



Contents lists available at ScienceDirect

Journal of Science and Medicine in Sport

journal homepage: www.elsevier.com/locate/jsams



The value of MRI STIR signal intensity on return to play prognosis and reinjury risk estimation in athletes with acute hamstring injuries

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ARTICLE INFO

Article history:

Received 10 November 2020

Received in revised form 26 January 2021

Accepted 14 February 2021

Available online xxx

Keywords:

Hamstring muscles

MRI

Reinjury

Return to play

Injury

Sports and exercise medicine

ABSTRACT

Objectives: Previous studies have shown low to moderate evidence for a variety of magnetic resonance imaging (MRI) features as prognostic factors in athletes with hamstring injuries. Short-tau inversion recovery (STIR) signal intensity has not yet been investigated for assessing the prognosis of acute muscle injuries. Our aim was to explore the relationship between MRI STIR signal intensity and time to return to play (RTP) and to investigate the association between MRI STIR and reinjury risk in athletes with acute hamstring injuries.

Study design: Case-control study.

Methods: We used MRI STIR to measure intramuscular signal intensity in patients with clinically diagnosed hamstring injuries at two time points: at injury and RTP. At injury, we calculated the association of MRI STIR signal intensity with the time to RTP and reinjury risk. At RTP, the association of MRI STIR signal intensity and reinjury risk and the change in MRI STIR signal intensity over time on reinjury risk was evaluated.

Results: 51 patients were included. We found increased MRI STIR signal intensity: (1) at time of injury not to be associated with time to RTP, (2) at time of injury to be associated with a slightly lower risk for reinjury: odds 0.986 (0.975–0.998, $p = 0.02$) and (3) at RTP not to be associated with reinjury risk. (4) We found no association between the change in MRI STIR signal intensity over time and reinjury risk.

Conclusion: Increased MRI STIR signal intensity at injury has no value in time to RTP prognosis, but is associated with a reduced reinjury risk.

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Practical implications

- Intra-muscular signal intensity after injury has no value in predicting time to RTP.
- Intra-muscular signal intensity after injury is associated with a slightly reduced risk on reinjury.

Abbreviations: MRI, magnetic resonance imaging; STIR, short-tau inversion recovery; RTP, return to play; PRP, platelet rich plasma.

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<https://doi.org/10.1016/j.jsams.2021.02.008>

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- The present findings may encourage clinicians to leave the MRI aside in decision making with regard to RTP.

1. Introduction

Hamstring strain injuries (HSI) are known to be one of the most common injuries in sports.^{1,2} They often result in lengthy absence from sport, ranging from a couple of weeks to several months and high recurrence rates, ranging from 12 to 33%.¹ There is a clear clinical need for either primary prevention or proper counseling to minimize the risk of recurrence.³

Systematic reviews have shown that there is no strong evidence for commonly used Magnetic resonance imaging (MRI) parameters

in predicting return to play (RTP) or reinjury risk.^{4,5} These MRI findings include but are not limited to: radiological grade,¹¹ radiological size,^{6,7,8} absence of hyperintensity^{6,8,9} and radiological location and tendon involvement.^{7,10} It was shown that the majority of the correlations were found by univariate analysis, had a high risk of bias and were often conflicting.^{4,5}

A potentially relevant MRI feature that has not yet been investigated is the signal intensity on fluid sensitive sequences and their changes over time. The use of fluid sensitive sequences is not new in HSI research.^{10,12} Some lesions may appear brighter white to clinicians than other lesions, the brightness (i.e. signal intensity) can be measured on fluid sensitive sequences. This has not yet been investigated. Commonly adopted methods to visualize edema on fluid sensitive sequences are (1) Short-tau inversion recovery (STIR), (2), frequency selective fat suppression and (3) Dixon.¹³ Quantification of signal intensity on fluid sensitive sequences has shown promise for assessing the severity of a variety of myopathies characterized by intra-muscular edema.¹⁴ Quantification of signal intensity has also been used in the assessment of wrist injuries of gymnasts,¹⁵ and to assess disease activity in juvenile idiopathic arthritis.¹⁶ As edema and hemorrhage are absorbed over time, changes in signal intensity may be associated with muscle recovery. We hypothesized that the extent of increased signal intensity on fluid sensitive sequences is associated with a longer period until RTP and an increased reinjury risk.

