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MLG-R: Nova proposta de classificació per les lesions musculars (Lesions dels isquiotibials)

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DOCTORAL THESIS

MLG-R: A new muscle injury classification proposal

(Hamstring injuries)

MLG-R: Nova proposta de classificació per les lesions musculars

(Lesions dels isquiotibials)

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“Mira y respeta al de delante como a un igual.”

"Look at and respect the person in front of you as an equal."

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ABSTRACT

Muscle injuries are common in many sports. They require medical consultation by athletes, resulting in a significant amount of time loss, and challenge even the most experienced health professionals. This happens because muscle injuries are not yet fully understood, and there are several reasons for that, including the lack of good epidemiological data, and an inconsistent classification.

The persistent unsuccessful attempts to establish a classification system with broad acceptance has resulted from different factors, such as: limited clinical applicability, inclusion of subjective findings, and use of ambiguous terminology. How a muscle injury is named has a deep impact not only on the communication with patients, colleagues, or technical staff, but also on the ability to extract collective knowledge from the event and experiences associated with the injury. The literature on muscle injuries uses multiple names for their description: myotendinous, musculotendinous, myoaponeurotic, myofascial, epymisial, among others. The primary aim of these names is to describe the topographical location of the injury in relation to the length of the affected myotendinous junction (MTJ) and, therefore, the thickness of the extracellular matrix affected. The reason behind the decision of health professionals to name an injury in a certain way depends on various factors (background, country of origin, previous work experiences, and place of training), and the consequent variability should be mitigated.

The aims of this thesis were the following: 1) design a classification system for muscle injuries based on the current scientific evidence (capable of describing the injury location, grade, and evolution in time, in an objective way); 2) test the ease of use and application of the injury classification system designed in a clinical setting 3) Use such system to identify predictive factors for Return to Play (RTP) following injury in elite football players.

We selected the hamstring muscle group because of their high injury incidence in athletes and the extensive literature available on hamstring injuries. The designing process of the initial proposal was divided in three stages: (1) identify existing evidence on the risk and prognostic factors for hamstring injuries; (2) discuss these factors with the institutions and experts involved in the project; and (3) elaborate the final classification system. The Classification of Malignant Tumors (TNM) was used as a model.

The extracellular matrix (ECM) and its role in force generation and transmission is a key factor in determining signs, symptoms, and prognosis of muscle injuries. Therefore, we designed our classification system for hamstring injuries with the main aim to evaluate the amount and severity of the ECM damage. Importantly, this is a novel approach.

Our system includes four main categories: mechanism of injury (M), location of injury (L), grading of severity (G), and number of muscle reinjuries (R). The classification system can therefore be abbreviated as MLG-R. Category M stands for direct and indirect muscle injuries. Category L (location) distinguishes injuries as located at the proximal, middle, or distal third of the muscle belly, with further subclassification according to the relationship with the proximal or distal region of the MTJ. For the grading (G) category, the injury is evaluated on the basis of MRI findings. Finally, reinjury (R) is defined as the occurrence of a muscle injury affecting the same muscle and/or MTJ as the initial injury during the rehabilitation process or within the next two months after the RTP.

Because of the different approach of our classification system and its original structure, a second article was published to describe the use the MLG-R proposal. This paper is not included as a part of this thesis, however for a finer understanding of the work, it has been added as a complementary source.

Finally, to achieve our third and last aim, we evaluated the capability of the MLG-R classification system to grade hamstring injuries by severity, offer a prognosis for the RTP, and identify injuries with higher risk of reinjury. Finally, to assess the consistency of our classification system, we investigated its intra- and inter-observer reliability.

We used a sample of hamstring injuries that occurred in male football players from FC Barcelona (FCB) — Senior A and B and the two U-19 teams—between February 2010 and February 2020. Seventy-six hamstring injuries were identified in 42 different players. Of these, 50 (65.8%) were Grade 3^r, 54 (71.1%) affected the biceps femoris long head (BFlh), and 33 (43.4%) were located at the proximal MTJ. The mean RTP for Grade 2, 3, and 3^r injuries was 14.3, 12.4, and 37.0 days, respectively. Injuries affecting proximal MTJ had a mean RTP of 31.7 days, while those affecting distal MTJ had a mean RTP of 23.9 days. The analysis of grade 3^r BFlh injuries located at the free tendon (FT) showed a median RTP of 56.0

days, while the injuries located at the central tendon (CT) had a shorter median RTP of 24.0 days (p=0.038).

The statistical analysis showed an excellent predictive power of the MLG-R classification system with a mean absolute error of 9.8 days and an R-squared of 0.48. The most important factors influencing RTP were the location of the injury (FT of the BFlh) and its Grade (Grade 3^r).

For all the items of the MLG-R classification system, the intra- and inter-observer reliability was excellent (k>0.93) except for fibers blurring (κ=0.68).

The main determinant for long RTP after hamstring injury is the involvement of connective tissue structures. The fact that the RTP for Grade 3^r injuries in the BFlh or the Semitendinosus (SMT) FT is longer than the RTP of injuries in the CT supports the concept that injuries affecting the proximal part of the MTJ are worse than the ones affecting its distal part.

To conclude, MLG-R is a new classification system for hamstring injuries and provides a consistent approach for clinical health professionals to adopt in professional football.

