoek. De avonden MRIs scoren waren altijd leuk en erg leerzaam. Je werk in wetenschap en onderwijs straalt plezier uit: dit is voor mij als lerende dokter/onderzoeker zeer motiverend. Ik hoop dat ik dat later ook op die manier kan overbrengen.

Don de Winter. Veel dank voor al je ondersteuning voor het onderzoek in het MCH. Je was altijd beschikbaar om tussen je drukke poli door de injecties en testen bij proefpersonen te verrichten. Ondanks dat ik als onderzoeker slechts soms aanwezig was gaf jij me wel het gevoel dat ook ik onderdeel van de Sportgeneeskunde afdeling was: dit heb ik zeer gewaardeerd!

Peter van Veldhoven. Bedankt voor al je hulp bij het onderzoek. Ten eerste als prikker bij de KNVB, maar vooral ook voor de rol als officiële hoofdonderzoeker nadat Adam naar Qatar vertrok. Ondanks alle andere drukte bij je aanstelling in MCH was je altijd direct beschikbaar voor HIT zaken en kon de studie soepeltjes doorgaan.

Wout van der Meulen. Dank voor je hulp bij het injecteren en testen van de proefpersonen in het UMC Utrecht.

Robert-Jan de Vos. Ook jij hebt een enkele patiënt behandeld voor het onderzoek. Ik wil je echter meer bedanken voor de periode daarna. Als huisgenoten en collega's in Qatar klikte het meteen goed en zijn we goede vrienden geworden. Naast het werk delen we ook op sportief gebied delen we dezelfde interesses (op voetbalclub na dan), met mooie ervaringen zoals het fietsen van de Marmotte en de vele tennispotjes in Qatar. Ik kijk uit naar meer.

Prof. dr. S.M.A. Bierma-Zeinstra. Bedankt voor de statistische hulp die we hard nodig hadden om de HIT-studie tot een succes te maken.

Collega's van Hs-104: Belle, Vincent, Tijs, Eline, Job en Desiree. Leuke collega's zijn essentieel voor plezier in het werk: daar hebben jullie zeker voor gezorgd! Met Belle mooie sportieve uitdagingen als Alpe d'Huzes, de kwart-traithlon, schaatsen (ik ben erg blij dat we collega Sportartsen gaan worden!), Vincent altijd in voor vrijdag frietdag, Tijs op maandag plagen met de resultaten van 'onze club' (het waren goede jaren), Eline altijd gezellig op Hs-104.

Max Reijman. Het is altijd lachen met jou: ik kan je humor goed waarderen. Je was niet direct betrokken bij ons onderzoek, maar dank dat ik altijd bij je kon aankloppen voor adviezen.

Simone. Dank dat je altijd klaar stond om me te helpen bij allerhande logistieke zaken.

Ook dank aan de stagestudenten **Hein en Lisette**. Hein, we waren een opmerkelijk gezelschap: jij met een gebroken arm, ik op krukken en een manke patiënt er achteraan. Ondanks de handicaps, wel een goed team en veel lol. Lisette, jouw stage is een goed artikel geworden met veel impact in het onderzoeksveld naar MRIs bij hamstringblessures.

Dank aan de radiologie medewerkers van de Bergman Kliniek en het Diagnostische Centrum, in het bijzonder **Hazel, Chantal, Kees en Mike**. Het was erg leuk met jullie samenwerken en veel dank dat jullie altijd bereid waren een MRI ergens tussen te plannen, ook als dit ten koste ging van jullie pauze of na werktijd.

Robert, bedankt voor je hulp bij het maken en onderhouden van de website.

Uiteraard een dank aan **mijn paranimfen**. **Max**, na je vertrek naar Engeland is het contact in frequentie minder, maar de basis is sterk: we blijven goede vrienden! **Arnold**, al die jaren huisgenootschap zegt genoeg. Bedankt dat jullie me bijstaan op de grote dag.