The purpose of this paper is to explore the relationship between MRI STIR signal intensity and time to return to play and to investigate the association between MRI STIR and reinjury risk in athletes with acute hamstring injuries. In order to do so, we calculate the associations of MRI STIR signal intensity: (1) at injury on time to RTP, (2) at injury on reinjury risk, (3) at RTP on reinjury risk and (4) the change in MRI STIR signal intensity on reinjury risk.

2. Methods

The patients in this study consist of a cohort that participated in a double blind randomized controlled trial on the effect of platelet-rich plasma (PRP): Dutch trial register number 2771. Participants were enrolled between February 2011 and November 2012. 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. Similar studies concerning MRI at injury with this cohort ($n = 165$, $n = 64$, $n = 70$) and RTP with this cohort ($n = 108$ & $n = 53$) were performed by our study group.¹⁷⁻²¹ These studies specifically looked at intra-muscular tendon injury, radiological size of the lesion, radiological grade of the injury and fibrosis, absence of increased intra-muscular signal intensity at RTP and the association with re-injury. The prognostic value of quantified MRI STIR signal intensity was not investigated as part of these studies. The methods and results of this study have been comprehensively described previously.²¹ In brief, patients were randomly allocated to the placebo or PRP group. The control group received 3 ml saline injections, the intervention group received 3 ml PRP injections. Both groups received two injections at the site of maximal muscle injury: the first within 5 days of injury, the second 5-7 days later. Participants of both groups completed an identical standardized rehabilitation program which has previously been described in detail.²¹ In brief: both groups performed an identical daily progressive phased, criteria-based rehabilitation program consisting of daily home exercises and twice weekly physiotherapist supervised training sessions. Patients were instructed to keep daily logs to improve and monitor adherence. The physiotherapist supervised program was modified from Heiderscheit et al., 2010.³

Table 1
 Eligibility criteria.

Inclusion criteria	Exclusion criteria
* Age 18-50 years	* Contraindication to MRI
* Clinical diagnosis of acute hamstring injury	* Chronic hamstring injury
* Presenting and MRI within 5 days of injury	* Cause of injury is an extrinsic trauma
* MRI confirmed grades I or II hamstring lesion	* Not capable of performing rehabilitation
* Second MRI available within 7 days of RTP	* No intention to return to full sports activity
* Presence of increased signal intensity on initial scan	* Unwilling to receive the intramuscular injections
	* No RTP MRI available
	* More than 7 days between RTP and second MRI
	* No Reinjury data available

RTP, Return to play; MRI, magnetic resonance imaging.

Clearance for sport resumption was given by a sports medicine physician once the athlete successfully and asymptotically fulfilled the rehabilitation program supervised by a sports physiotherapist. The athlete had to be symptom-free (e.g. pain and stiffness) during: full range of motion, full speed sprinting and during sport-specific movements such as jumping and cutting.

Participants were followed over the course of one year after initial injury to register reinjuries. Reinjury was defined as an acute onset of posterior thigh pain at the same side as the initial injury resulting in absence from play. Athletes were requested to contact the coordinating researcher immediately in the event of a suspected reinjury, and reinjury occurrence was monitored at 4, 8, 16, 26, and 52 weeks with telephone calls to the participants. This original study found no differences between PRP and placebo injections on the time to RTP and reinjury rate within one year, neither on any of the hamstrings function related secondary outcome measures (e.g. strength, flexibility, subjective recovery). Eligibility criteria of the present study are presented in Table 1. These criteria consists of the eligibility criteria of the PRP study and the presence of both a baseline and RTP MRI.

All participants underwent MRI twice. The first MRI was performed within 5 days of the initial injury and the second within 7 days of RTP. In all cases the initial MRI preceded the injection procedure. Participants of the current study were both from the PRP and Saline group. Since the baseline MRI is made prior saline and PRP administration, the injection will not have effect on the measurements taken of the baseline MRI. To correct for a possible confounding effect of the Saline or PRP injection on the RTP MRI measurements we will adjust for the intervention of a PRP or Saline injection. Effect of these injections seem unlikely as histopathological rodent studies with saline injections showed only minimal edematous changes for the first two days and RTP MRI was conducted at a median of 14 days after the final injection.²²

MRI settings were kept constant across patients. Please see Supplementary Appendix for MRI protocol details.