RESUMEN EN CASTELLANO

Las lesiones musculares son frecuentes en muchos deportes. Los deportistas consultan de forma frecuente debido a ellas, causan importantes tiempos de baja y suponen un reto incluso para los profesionales sanitarios más experimentados. Esto es a causa de un incompleto conocimiento sobre ellas por la falta de buenos datos epidemiológicos y clasificaciones mejorables.

Los diversos intentos infructuosos de establecer un sistema de clasificación con amplia aceptación se han debido a diferentes factores, como: aplicabilidad clínica limitada, exceso de subjetividad y uso de terminología ambigua. La forma de denominar una lesión muscular tiene un profundo impacto no sólo en la comunicación con pacientes, colegas o personal técnico, sino también en la capacidad de extraer conocimiento colectivo del episodio y lo relacionado a la lesión. Las lesiones musculares en la literatura se nombras de diversas maneras: miotendinosa, musculotendinosa, mioaponeurótica, miofascial, epimisial, entre otros. El objetivo principal de estas denominaciones es describir la localización topográfica de la lesión en relación con la anatomía de la unión miotendinosa (UMT) afectada y, por tanto, el grosor de la UMT en la zona de la lesión. El motivo que lleva a los profesionales sanitarios a denominar una lesión de una determinada manera depende de diversos factores (experiencia, país de origen, experiencias laborales previas y lugar de formación), es necesario reducir esta subjetividad.

Los objetivos de esta tesis eran los siguientes 1) diseñar un sistema de clasificación de lesiones musculares basado en la evidencia científica actual (capaz de describir la localización de la lesión, el grado y la evolución en el tiempo, de forma objetiva); 2) que sea de fácil aplicación en un entorno clínico 3) utilizar dicho sistema para identificar factores predictivos del Return to Play (RTP).

Se eligió el grupo muscular de los isquiotibiales debido a su alta incidencia de lesiones en deportistas de diferentes deportes y a la extensa literatura disponible. El proceso de diseño de la propuesta inicial se dividió en tres etapas: (1) identificar las evidencias científicas existentes sobre los factores de riesgo y pronóstico de las lesiones de isquiotibiales; (2) debatir estos factores con las instituciones y los expertos implicados en el proyecto; y (3) consensuar

una propuesta final para el sistema de clasificación. Se utilizó como modelo la Clasificación de Tumores Malignos (TNM).

La matriz extracelular (MEC) y su papel en la generación y transmisión de fuerza es un factor clave para determinar los signos, síntomas y pronóstico de las lesiones musculares. Por lo tanto, diseñamos nuestro sistema de clasificación para las lesiones de isquiotibiales con el objetivo principal de evaluar la cantidad y la gravedad del daño de la MEC. Destacar que este es un enfoque novedoso.

El sistema incluye cuatro categorías principales: mecanismo de lesión (M), localización de la lesión (L), grado (G) y número de relesiones (R). Por tanto, el sistema de clasificación puede abreviarse como MLG-R. La categoría M corresponde a las lesiones musculares directas e indirectas. La categoría L (localización) distingue entre lesiones localizadas en el tercio proximal, medio o distal del vientre muscular, con una subclasificación adicional segúnsi la lesión está en relación a fibras dependientes de la UMT proximal o distal. Para la categoría de grado (G), la lesión se evalúa en base a los hallazgos de la RM. Por último, relesión (R) se define como la aparición de una lesión muscular que afecta al mismo músculo y/o UMT que la lesión inicial durante el proceso de rehabilitación o en los dos meses siguientes a la RTP.

Debido al novedoso enfoque de nuestro sistema de clasificación y a su estructura original, se publicó un segundo artículo para describir el uso de la propuesta MLG-R. Este artículo no se incluye como parte de esta tesis, sin embargo, es muy útil para una mejor comprensión del trabajo, por ello se ha añadido como fuente complementaria.

Posteriormente se evalúa la capacidad del sistema para clasificar las lesiones de isquiotibiales según su gravedad, ofrecer un pronóstico para el RTP e identificar las lesiones con mayor riesgo de volver a lesionarse. Por último, se determina la coherencia de nuestro sistema de clasificación, investigamos su fiabilidad intraobservador e interobservador. Para todo ello se utilizó una muestra de lesiones de isquiotibiales que se produjeron en jugadores de fútbol masculino del FC Barcelona (FCB) - Senior A y B y los dos equipos sub-19 - entre febrero de 2010 y febrero de 2020. Se identificaron 76 lesiones de isquiotibiales en 42 jugadores diferentes. De ellas, 50 (65,8%) eran de Grado 3r, 54 (71,1%) afectaban a la cabeza larga del bíceps femoral (BFlh) y 33 (43,4%) estaban localizadas en la UMT proximal. La media de RTP para las lesiones de grado 2, 3 y 3r fue de 14,3, 12,4 y 37,0 días, respectivamente. Las lesiones que afectaron a la UMT proximal tuvieron una RTP media de 31,7 días, mientras que las que afectaron a la UMT distal tuvieron una RTP media de 23,9 días. El análisis de las lesiones de grado 3r BFlh localizadas en el tendón libre (FT) mostró una mediana de RTP de 56,0 días, mientras que las lesiones localizadas en el tendón central (CT) tuvieron una mediana de RTP más corta de 24,0 días (p=0,038).