Ten slotte mijn familie. **Papa en mama**. Bedankt voor alle onuitputtelijke liefde, zorgen en inspanningen; eerst voor het grootbrengen van ondergetekende en tegenwoordig bij het grootbrengen van onze Koen. Mijn broers **Aart en Arjan**, naast het goede broederschap ook een bedankje voor jullie bijdrage als proefpersoon aan het onderzoek; de bijnaam bij ons oude voetbalclubje als de familie Scheurink hebben jullie in ere weten te houden.

Hermien, mijn lieve vrouw. Jij bent mijn levensmaatje: bedankt dat je er altijd en overal voor me bent. Ik ben ronduit gelukkig met jou en ons zoontje Koen. En ik ben ervan overtuigd dat dit in de toekomst zo zal blijven.

CURRICULUM VITAE

Gustaaf Reurink was born on the 18th of May 1982 in Yogyakarta (Indonesia). After High School graduation at the Sint Vitus College in Bussum (The Netherlands) in 2000 he studied Human Movement Sciences at the Free University of Amsterdam. In 2006 he received his Master degree in Human Movement Sciences. Subsequently he studied Medicine at the Leiden University Medical Centre and received his Medical degree in 2010.

In 2011 he started a PhD research project on hamstring injuries at the Orthopaedic Department of the Erasmus Medical Centre in Rotterdam. The work performed in this project is described in this thesis. As part of the PhD project he worked for 6 months at the Aspetar Orthopaedic and Sports Medicine hospital in Doha (Qatar) in 2013. This collaboration resulted in several scientific publications on hamstring injuries.

In 2014 he started his traineeship in Sports Medicine at the Sport Physicians Group in Amsterdam.

PHD PORTFOLIO SUMMARY

Name PhD student:	Gustaaf Reurink
Erasmus MC Department:	Orthopaedics
PhD period:	2011 – 2015
Promotor:	Prof. dr. J.A.N. Verhaar
Supervisors:	Dr. J.L. Tol, dr. M.H. Moen, dr. A. Weir

1. PhD training	Year
Courses	
Basiscursus Regelgeving en Organisatie van Klinische trials (BROK), Rotterdam, the Netherlands	2012
Regression analysis (NIHES), Rotterdam, the Netherlands	2013
(Inter)national conferences – attendance	
FIFA Football Medicine Conference, London, Great Britain	2015
ESSKA Congress (2x), Geneva, Switserland & Amsterdam, the Netherlands	2012-2014
Danish Sports Medicine Annual Congress, Kolding, Denmark	2014
Dutch Sports Medicine Society Annual Congress (4x), Kaatsheuvel & Ermelo, the Netherlands	2011-2014
Aspetar Sports Groin Pain Conference, Doha, Qatar	2013
Dutch Orthopedic Society Annual Congress, Amsterdam, the Netherlands	2013
World Sports Trauma Congress & 7th EFOST Congress, London, Great Britain	2012
Sports & Orthopedics Foundation Lustrum Congress	2012
Dutch Society of Arthroscopy, 'sHertogenbosch, the Netherlands	2012
(Inter)national conferences – podium presentations	
The use of PRP in muscle injuries FIFA Football Medicine Conference, London, Great Britain – Invited lecture	2015
No association between MRI detected fibrosis at return to play and hamstring re-injury. Dutch Sports Medicine Society Annual Congress, Ermelo, the Netherlands ***Best Abstract Award***	2014
Therapeutic interventions for acute hamstring injuries: a systematic review. 6th Muscle Tech Network Workshop, Barcelona, Spain – Invited lecture	2014
Platelet-rich plasma injections in acute hamstring muscle injuries: a randomised controlled trial. ESSKA Congress, Amsterdam, the Netherlands ***Theo van Rens Best Paper Award***	2014
Hamstring muscle injuries (Orthopedic and Sports Medicine Review Course). ESSKA Congress, Amsterdam, the Netherlands – Invited lecture	2014
Medical treatment of acute muscle injuries. Danish Sports Medicine Congress, Kolding, Denmark – Invited lecture	2014
PRP injections in acute hamstring injuries: a double-blind randomized placebo-controlled trial. Dutch Sports Medicine Society Annual Congress, Ermelo, the Netherlands	2013