Image acquisition is described in detail in Supplementary Appendix, in brief: two MRI images per patient were recorded using the ImageJ software program (National Institutes of Health, Bethesda, Maryland, USA): one T0 image (MRI at time of injury) and the corresponding RTP image. As we were specifically interested in intra-muscular edema and hemorrhage, we only measured increased signal intensity within the muscle. Increased signal intensity was defined as an abnormally increased signal in the intra-muscular tissue compared with the unaffected surrounding muscle tissue. Images were matched using anatomical landmarks. Signal intensity was quantified using the gray value measurement tool of ImageJ. Signal intensity is expressed in Gray value. Gray value is

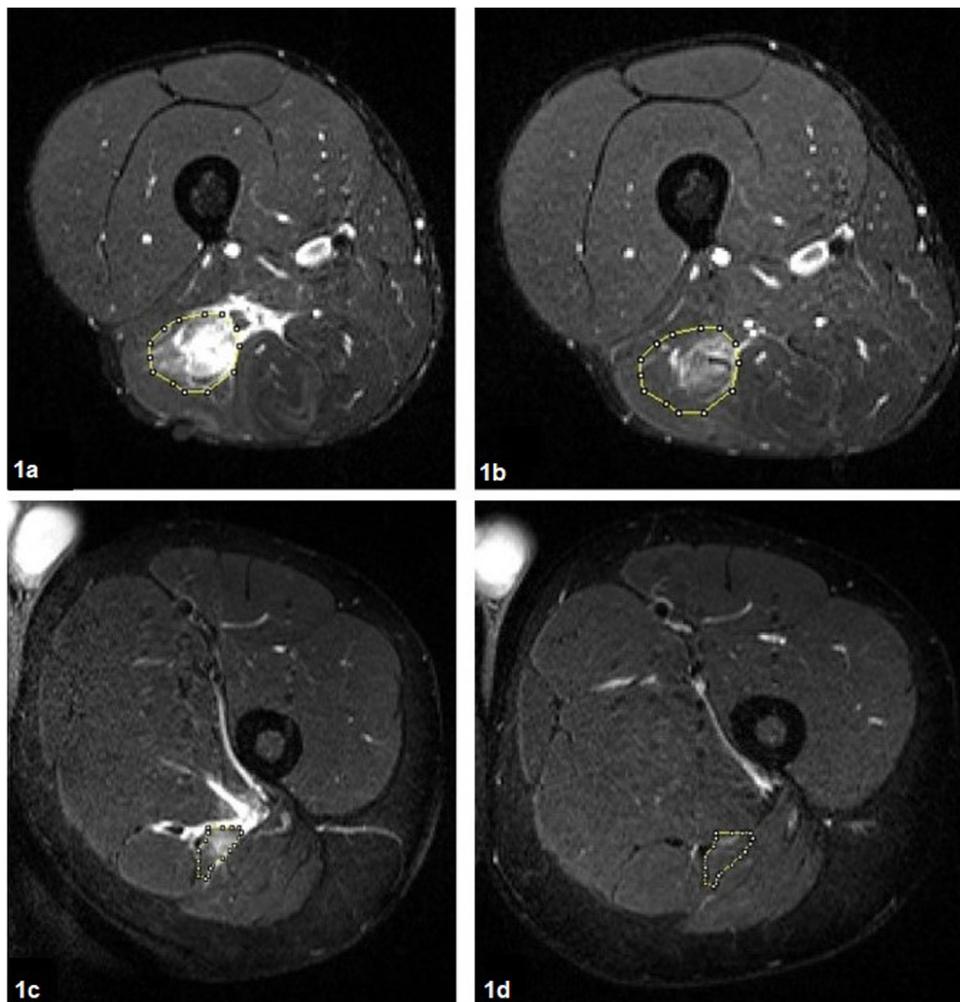


Fig. 1. (A) Short tau-inversion recovery (STIR) image of the initial injury showing increased intra-muscular signal intensity of the musculus biceps femoris, indicating edema and hemorrhage. The area of increased signal intensity is encircled in order to measure the mean intra muscular signal intensity. (B) STIR image at RTP showing a reduction of edema and hemorrhage compared to the initial injury. The measurement template used for the initial injury was positioned in such a way that it would correspond to the image of initial injury. Measurements were taken and recorded for further analysis. (C) STIR image at injury depicting an example of minor increased signal intensity. (D) STIR image at RTP showing an almost complete resolution of edema and hemorrhage compared to the initial injury.

defined as the sum of the gray values of all the pixels divided by the number of pixels within a selection (Fig. 1).