El análisis estadístico mostró un excelente poder predictivo del sistema de clasificación MLG-R, con un error absoluto medio de 9,8 días y un R-cuadrado de 0,48. Los factores más importantes que influyeron en el RTP fueron la localización de la lesión (FT del BFlh) y el grado (Grado 3r).

Para todos los ítems del sistema de clasificación MLG-R, la fiabilidad intraobservador e interobservador fue excelente (k>0,93) excepto para la borrosidad de las fibras (κ=0,68).

El principal factor determinante de un RTP prolongado tras una lesión de isquiotibiales es la afectación de las estructuras del tejido conjuntivo. El hecho de que el RTP de las lesiones de grado 3r en el BFlh o el Semitendinoso (SMT) FT sea más largo que el RTP de las lesiones en el CT apoya el concepto de que las lesiones que afectan a la parte proximal del UMT son peores que las que afectan a su parte distal.

En conclusión, el MLG-R es un nuevo sistema de clasificación de las lesiones de los músculos isquiotibiales que proporciona un enfoque coherente para que los profesionales de la salud clínica lo adopten en el fútbol profesional.

LIST OF PAPERS

This thesis is based on two studies, referred to in the text by their Roman Numerals (I and III), and a complementary paper (II) necessary for the finer understanding of the work:

I. Valle, X., Alentorn-Geli, E., Tol, J. L., Hamilton, B., Garrett, W. E., Pruna, R., ... & Rodas, G. (2017). Muscle injuries in sports: a new evidence-informed and expert consensus-based classification with clinical application. Sports medicine, 47(7), 1241-1253. DOI: 10.1007/s40279-016-0647-1.

II. Valle, X., Mechó, S., Pruna, R., Pedret, C., Isern, J., Monllau, J. C., & Rodas, G. (2019). The MLG-R muscle injury classification for hamstrings. Examples and guidelines for its use. Apunts. Medicina de l'Esport, 54(202), 73-79. DOI: 10.1016/j.apunts.2018.11.002.

III. Valle, X., Mechó, S., Alentorn-Geli, E., Järvinen, T. A., Lempainen, L., Pruna, R., ... & la Torre, A. M. D. (2022). Return to Play Prediction Accuracy of the MLG-R Classification System for Hamstring Injuries in Football Players: A Machine Learning Approach. Sports Medicine, 1-12. DOI: 10.1007/s40279-022-01672-5.

OTHER PUBLICATIONS BY THE AUTHOR NOT INCLUDED IN THE THESIS

IV. Hamilton, B., Valle, X., Rodas, G., Til, L., Grive, R. P., Rincon, J. A. G., & Tol, J. L. (2015). Classification and grading of muscle injuries: a narrative review. British journal of sports medicine, 49(5), 306-306. DOI: 10.1136/bjsports-2014-093551.

V. Valle, X., Malliaropoulos, N., Párraga Botero, J. D., Bikos, G., Pruna, R., Mónaco, M., & Maffulli, N. (2018). Hamstring and other thigh injuries in children and young athletes. Scandinavian journal of medicine & science in sports, 28(12), 2630-2637. DOI: 10.1111/sms.13282.

VI. Valle, X., Tol, J. L., Hamilton, B., Rodas, G., Malliaras, P., Malliaropoulos, N., ... & Jardi, J. (2015). Hamstring muscle injuries, a rehabilitation protocol purpose. Asian journal of sports medicine, 6(4). DOI: 10.5812/asjsm.25411.

VII. Lempainen, L., Kosola, J., Pruna, R., Sinikumpu, J. J., Valle, X., Heinonen, O., ... & Maffulli, N. (2021). Tears of biceps femoris, semimembranosus, and semitendinosus are not equal—a new individual muscle-tendon concept in athletes. Scandinavian Journal of Surgery, 110(4), 483-491. DOI: 10.1177/1457496920984274.

VIII. Malliaropoulos, N., Bikos, G., Meke, M., Vasileios, K., Valle, X., Lohrer, H., ... & Padhiar, N. (2018). Higher frequency of hamstring injuries in elite track and field athletes who had a previous injury to the ankle-a 17 years observational cohort study. Journal of foot and ankle research, 11(1), 1-8. DOI: 10.1186/s13047-018-0247-4.

Jokela, A., Valle, X., Kosola, J., Rodas, G., Til, L., Burova, M., ... & Lempainen, L. (2022). Mechanisms of Hamstring Injury in Professional Soccer Players: Video Analysis and Magnetic Resonance Imaging Findings. Clinical Journal of Sport Medicine, 10-1097. DOI:10.1097/JSM.0000000000001109.