Force measurements in acute hamstring injuries: reliability and prognostic value of handheld dynamometry. 2013
Dutch Sports Medicine Society Annual Congress, Ermelo, the Netherlands

Myotoxicity of injections for acute muscle injuries: a systematic review. 2013
Dutch Sports Medicine Society Annual Congress, Ermelo, the Netherlands

Conservative treatment of proximal hamstring tendon avulsions: a prospective case series. 2013
Dutch Sports Medicine Society Annual Congress, Ermelo, the Netherlands

Reliability and validity of diagnosing acetabular labral lesions using magnetic resonance arthrography. 2013
Groin conference Aspetar Orthopaedic and Sports Medicine hospital, Doha, Qatar – Invited lecture

ACP applications in hamstring pathology. 2012
Sports & Orthopedics Foundation Lustrum Congress, Utrecht, the Netherlands – Invited lecture

Intertester reliability of the active and passive knee extension test in acute hamstring injuries. 2012
Dutch Sports Medicine Society Annual Congress, Ermelo, the Netherlands
Best Abstract Award

MRI observations at return to play after recovery from hamstringinjuries: a prospective descriptive case series. 2012
Dutch Sports Medicine Society Annual Congress, Ermelo, the Netherlands

Treatment of acute hamstring injuries; a systematic review. 2011
Dutch Sports Medicine Society Annual Congress, Kaatsheuvel, the Netherlands

Reliability and validity of diagnosing acetabular labral lesions using magnetic resonance arthrography. 2011
Dutch Sports Medicine Society Annual Congress, Kaatsheuvel, the Netherlands

Other podium presentations

Hamstring injuries 2015
Arsenal FC SEMS Conference – The muscle in sports, London, Great Britain

Recurrent hamstring muscle injury: applying the limited evidence in the professional football setting. 2015
13th Groningen Sports Medicine Symposium, Groningen, the Netherlands

The Dutch hamstring injection therapy study: results of the Dutch HIT-study. 2014
College of Club Doctors and Consultancies Symposium, Zeist, the Netherlands

Platelet-rich plasma injections in acute hamstring injuries: a double-blind randomised controlled trial. 2014
Medical Centre The Hague science day, The Hague, the Netherlands

Platelet-rich plasma injections in acute hamstring muscle injuries. 2014
12th Sportho Symposium Medical Centre The Hague, The Hague, the Netherlands

Diagnostic value of hip MR arthrography in acetabular labral lesions. 2012
Rijnland Hospital annual science day, Leiderdorp, the Netherlands
Science Award

Platelet-rich plasma injections in acute hamstring injuries. 2012
College of Club Doctors and Consultancies Symposium, Venlo, the Netherlands

Platelet-rich plasma injections in acute hamstring injuries. 2012
Professional Football Physiotherapists Society Annual Congress, Zeist, the Netherlands

Dutch hamstring injection therapy study; Dutch HIT-study. 2011
10th Sportho Symposium Medical Centre The Hague, The Hague, the Netherlands

Hamstring injuries; a returning problem. 2011
Korfball Medical Congress, Rotterdam, the Netherlands