As in principle, absolute signal intensities cannot be compared directly between different scans, signal intensity was normalized before analysis, please see Supplementary Appendix for a detailed description of this procedure. In brief: we performed normalization by taking 3 reference measurements of the vastus intermedius in the same image, and dividing the mean signal intensity within the ROI in the injury by the mean signal intensity in these reference measurements as illustrated in Fig. 2 in Supplementary Appendix.

Statistical analysis was performed using SPSS software (V.20.0; SPSS, Chicago, Illinois, USA). We used the independent *t*-test to analyze differences in intra-muscular signal intensity between groups. To assess the association of increased intra-muscular signal intensity on time to RTP and reinjury risk, linear regression and logistic regression were deployed respectively. We adjusted for ipsilateral hamstring injuries, Saline and PRP injections and age by adding these variables as covariates to the linear and logistic regression analysis. Intra- and interobserver reproducibility was determined by computing the intraclass correlation coefficients (ICC) from two-way mixed-effects ANOVA. Please see Supplementary Appendix for details on the reliability analysis and details about statistics.

3. Results

We included 51 patients that met the eligibility criteria (Table 1) in the analysis. In total 29 of 80 patients were excluded of which the majority ($n = 16$) were excluded due no follow-up MRI was available. In the original study 6 of 80 patients did not complete the 1 year follow-up, 4 were censored as they sustained another injury before they returned to play. 1 patient was lost to follow-up after RTP and 1 patient did not return to play within the study period. All of these patients were excluded in the current study either due no RTP MRI was available or the lack of reinjury data. The flow diagram (Fig. 3) in Supplementary Appendix gives an overview on exclusion criteria. Patient characteristics are summarized in Table 2. The median time to RTP was 42 days (range 14–99 days). The median time between injury and the first MRI was 2 days (range 1–5 days). The median time between RTP and second MRI was 4 days (range 0 days before – 7 after RTP). The median time between final injection and second MRI was 23 days (range 5–71 days).

Intra-observer variability of the outcome measurement RTP_N and $T_{0,N}$ after normalization were excellent: $ICC = 0.98$ (0.96–0.98). Inter-observer variability of these measurements were excellent as well: $ICC = 0.98$ (0.94–0.97).

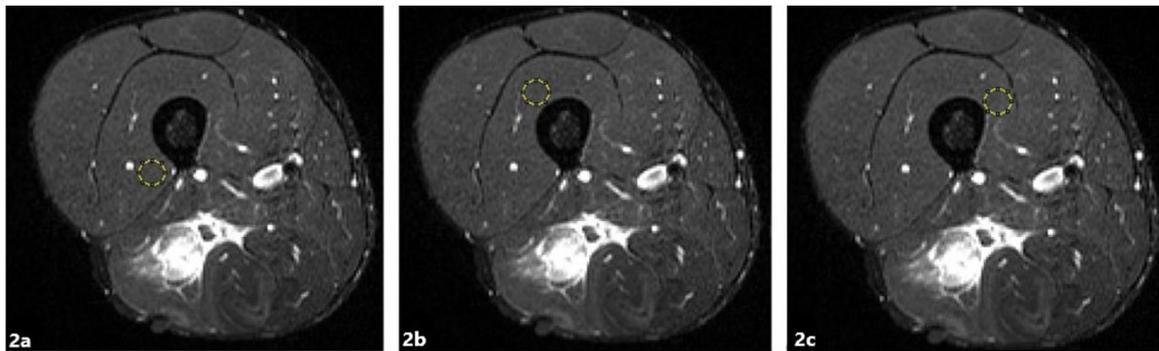


Fig. 2. (A,B&C) STIR images of the initial injury showing increased intra-muscular signal intensity of the biceps femoris muscle indicating edema and hemorrhage. Normalization measurements were taken at the vastus intermedius muscle in such a way that no vessels or fibrous tissue was incorporated. Generally, one measurement was taken at the (A) lateral section of the vastus intermedius muscle, one at the (B) middle section) and one at the (C) medial section. In rare occasions, presence of vessels or the size of the intermedius muscle did not allow for measurements according to the described method. In this case two measurements would be taken at either the lateral, medial or inner section depending on which section was not measurable.