ABBREVIATIONS:

BFlh	Biceps Femoris long head
BFsh	Biceps Femoris short head
BM	Basement Membrane
CCL	Cranio-Caudal Length
COR	Conocimiento, Organización y Rendimiento (Knowledge, Organization, and Performance)
CSA	Cross Sectional Area
DOMS	Delayed Onset Muscle Soreness
ECIS	The UEFA Elite Club Injury Study
ECM	Extracellular matrix
EIMD	Exercise Induced Muscle Damage
FCB	Football Club Barcelona
FT	Free Tendon
HMI	Hamstring Muscle Injury
MLG-R	Mechanism, Location, Grade, and Reinjury
MRI	Magnetic Resonance Imaging
MTJ	Myotendinous Junction
MyHC	Myosin Heavy Chain
NCAM	Neural Cell Adhesion Molecule
RTP	Return to Play
SMB	Semimembranosus
SMT	Semitendinosus
TL	Time Loss
US	Ultrasound
TNM	(Tumor, Nodes, Metastases) Classification System of Malignant Tumors
UEFA	Union of European Football Associations
UICC	Union for International Cancer Control

1 INTRODUCTION

Because of their good prognosis and low repercussion on people's daily lives, some of the most common injuries in sports received little attention for many years, so our knowledge about them was based on low-quality studies. In particular, this was the case of muscle injuries until very recently. However, there is great interest in them in the world of professional sports and elite competition: the will to win (1) makes muscle injuries one of the main daily task for health professionals. Indeed, reducing muscle injury-related time loss (TL) can change results, seasons, and even careers.

During the 20th century, several classification systems became popular and widely used in medical literature (2-4), laying the groundwork for future proposals. Indeed, some concepts are still useful like to divide injuries by the mechanism (direct or indirect) or grade (correlation between symptoms and amount of injury, and, posteriorly, between symptoms and results of imaging tests) (5).

The development of imaging technics, first ultrasound (US) and posteriorly Magnetic Resonance Imaging (MRI), allowed to directly visualize injuries, correlate symptoms and evolution with the anatomical findings, and develop new classification systems (5). However, both clinical and imaging-based findings were not validated and had little pathophysiological or prognostic value (5).

I. FUNCTIONS AND TYPES OF MUSCLES

Muscles allow us to walk, run, and jump by transforming chemical energy from several sources (carbohydrates, fats, phosphagen, among others) into mechanical energy, and so movement. With over 600 muscles, skeletal muscle is the largest body compartment in healthy adults (with the exception of some obesities). The peak in muscle mass is reached during the third decade of life, and depends on many factors (size, race, activity, hormones, and diet, among others). Then, starting from the fourth decade of life, there will be a gradual loss in skeletal muscle mass (6). Muscles respond and adapt to stimuli. Depending on our type and level of physical activity, we will have more or less muscle mass, with different metabolic characteristics (obtaining more energy from one source than from another) and functional properties (being more efficient in strength, power, or long performance) (7, 8).

Muscle fibers are different in their mechanical, metabolic, and biochemical properties (9), they have been classically divided in two types depending on their contraction characteristics and fatigability: type I (the slow type), with slow contraction and low mechanical power, but high resistance to fatigue; and type II (the fast type), with fast contraction and high power. This latter are subdivided in type IIa (fast-resistant) and type IIb (fast-fatigable) (8).

Muscle fibers have also been classified according to other criteria: histochemical methods, dominant enzymatic pathway, or expression of myosin heavy chain (MyHC) isoform (9).Myosin is the most abundant protein in the sarcomere, representing around 25% of the total muscle proteins, and has a role in contraction. Therefore, changes in the amount and type of myosin will have effects on muscle function. In humans, there are three isoforms of MyHC: type I, type IIx, and type IIa. A fiber can express a single isoform or co-express multiple ones (9). Fibers principally expressing type I MyHC (slow-twitch) have a slow speed of contraction and principally present an oxidative metabolism; fibers principally expressing type IIx MyHC are characterized by a fast speed of contraction, and use glucose as principal metabolic substrate trough the glycolytic pathway; and fibers that principally express type IIa MyHC have fast speed of contraction and mixed metabolism (glycolytic/oxidative) (9). Finally, different fibers perform specialized functions: type I fibers are specific for endurance exercise; type IIx for exercises requiring higher levels of strength; and type IIa for mixed activities requiring both power and endurance (9).

As muscle fibers are plastic and change during life, the number of hybrid fibers (combining more than one isoform of myosin) increases as a consequence of several stimuli. Exercise in one of the main modulators of muscle plasticity and acts by activating several intracellular signaling pathways that mediate modifications at different levels: contractile proteins' structure and function, satellite cells and myonuclei, mitochondrial homeostasis, metabolic profile, and capillary density (9). Finally, the switch from a type of muscle fiber to another is believed to be caused by calcineurin levels, with high levels of calcineurin promoting the formation of type I fibers, and low levels promoting the formation of type II fibers (9).

When rehabilitating a muscle injury, it is important to consider all the above-mentioned properties of muscle fibers, and design a rehabilitation focused on the demands that the muscles of our patient will have to face.

II. ROLE OF THE MYOTENDINOUS JUNCTION

The myotendinous junction (MTJ) is the zone where skeletal muscle fibers are connected to tendons. It is a transition zone where the force generated by muscles is transmitted to tendons (10). Also, it is the main location of muscle injuries (11).

Despite the relationship between eccentric contraction and muscle injury (11) and the location of muscle injuries to MTJ, insufficient attention has been paid to MTJ for a long time (12).

In humans, MTJ are shaped in a way to maximize the contact area between the tendon and the muscle: folds from the tendon protrude into invaginations of the muscle membrane. This way, the force from muscle fibers will be distributed through a large area, minimizing the stress and maximizing the breaking strength of the MTJ (12).

Studies in animal models showed that the area of MTJ in type II fibers is 40% larger than in type I fibers (13), but it is not known if this is also the case for humans (12). A relationship between type of fibers and risk of injuries has been previously suggested in the literature (14). In particular, type II fibers are dominant in most commonly injured muscles (12), such as biarticular muscles (15).