2. Teaching	Year
Lecturing	
Hamstring injuries Boerhaave refresher course Sports Medicine, Leiden University MC, Leiden, the Netherlands	2015
PRP and its applications Sports Orthopedics Lecture Evening, Erasmus MC, Rotterdam, the Netherlands	2013
Evidence of the treatment of hamstring injuries Orthopedics Annual Science Day, Erasmus MC, Rotterdam, the Netherlands	2013
Hamstring injuries: cause and consequences Muscle injuries: new developments Expert Lectures Graduation Symposium Master Sports Physiotherapy SOMT, Amersfoort, the Netherlands	2012
Sports related muscle injuries Minor Orthopedic Sports Traumatology, Erasmus MC, Rotterdam, the Netherlands	2012
Tutor Orthopedic Sports Traumatology, Erasmus MC, Rotterdam, the Netherlands	2012
MRI of hamstring injuries 'Meet the expert' Sports Medicine Registrars Medical Centre The Hague, the Netherlands	2012
ACP in acute hamstring injuries Workshop Arthrex Annual congress Dutch Society of Arthroscopy, 'sHertogenbosch, the Netherlands	2012
Management of acute muscle injuries Meeting Olympic Medical Panel NOC*NSF, Utrecht, the Netherlands	2011
ACP injections for acute hamstring injuries; the Dutch Hamstring Injection Therapy Study Arthrex 2nd users/interest group meeting for ACP, London, United Kingdom	2011
Supervising	
Master's thesis: Prognostic value of magnetic resonance imaging for time to return to play in athletes with an acute hamstring injury: a systematic review. E.G. Brilman, Medical student Erasmus MC, Rotterdam, the Netherlands	2013
Master's thesis: Reliability of the active and passive knee extension test in patients with acute hamstring injuries. H.G. Oomen, Medical student Erasmus MC, Rotterdam, the Netherlands	2012

3. Other	Year
Reviewer for international journals: *British Medical Journal* *British Journal of Sports Medicine* *American Journal of Sports Medicine* *Journal of Science and Medicine in Sport* *Medicine & Science in Sports & Exercise* *Journal of Sport Rehabilitation* *Journal of Sport and Health Science*	2012-2015
Podcast *British Journal of Sports Medicine* Diagnosing and treating hamstring injuries	2014

LIST OF PUBLICATIONS

Reurink G, Whiteley R, Tol JL.
Hamstring injuries and predicting return to play: 'bye-bye MRI?'
Br J Sp Med 2015;49(18):1162-1163.

Pas HI, **Reurink G**, Tol JL, Weir A, Winters M, Moen MH.
Efficacy of rehabilitation (lengthening) exercises, platelet-rich plasma injections, and other conservative interventions in acute hamstring injuries: an updated systematic review and meta-analysis.
Br J Sp Med 2015;49(18):1197-1205.

Reurink G, Goudswaard GJ, Moen MH, Weir A, Verhaar JAN, Bierma-Zeinstra SM, Maas M, Tol JL.
Rationale, secondary outcome scores and 1-year follow-up of a randomised trial of platelet-rich plasma injections in acute hamstring muscle injury: the Dutch Hamstring Injection Therapy study.
Br J Sp Med 2015;49(18):1206-1212.

Reurink G, Almusa E, Goudswaard GJ, Tol JL, Hamilton B, Moen MH, Weir A, Verhaar JAN, Maas M.
No association between fibrosis on magnetic resonance imaging at return to play and hamstring reinjury risk.
*Am J Sports Med 2015;*43(5):1228-34.

Reurink G, Tol JL, De Vos RJ.
[Acute hamstring injuries in athletes].
Ned Tijdschr Geneeskd 2014;159:A8152. Article in Dutch.

Van der Made AD, **Reurink G**, Gouttebarge V, Tol JL, Kerkhoffs GM.
Outcome after surgical repair of proximal hamstring avulsions: a systematic review.
Am J Sports Med 2014; Epub ahead of print.

Reurink G, Brilman EG, De Vos RJ, Maas M, Moen MH, Weir A, Goudswaard GJ, Tol JL.
Magnetic resonance imaging in acute hamstring injury: can we provide a return to play prognosis? A systematic review.
Sports Med 2015;45(1):133-146.

Moen MH, **Reurink G**, Weir A, Tol JL, Maas M, Goudswaard GJ.
Predicting return to play after hamstring injury.
Br J Sports Med 2014;48(8):1358-1363.

De Vos R-J, **Reurink G**, Goudswaard GJ, Moen MH, Weir A, Tol JL.
Clinical findings just after return to play predict hamstring re-injury, but baseline MRI findings do not.
Br J Sports Med 2014;48(18):1377-1384.

Reurink G, Goudswaard GJ, Moen MH, Weir A, Verhaar JAN, Bierma-Zeinstra SM, Maas M, Tol JL.
Platelet-rich plasma injections in acute muscle injuries.
N Engl J Med 2014;370(26):2546-2547.