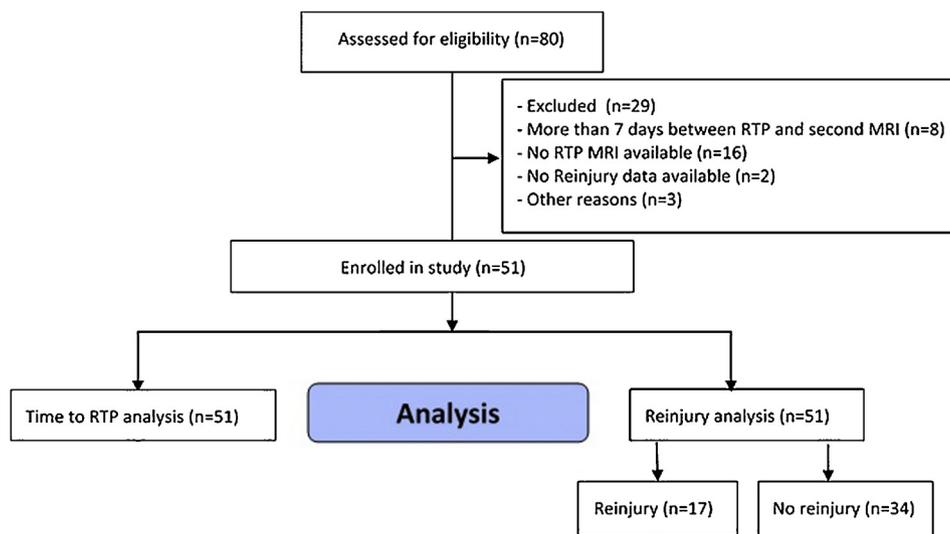


Fig. 3. Flow diagram depicting patients included in the study.

Table 2
 Patient characteristics *n* = 51.

Median age (range)	27 (18–45)
Gender, male/female	50/1
Sports	
Football	39
Field hockey	7
American football	1
Tennis	1
Athletics	3
Level of sports	
Competitive	38
Recreational	13

A Kolmogorov-Smirnov test indicates that the T0 and RTP signal intensity measurements were normally distributed $D(53)=0.06$, $p > 0.20$ and $D(53)=0.09$, $p > 0.20$. Linear regression showed no significant association between baseline STIR values and time to RTP: beta coefficient -0.001 ($-0.008-0.007$, $p = 0.98$).

The participants without a reinjury within 1 year after primary injury, had significantly increased intra-muscular signal intensity on the baseline MRI compared to the participants with a reinjury; 241 (95% CI, 221–261) vs. 198 (95% CI, 169–227), $p = 0.02$, Cohen's $d = 0.74$ indicating a medium effect size. The significant difference between groups at baseline was further analyzed using logistic regression showing an odds ratio of 0.986 (0.975–0.998, $p = .02$),

indicating an increased risk of reinjury in patients with lower intra-muscular signal intensity at time of injury. No evidence was found of a confounding effect of the variables: previous hamstring injury, PRP-, Saline injection or age.

No significant difference was detected at the MRI at RTP_N between the group without a reinjury and with reinjury; 139 (95% CI, 125–153) vs. 122 (95% CI, 104–140), odds 0.987 (0.970–1.005, $p = 0.15$).

No significant difference was detected in 'intra-muscular signal intensity' reduction between the injury MRI and the RTP MRI, odds 0.986 (0.972–1.001, $p = 0.06$) (Table 3).

4. Discussion

This is the first study that evaluated the value of MRI STIR signal intensity for acute hamstring injuries. There are two main findings. Firstly, intra-muscular signal intensity on fluid sensitive MRI images at time of injury is not associated with the time to RTP. Secondly, lower signal intensity at injury is associated with an increased risk for reinjury.

We did not find an association between MRI STIR signal intensity at time to RTP MRI and reinjury risk. There was no association between time-course MRI changes of intra-muscular signal intensity and reinjury risk.

Table 3
 Mean increased intra-muscular signal intensity values on fluid sensitive MRI Sequences in patients with and without reinjury.