The adaptability of MTJ to physical activity has mainly been investigated in animal models; in humans, differences in training models and measurement criteria of MTJ area make it difficult to draw conclusions. However, it seems that the complexity and extension of the tendon folds are directly proportional to training loads; and there is a directly proportional increase in the interface between tendons and muscles with increasing physical activity (12).

Finally, muscle fibers close to MTJ have a higher rate of remodeling than farther fibers (16): they present more centralized nuclei and stain positive for Neural Cell Adhesion Molecule (NCAM), a marker of remodeling (12), (17). Also, the same muscle fiber can present higher expression of NCAM in the part closer to the MTJ (12).

III. ANATOMY OF HAMSTRINGS AND BIOMECHANICS

Hamstring muscles are biarticular, they cross the hip and the knee, except for the short head of BF; their main actions are to extend the hip and flex the knee, with slight rotational capacities. Their distal attachment act as horse reins for rotational stabilization, and reinforce the capsule while stabilizing the posterior structures, such as the menisci (18).

The ischial tuberosity is the proximal common origin of the hamstring muscles, with the exception of the short head of the BF that has its origin on the posterior aspect of the femur at the *linea aspera* (19). The SMB at the anterolateral portion, and the common tendon formed by SMT and BF at the posteromedial part of the ischia tuberosity (20).

The distal insertion of the SMT is at the superior aspect of the medial tibiae as part of the pes anserinus (19). The SMB attaches distally through several tendinous branches joined to the popliteal fascia and the oblique popliteal ligament and attached to the posterior part of the medial tibial condyle (18). The BF distal tendon ends at the anterior and posterior border of the proximal part of the fibular head (21).

This biarticular anatomy causes the hamstring muscles to be sometimes simultaneously stressed over two joints, as in contracting eccentrically at the hip and knee while lengthened in terminal swing phase of running (22, 23).

As biarticular muscles with high proportion of fast-twitch fiber and complex architecture, hamstrings, together with rectus femoris, adductor longus, and medial head of the gastrocnemius, are the most commonly injured muscles in sport (15).

Depending on their mechanism, muscle injuries have been classically classified as direct (caused by an external force), and indirect (caused by an intrinsic force), also called contusions and strains, respectively (5, 15, 24). Direct injuries are located where a traumatism occurs (25), whereas indirect injuries are located close to the MTJ (26).

Indirect hamstring injuries can be subdivided into two subtypes, stretching and sprinting type. The first one occurs during movements with combined hip flexion and knee extension, and mostly involves the SMB proximal MTJ (27). The second one occurs during running, and typically involves the BFlh (28). Therefore, the mechanism and moment when the injury occurs will help us for the diagnosis.

However, sometimes the mechanisms of hamstring injuries are not so easily classifiable, as there could be many movements involved. In these cases, biomechanical characteristics of both sprinting-type and stretching-type injuries might be present, as initially described by Worth (29), and later confirmed by a recent paper by Gronwald (30). Such mixed-type injuries occur while the players are with the trunk in flexion and running at high speed.
The moment when the hamstring injury happens can be defined according to the running gait cycle, which is divided in stance and swing phases (31). Sprinting-type hamstring injuries have been associated with both late swing (22, 32) and early stance phases (33). Indeed, hamstrings are activated during the whole running cycle with peaks during these phases (34). In particular, during the terminal swing, hamstrings are lengthening and absorbing energy, producing their peak force, reaching peak strain, and performing the highest negative work (23).

IV. BIOLOGY OF MUSCLE AND TENDON INJURIES

In animal models, skeletal muscle healing is characterized by a reparative process (4) that involves formation of a scar (35). Scar tissue formation has been observed from 6 weeks (36) up to 23 months (37) after the injury. In this animal model, muscle healing is divided in three phases: destruction, repair, and remodeling (4). The destruction phase involves myofibers rupture and necrosis, hematoma formation, and initiation of an inflammatory reaction. The repair phase is characterized by phagocytosis, connective tissue production, and subsequent revascularization. In the remodeling phase, there is scar organization, neo-myofibers maturation, and recovery of the functional capacities with a newly-generated MTJ (4). An optimal healing process is obtained by stimulating regeneration and minimizing reparation, to minimize the size of the scar.
A recent paper has described muscle injuries in humans using electrostimulation (38). Some characteristics of the healing process are in common with animal models, but there are also important differences. The injured myofibers undergo a necrotic process, and they are at the same time removed and restored within the same basement membrane (BM) scaffold (38). The original BM is preserved throughout the whole process till complete healing, when a new BM is created on the surface of the new myofibers (38), BM are thin layers of a specialized