Reurink G, Goudswaard GJ, Moen MH, Weir A, Verhaar JAN, Tol JL.
Myotoxicity of injections for acute muscle injuries: a systematic review.
Sports Med 2014;44:943-956.

Reurink G, Tol JL.
Muscle research: Future perspectives on muscle analysis.
In Kerkhoffs GMMJ & Servien E (eds), *Acute Muscle Injuries,* Springer International Publishing, Switzerland, 2014;pp 129-134.

Reurink G, Goudswaard GJ, Tol JL, Almusa E, Moen MH, Weir A, Verhaar JAN, Hamilton B, Maas M.
MRI observations at return to play of clinically recovered hamstring injuries.
Br J Sports Med 2014;48(18):1370-1376.

Reurink G, Holmich P, Tol JL.
Which direction to go in hamstring research? The future of science in a field of short history.
Aspetar Sports Medicine Journal 2013;2:500-505.

Reurink G, Goudswaard GJ, Oomen HG, Tol JL, Moen MH, Verhaar JAN, Weir A.
Reliability of the active and passive knee extension test in acute hamstring injuries.
Am J Sports Med 2013;41(8):1757-1761.

Schueller-Weidekamm C, De Jonge M, **Reurink G**.
Muscle lesions
In Kramer J (eds), *MRI of the Knee,* University Publisher 3.0, Austria, 2013; pp 261-287.

Reurink G, Goudswaard GJ, Tol JL, Verhaar JAN, Weir A, Moen MH.
Therapeutic interventions for acute hamstring injuries: a systematic review.
Br J Sports Med 2012;46(2):103-109.

Reurink G, Jansen SPL, Bisselink JM, Vincken PWJ, Weir A, Moen MH
Reliability and validity of diagnosing acetabular labral lesions using magnetic resonance arthrography.
J Bone Joint Surg Am 2012;94:1643-1648.

Moen MH, Weir A, **Reurink G**, Tol JL, Backx F.
Medial tibial stress syndrome induced by methotrexate: a case report.
Turk J Rheumatol 2011;26:258-261.

Pijnappels M, Kingma I, Wezenberg D, **Reurink G**, van Dieen JH.
Armed against falls: the contribution of arm movements to balance recovery after tripping.
Exp Brain Res 2010;201:698-699.

DUTCH HIT-STUDY REHABILITATION PROGRAM

Physiotherapist supervised program
(Modified from Heiderscheit et al. 2010[103])

Phase 1:
Goals – Protection of scar formation, minimizing muscle atrophy and stimulating neuromuscular control.

Protection – Exercises limited to pain-free range of motion (ROM). No excessive lengthening or resistance training of the hamstrings

Ice application – For pain reduction ice can be applied 2-3 times a day (maximal 3-5 minutes when using ice and maximal 15-20 minutes when using a cool pack).

Exercises – Ergometer cycling, low to moderate intensity stepping exercises (such as side, grapevine and in place fast feet stepping), isometric exercises for lumbopelvic musculature, single limb balance exercises and core-stability exercises (such as prone body bridge, side body bridge and supine bent knee bridge). Exercises should be performed without pain.

Criteria for progression to next phase – 1) Normal walking stride without pain; 2) very low speed jog without pain; and 3) Pain-free isometric contraction against sub-maximal (50-70%) resistance during prone knee flexion manual strength test in 90° knee flexion.

Phase 2:
Goals – Regaining pain-free ROM and development of trunk and pelvis neuromuscular control with progressive increase in movement speed.

Protection – No end-range lengthening of the hamstrings when muscle weakness is still present.

Ice application – For pain reduction ice can be applied after exercises (maximal 3-5 minutes when using ice and maximal 15-20 minutes when using a cool pack).

Exercises – Gradual increase in hamstring lengthening and intensity of exercises. Agility drills and core-stability exercises are performed with a progressive increase in speed and intensity. Based on the patient's tolerance exercises are gradually increased in hamstring lengthening. Submaximal eccentric exercises are performed near mid hamstring length. Start with anaerobic training and sport-specific skills, but with taking care to avoid end-range lengthening of the hamstrings or substantial eccentric work. Running should not be performed at a speed greater than 50% of maximal speed.