	Reinjury (95% CI) (n = 17)	No reinjury (95% CI) (n = 34)	Total (95% CI) (n = 51)	Independent T-test p
$T_{0,N}^*$	198 (169–227)	241 (221–261)	227 (210–244)	0.02*
RTP_N	122 (104–140)	139 (124–153)	133 (122–144)	0.15
$\Delta RTP_N - T_{0,N}^\circ$	76 (55–98)	102 (86–118)	94 (81–107)	0.06

$T_{0,N}$ time of initial injury; RTP_N , Return to play; MRI, magnetic resonance imaging.
 √95% CI interval of the mean.

*Statistically significant difference between reinjury and no reinjury $p = 0.01$.

° Mean difference in increased intra-muscular signal intensity between RTP and T0 relative to T0.

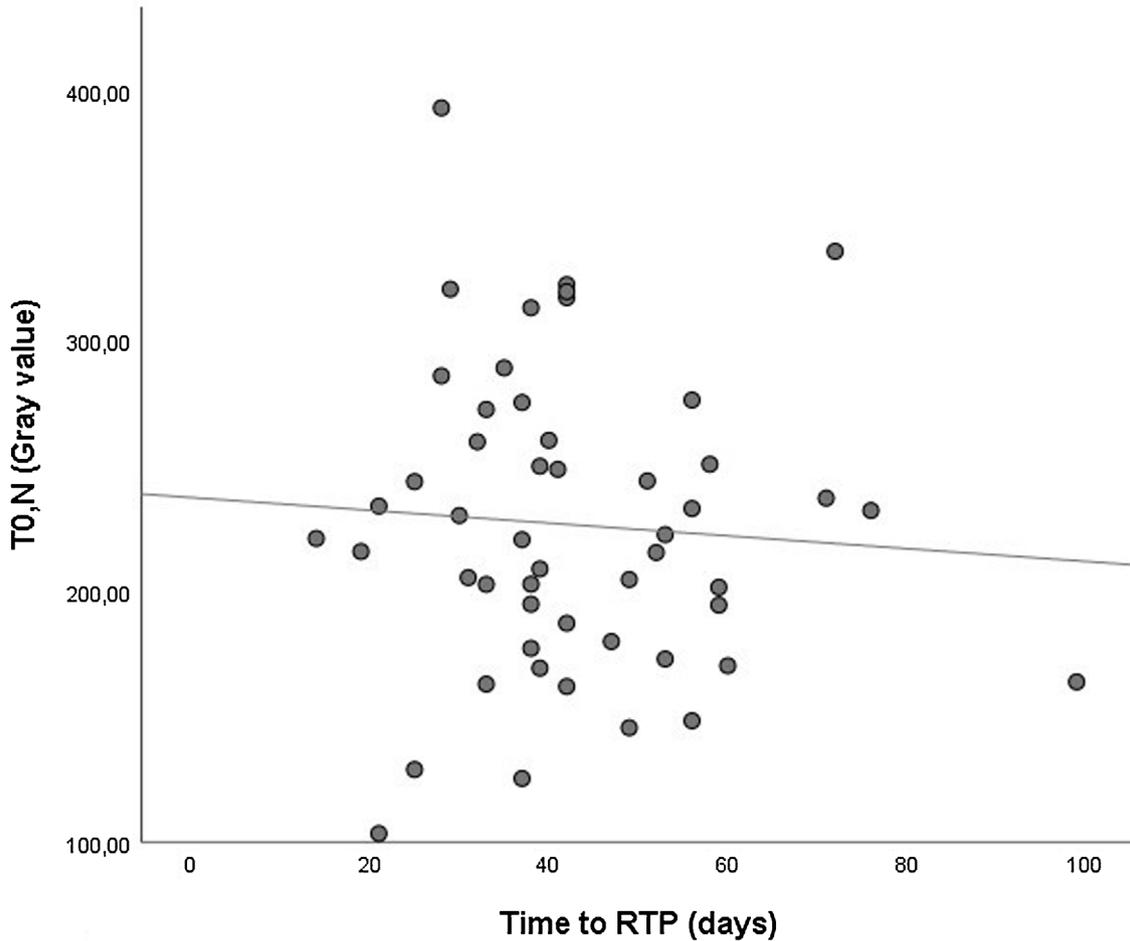


Fig. 4. Scatterplot depicting the relationship between time to RTP and ‘intra-muscular signal intensity’ at time of injury.