extracellular matrix (39). During this process of myogenesis, myotubes form and fuse with each other, then myofibrillogenesis follow (38). These findings further highlight the extracellular matrix (ECM) in the regulation of myofiber repair (38).
As described, during the healing process in humans, the old BM around necrotic fibers will be preserved until new fibers form a new BM; indeed, 30 days after the initial injury, a double BM can be observed, where the one with a folded appearance corresponds to the original (38).
The presence and role of the old BM as a template on which myogenesis occurs is a main distinctive characteristic that differentiate adult regenerative myogenesis from fetal myogenesis (38). Indeed, at 7 weeks of fetal life, myotubes are present (40), but BM is not detected until the 14-15 weeks (41), meaning that myotubes form without a BM scaffold during fetal myogenesis.
The double membrane structure described in humans is similar to the one observed in in animal models through electron microscopy (38). In the latter, the importance of the basement membrane for successful regeneration has been highlighted (38). Whether this process continues for several months (until only the new BM is visible) and the implications of it are not fully understood. The new BM and sarcolemma represent a new satellite niche for a renovated set of satellite cells. The main event observed in this study was the substitution of a necrotic muscle fiber with a new one through myogenesis (38). The space occupied by the original myofibers (prior to injury) is lost, and a strong growth stimulus is necessary for new fibers to regain the same space; this requires significant and continuous remodeling of the BM and ECM surrounding the fibers (38).
The process of muscle injury healing in humans has some aspects in common with the one described in animal models, but there are still differences to be clarified, possibly due to the fact that the injuries studied in humans have been caused by electrical stimulation.

For the purpose of this thesis, it is essential to emphasize the role of the ECM in muscle regeneration after injury. As mentioned several times in this thesis, ECM plays a key role to transmits the force generated by the muscle, but it also has a significant role in this other basic process.

It is also important to understand the healing process of tendon tissue. The biological process of healing of a damaged tendon comprises three phases that may overlap, and with variations in duration depending on the location and severity of the damage. First, there is an inflammatory phase that starts with the formation of a hematoma and an inflammatory response (neutrophils, monocytes, macrophages, cytokines, and angiogenic factors). This stimulates the generation of a vascular network that will give support to the new fibrous tissue. Then, ECM components (collagen type III, proteoglycans) will be synthesized by fibroblasts, and randomly arranged (42). A remodeling phase starts 6-8 weeks after injury, can last 1-2 years, and is divided in two stages. The initial stage is characterized by a decrease in cellularity and matrix production; tissue will be more fibrous because collagen type III will be replaced by collagen type I, and collagen fibers will organize along the longitudinal axis of the tendon. After around 10 weeks, the maturation stage is initiated, by increasing cross-linking of collagen fibrils and developing a mature tendon tissue (42).

Throughout the healing process, tendon cells are activated to synthesize and degrade ECM elements, contributing to the continuous and gradual process of remodeling. In the healed tendon, there is less integration of collagen fibers, with a higher content of type III collagen than type I collagen. As a consequence, the tendon thickens and stiffens to overcome the lower unit mechanical strength. Thus, in most patients (especially in older ones), the healed tendon does not recover the original mechanical properties and strength (42). The understanding of the muscle and tendon healing processes will help to avoid reinjuries affecting the MTJ, we have to consider the difference in heling time between muscle and tendon.

V. EPIDEMIOLOGY OF INJURIES IN FOOTBALL AND THE ECIS STUDY

As previously mentioned, the most commonly injured muscles in sport are biarticular muscles with high proportion of fast-twitch fiber and complex architecture: hamstrings, rectus femoris, adductor longus, and medial head of the gastrocnemius (15).

Ninety percent of muscle injuries are caused by indirect or direct mechanisms (4), and they are among the most frequent in some of the most popular sports, such as: football (43), rugby (44), American football (45-47), Australian football

(48, 49), and track and field (50, 51). For example, incidence of muscle injuries can reach 31% in football and 28.2% in track and field (43, 51). They account for more than one-third of time-loss injuries and cause more than a quarter of injury-related absence time in high-level European professional football clubs (43).

In football, hamstring muscle injuries are the most frequent ones, accounting for 12% of all injuries. A European professional football team with a squad of 25 players typically present 5 to 6 hamstring injuries per season, which results in more than 80 days of training or matches lost (43).

In order to have a complete vision about injuries in football, the reference is the Elite Club Injury Study (ECIS), an injury surveillance study launched in 2001 by UEFA. It collected data from 69 top-level teams from 20 different European countries over 18 seasons. The duration of the study and the size of the sample allow us to have a representative vision of football injuries: their trends in time and how the changes in the game influenced their profile (52) (i.e., at the moment, athletes play a similar number of games per week (52), but they run more and faster than they used to at the beginning of the study (53).

The latest paper published from the ECIS study covered 18 seasons and analyzed 265 "team seasons" from 49 different teams. The average number of players on each team's roster was 25 (95% CI 22 to 28); each team performed an average of 215 (95% CI 177 to 253) training sessions and played 60 (95% CI 52 to 68) matches per season, with an average of 3.6 (95% CI 3.0 to 4.2) training sessions per match (54). A total of 11,820 injuries were recorded during 1,784,281 hours of exposure, with an injury incidence of 6.6/1000 hours (95% CI 6.5 to 6.7) (54). Of these injuries, 5,035 occurred during training sessions, and 6,785 during matches, with a higher incidence in matches (23.8/1000 hours) than in training sessions (3.4/1000 hours) (54).

Muscle and ligament injuries (4,763 and 1,971, respectively) represented 57% of the total (54). In the 18 seasons, the incidence of total injuries decreased of 3% per season, both in training sessions and in matches; the incidence of muscle injuries did not change (54); and the incidence of ligament injuries decreased of 5% and 4% per season, respectively in training sessions and matches.