Criteria for progression to next phase – 1) Pain-free full strength (5/5) during prone knee flexion manual strength test in 90° knee flexion; 2) Pain-free forward and backward jogging at 50% of maximum speed.

Phase 3:
Goals – Symptom-free during all activities, normal concentric and eccentric hamstring strength through full ROM and full speeds, improvement neuromuscular control of trunk and pelvis, and improvement control in sport-specific movements.

Protection – ROM is unrestricted. Sprinting and explosive acceleration should be avoided until full ROM and functional movement patterns (such as running, jumping and cutting) can be performed pain-free.

Ice application – For pain reduction ice can be applied after exercises (maximal 3-5 minutes when using ice and maximal 15-20 minutes when using a cool pack).

Exercises – More challenging core-stability exercises by incorporating asymmetrical postures and motions exercises. Eccentric exercises toward end range of motion and increasing resistance (e.g. lunche walk with trunk rotation, supine single limb chair-bridge). Agility and sport-specific drills involving quick direction changes and technique training.

Criteria for clearance to return to play – Symptom-free (e.g. pain and stiffness) during: 1) full ROM; 2) full speed sprinting; and 3) sport-specific movements (such as jumping and cutting).

Home exercise program

The home exercise program consists of the exercise program for individuals in the progressive agility and trunk stabilization (PATS) group from the study of Sherry and Best 2004[208]. Exercises are performed daily until subjects returned to unrestricted sports activity. Instructional videos of the exercises were supplied on the study website (http://www.hamstringonderzoek.nl/51/Video%27s+oefeningen).

Phase 1:
- Low- to moderate-intensity sidestepping, 3 × 1 minute;
- Low- to moderate-intensity grapevine stepping (lateral stepping with the trail leg going over the lead leg and then under the lead leg), both directions, 3 × 1 minute;
- Low- to moderate-intensity steps forward and backward over a tape line while moving sideways, 2 × 1 minute;
- Single-leg stand progressing from eyes open to eyes closed, 4 × 20 seconds;
- Prone abdominal body bridge (performed by using abdominal and hip muscles to hold the body in a face-down straight-plank position with the elbows and feet as the only point of contact), 4 × 20 seconds;
- Supine extension bridge (performed by using abdominal and hip muscles to hold the body in a supine hook lying position with the head, upper back, arms, and feet as the points of contact), 4 × 20 seconds;
- Side bridge, 4 × 20 seconds on each side;
- Ice while sitting for 20 minutes.

Criteria for progression to next phase:
1) Able to walk pain-free with normal gait pattern (e.g. same stride length and stance time on the injured leg and stance leg;
2) Able to do a pain-free high knee march.

Phase 2

- Moderate- to high-intensity sidestepping, 3 × 1 minute;
- Moderate- to high-intensity grapevine stepping, 3 × 1 minute;
- Moderate- to high-intensity steps forward and backward while moving sideways, 2 × 1 minute;
- Single-leg stand windmill touches, 4 × 20 seconds of repetitive alternate hand touches;
- Push-up stabilization with trunk rotation (performed by starting at the top of a full push-up, then maintain this position with 1 hand while rotating the chest toward the side of the hand that is being lifted to point toward the ceiling, pause and return to the starting position), 2 × 15 repetitions on each side;
- Fast feet on the spot (performed by jogging in place with increasing velocity, picking the foot only a few inches off the ground), 4 × 20 seconds;
- Proprioceptive neuromuscular facilitation trunk pull-downs with Thera-Band, 2 × 15 to the right and left;
- Symptom-free practice without high-speed maneuvers;
- Ice for 20 min if any symptoms of local fatigue or discomfort are present.

Notifications:

- Intensity of each exercise should be such that the patient can perform the exercise pain-free;
- Low intensity: a velocity of movement that is less than or near that of normal walking;
- Moderate intensity, a velocity of movement greater than normal walking but not as great as sport;
- High intensity, a velocity of movement similar to sport activity.