We found no association between increased intra-muscular signal intensity on MRI at injury and the time to RTP. The association between signal intensity at injury and time to RTP has never been investigated before. Before the study we hypothesized that increased signal intensity could be associated with increased time to RTP as it may reflect the extent of inflammation. Based on our findings, clinicians should not use signal intensity on fluid sensitive MRI sequences for RTP prediction. The lack of correlation is depicted in Fig. 4.

We found increased intra-muscular signal intensity after injury to be associated with a lower risk for reinjury. We had hypothesized that increased signal intensity after injury would be associated with a greater risk of reinjury. The association we found is counterintuitive as it shows increased signal intensity was associated with a better outcome. The difference in signal intensity between groups suggests a possible protective association of increased-intra-muscular signal intensity on reinjury risk. Increased intra-muscular

signal intensity on MRI fluid sensitive sequences is commonly considered to reflect increased intracellular or extracellular free water, typically described as muscle edema.^{23,24} At present the pathophysiological significance of increased signal intensity on MRI after injury remains unclear.²⁵ There is no research to compare our results with as this has not been investigated in humans before. Cutlip et al. used a contraction-induced hamstring injury rat model to study the effect of increasing stretch-shortening contraction (SSC) repetition on MRI signal intensity and histopathological findings. They found that increasing the SSC repetition (i.e., increasing stress on the hamstring muscles) corresponded with increased signal intensity on fluid-sensitive MRI sequences and increased inflammatory cells and degenerative myofibers on histologic analysis.²⁶ This finding shows that signal intensity can represent damage but also the extent of inflammation, which is one of the first important steps in muscle recovery.

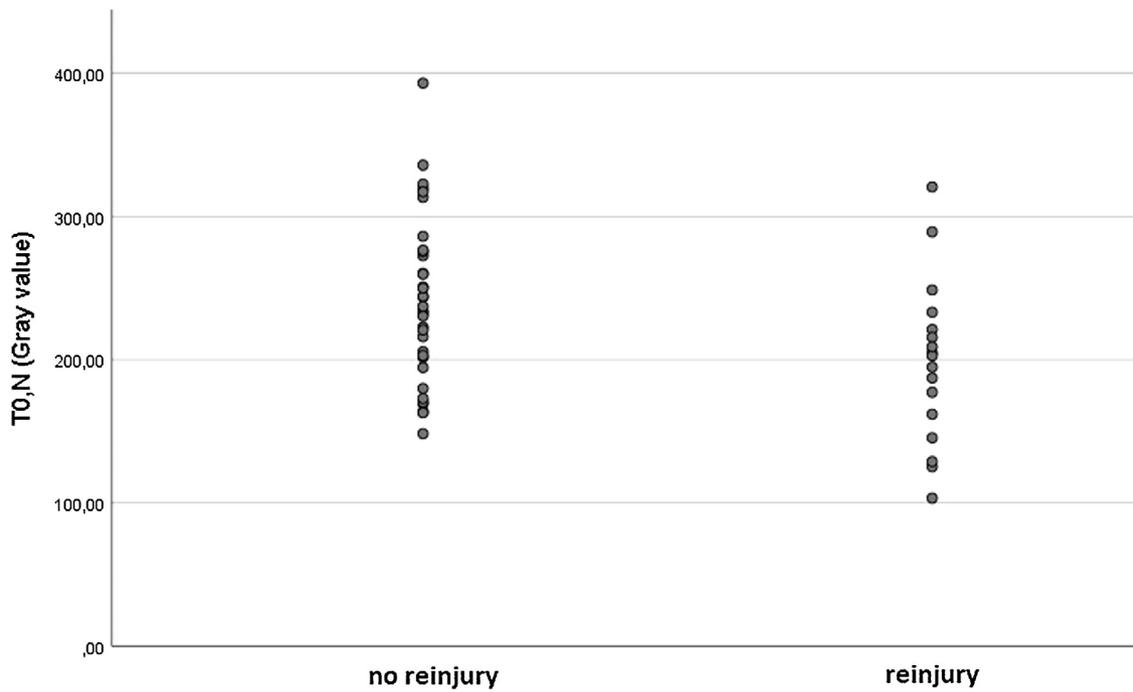


Fig. 5. Scatterplot depicting the overlap of normalized mean signal intensity at injury between subjects with and without reinjury. The values shown are all measurements of the study.