There was no significant change in injury severity (mean number of days lost) of all or muscle injuries in training sessions (54). Also, although general injury

severity increased of 1% per season in matches, no significant changes were specifically observed in muscle injury severity (54).
Moreover, no significant trends were detected in the burden of ligament or muscle injuries, either in training or in matches (54).
The incidence of injury recurrences decreased of 5% per season, both in training sessions and matches. However, muscle injury recurrences did not change in training sessions, but only decreased of 4% in matches (54).
Finally, ligament injury recurrences decreased of 6% in training sessions and 7% in matches.
In summary, both in training sessions and matches, overall and ligament injury rates per season were reduced; on the contrary, the rate of muscle injuries did not change neither in training sessions nor in matches. Finally, injury burden did not change, and reinjury rate decreased together with the absence of players from training sessions and matches (54). All this information makes us understand the importance of muscle injuries in football and their evolution during the last 18 years.
An earlier ECIS study reviewed a 13-year sample of 1,614 hamstring injuries, of which 564 (35%) happened during training sessions, and 1,050 (65%) during matches (52).
Two thirds of them presented with an acute onset (n=1060, 66%), and one third with a gradual onset (n=554, 34%).
The overall hamstring injury rate was 1.20 (95% CI 1.14 to 1.26) injuries per 1000 hours; 4.77 (95% CI 4.49 to 5.06) in matches, and 0.51 (95% CI 0.47 to 0.55) in training sessions (nine times lower than in matches).
The number of days lost per injury ranged from 0 to 395, with a mean±SD of 17±21 (52).I
The overall mean injury burden was 19.7 days/1000 hours of exposure; 6.3 and 88.5 days/1000 hours of exposure, respectively during training sessions and matches (52).
On average, 21.8% of players experienced at least one hamstring injury during a season. The mean annual prevalence was 9.3% per season (range 6.7-11.5%) during training, and 15.1% (range 12.0-17.4%) during matches. Finally, the rate of reinjuries was 13% (total of 216) (52).

These findings serve to understand the significance of hamstrings injuries in football, allowing us to have more reliable diagnosis and prognosis, and thus decrease the risk of reinjuries.

VI. CLASSIFICATION SYSTEMS FOR MUSCLE INJURIES

The lack of information on muscle injury definition and classification has been highlighted by several authors (5, 55). We here summarize Hamilton's paper on the evolution of the most commonly used classification systems for muscle injuries (5).

At the beginning of the 20th century, the first classification systems divided injuries depending on the mechanistic forces (internal/external) and anatomical location, and constituted the basis for all the future ones (5).

Posterior research with animal models and imaging techniques helped to better distinguish between external and internal forces and describe anatomical locations. In particular, in the early 21st century, the interest in muscle injury classification gained attention thanks to the improvement of imaging techniques and to the work of Askling describing the relationship between mechanism of injury, anatomical location, and prognosis (27, 28).

Another important step was to identify "central tendon" injuries as a prognostic factor (56, 57), providing evidence that the tissue affected was relevant to the prognosis.

Hamilton divides the history of muscle injury classification in the clinical era (the 20th century until the 80s), the imaging era (1985-2000), and the modern era (after 2000).

During the clinical era, muscle injuries were classified according to their severity (intended as the amount of fiber rupture) by indirect means: symptoms and signs were considered to reflect the severity and location of injuries (5). Before the 80s, more than 1500 muscle injuries were described in the literature, with only one study trying to correlate the clinical finding to the outcome (58).

In the imaging era, muscle anatomy and injury were indirectly assessed through US and MRI; however, early imaging grading systems did not have any pathophysiological or prognostic validity (5). Indeed, only one of the first studies with imaging techniques tried to establish the time of recovery starting from the injury extension assessed through MRI (56). In more recent years, other two studies evaluated the reliability and prognostic validity of imaging grading systems, obtaining low evidence (59, 60).

During the modern era, there have been more attempts to find a correlation of clinical and imaging grading systems with injury severity. With a better knowledge provided by imaging systems, the awareness of the need for better classification systems increased, and led to the proposal of new ones.

For years, several studies tried to find a correlation between injury extension (observed through imaging) and prognosis, rather than focusing on other injury characteristics (e.g., oedema from fiber rupture) and the type of tissue affected (60, 61). Difficulties derived from an unclear terminology, with no consensus in definitions (62).

Other studies attempted to find a relationship between other MRI/US findings (injury type, location, tendon involvement, and extent) and the prognosis of the injury (63-83). Hamstrings and rectus femoris were the most commonly studied muscles (65, 77, 84). Specifically, percentage of the cross-sectional area (%CSA), craniocaudally length (CCL), and injury volume were evaluated through MRI. Their relationship with the amount of disrupted fibers, and so to the degree of muscle dysfunction, was thought to suggest the recovery time.

A particular type of injury was described, patients with a clinical suspicion of hamstrings injury but negative MRI, these patients showed less time loss (63-67, 70, 85).

The importance of the injuries affecting the intramuscular tendons also became clear. MRI/US studies in rectus femoris found that recovery time was longer when the central tendon was disrupted (78, 86, 87). Similar findings were reported in the soleus muscle (83): injuries in the central aponeurosis had a longer recovery time than injuries in the lateral and medial aponeuroses and myofascial sites (83). Finally, the recovery time from injuries affecting the main structure of the MTJ was higher, and so it was the risk of recurrence (88, 89).