In our cohort 17 of the 51 athletes (33%) sustained a reinjury within 12 months after primary injury yielding a pretest probability of 33%. This corresponds with a pre-test odds for sustaining a reinjury of: $\frac{\text{Probability reinjury}(33\%)}{\text{Probability no reinjury}(66\%)} \approx 0.5$. The patients that sustained a reinjury had a mean signal intensity at injury of 198 (gray value) whereas patients that did not sustain a reinjury had a mean signal intensity of 241 (gray value). To illustrate the magnitude of the association we found, we present two dummy athletes. Athlete A and B had at injury an intra-muscular signal intensity of 200 and 250 (gray value) respectively. We found in our cohort an odds ratio of 0.986 (0.975–0.998, $p = .02$). This implies that a change of 1 unit in intra-muscular signal intensity after injury is associated with a change of odds of 0.986 on sustaining a reinjury. For dummy athlete B with a signal intensity of 50 units higher than dummy athlete A, the change of odds is $0.986^{50} \approx 0.5$, resulting in a post-test odds for sustaining a reinjury of $0.5 \cdot 0.5 = 0.25$. As the probability is equal to odds divided by (1 + odds), we can calculate the post-test probability of sustaining a re-injury is 20% (95%CI, 12–31%). This finding means that the specific MRI finding of an increased intra muscular signal intensity of 50 (gray value) reduces the pretest probability of 33% to a posttest probability of 20% (95%CI, 12–31%), which will not make it easier for the clinician in terms of reinjury risk estimation due to the very small decrease in probability and the relatively wide confidence interval. Also, due to the considerable overlap in increased intra-muscular signal intensity between groups, this finding is likely to be of limited value for the individual athlete in clinical practice (Fig. 5).

Participants received two injections of PRP or Saline which may influence the findings on RTP MRI's. These RTP MRI's were performed at a median of 23 days (range: 5–71) after the last injections. Histopathological studies in laboratory rodents and rabbits showed only minimal edematous changes for the first two days after administration of saline injections. This makes it unlikely that the injections significantly affected the results three weeks after the injections. Less is known about PRP injections. Tsai et al., used a rodent model with partial transverse incisions in the gastrocnemius muscle to mimic muscle injury and subsequently assessed

the effect of PRP injections vs. a control group where no injection was given. Histopathology showed no significant difference in inflammation after 5 days of injury between both groups.²⁷ It seems unlikely that PRP injections had an effect on edema on the MRI at RTP due to: (1) the median time of 23 days (range 5–71 days) between the final PRP injection and MRI assessment at RTP and (2) the absence of evidence of PRP injections to be a confounder as shown by our study.

Our study has a number of strengths and limitations. Please see Supplementary Appendix.

5. Conclusion

In summary this is the first study to investigate the value of intra-muscular signal intensity on time to RTP prognosis and reinjury risk estimation after acute hamstring injury. Intra-muscular signal intensity at injury was not associated with the time to RTP. Having higher signal intensity present on the baseline MRI was associated with a slightly lower risk of reinjury. Due to considerable overlap in increased intra-muscular signal intensity between groups, this finding is of limited value for reinjury risk estimation in the individual athlete.

Data sharing statement

Additional unpublished data are available on request by contacting the corresponding author. The unpublished data contains the detailed measurements of the increased intra-muscular signal intensity and the intra and inter-observer variability measurements.

Funding

The Dutch randomized controlled trial was supported by the Royal Dutch Football Association and Arthrex Medizinische Instrumente GmbH. No funding was received for the current study.

Declarations of interest

None declared.

Acknowledgements

RAH was involved in the study design, analysis and interpretation of data and drafting of the manuscript. GR was involved in data collection, study design and drafting of the manuscript. JLT, AW, MHM, JMH and MM were involved in data interpretation and drafting of the manuscript. The authors would like to thank Amsterdam University Medical Centers for granting research approval. This study was conducted using data of the Hamstring Injection Therapy (Dutch) study. The hamstring injection therapy study was supported by Arthrex Medizinische Instrumente GmbH and the Royal Dutch Football Association. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.jsams.2021.02.008>.

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