This new knowledge gave rise to several new proposals, two of which deserve particular attention.

First, in 2012, a new classification system for muscle injury was generated in the Munich meeting (55); posteriorly, it was adopted with the support of UEFA; and it is now used to register muscles injuries in the ECIS study. This classification system was tested in a sample of football players from the ECIS study (90); it was the first time that a classification system was tested on a large volume of data (5). A validation study concluded that the proposal was better for “structural” than for “functional” injuries (91).

Second, a classification system for non-contact muscle injuries was published by the British Athletics group (92), and demonstrated reproducibility and consistency (93). In particular, it is able to ascertain that injuries extending into the tendinous portion are associated with longer time loss and increased recurrence rate (89).

A recent work from Hamilton et al. (94) evaluated these two systems in detail discussing their strengths and weaknesses, and we will review the most relevant points in the discussion.

2 RATIONALE FOR THIS THESIS

Originally, this work derived from an assignment by the medical services of FC Barcelona (FCB) to write two chapters as part of the muscle guide published in collaboration with ASPETAR in 2016 (95). The first chapter had to be on the design of a rehabilitation protocol for muscle injuries; and the second one on a proposal for a classification system of muscle injuries. The first chapter gave rise to a publication (96) in which we presented a rehabilitation proposal for muscle injuries according to the standards of the time, providing an original idea on the selection of the exercises. Rather than establishing a fixed protocol of exercises, we proposed a set of criteria for the design of the exercises in every phase, adapting the rehabilitation protocol to the characteristics of the patient and the sport.

The second chapter gradually became something special. First, it required me to read many articles on the topic; eventually, this duty became a pleasure and I enlarged my knowledge in the field, going deeper and deeper into the subject. This naturally transformed what was supposed to be a chapter into my doctoral thesis.

To better understand and prevent injuries, I needed to get a detailed knowledge of their epidemiology, risk factors, diagnosis, and therapeutic options, by reviewing the literature. The two articles I wrote for the muscle guide allowed me to complete this initial phase, and understand the importance to classify muscle injuries.

On the basis of the epidemiological information previously presented (incidence and related time off), the importance of muscle injuries, and of hamstring injuries in particular, is obvious. However, for a long time, muscle injuries have been overshadowed by others causing longer periods of time off. Then, the ECIS group studies comprehensively assessed the injury profile of elite football players, leading to recognize the importance of muscle injuries to players and teams, and their influence on winning a competition.

A good muscle injury classification system gives information on prognosis, treatment, and associated risks; therefore, its importance is evident to health professionals.

When we started the project, there were several classification and grading systems, but, as previously described, their evidence and the consensus on their use was limited (5).
Our final objective was to develop a practical, objective, and helpful muscle injury classification system for health professionals. We achieved this by reviewing the existing scientific evidence in the field and combine it with the experience of experts from medicine centers of elite sports.

3 AIMS

GENERAL AIM

The main aim of this thesis was to design a classification system for muscle injuries based on scientific evidence published in the field, with a posterior consensus within the medical centers and experts participating in the project. The classification system was then tested and validated.

SPECIFIC AIMS

Study I

We aimed to develop a classification system for muscle injuries base on the existing scientific evidence, with an easy clinical application, grouping injuries with similar functional impairments, avoiding confusing terminology.

Study II

This letter is not part of the thesis but since the approach of our classification system was radically different from the existing ones, it was decided, during the thesis, to publish an educational paper. This paper aimed to describe the process of using the MLG-R classification system. For that, we codified injuries using several examples of hamstring injuries.

Study III

The principal aim of the last study was to evaluate the capability of the MLG-R classification system to grade injuries by severity, give a prognosis for RTP, and assess the risk of reinjury in a sample of hamstring injuries, in top-level professional athletes from FCB teams. The secondary goal was to assess the consistency of our proposed classification system by investigating its intra- and inter-observer reliability.

4 METHODS

Study I

This study was designed using published scientific evidence and in consultation with experts in the field of muscle injuries. The methodology employed in the present research was based on previous publications on consensus statements in medicine (97-99). Three centers (FCB medical department, Aspetar, and Duke Sports Science Institute) from three continents (respectively, Europe, Asia, and America) were involved. All of them use to deal with many muscle injuries and have extensive experience in elite sports medicine.

The study was designed in three phases: 1) identify the existing evidence related to risk and prognostic factors for muscle injuries; 2) discuss these factors with two of the centers and establish a consensus based on the quality of the studies in combination with the experience of the experts; and 3) elaborate the final classification.

One of the authors (XV) first performed an electronic literature search for relevant clinical studies on muscle injuries, to identify the risk and prognostic factors, using the PubMed (MEDLINE) database. The following search terms were employed and restricted to the English language: (muscle injury OR muscular injury OR muscle injuries OR muscular injuries OR muscle lesion OR muscular lesion OR muscle lesions OR muscular lesions OR muscle strain OR muscular strain OR muscle strains OR muscular strains OR muscle damage OR muscular damage) AND [(classification OR classifications OR rating OR grading OR severity) OR (risk factor OR risk factors OR prognostic factor OR prognostic factors OR predisposing OR predisposition)]. To be considered, articles must be original clinical research; however, review articles were also used to manually search for references potentially missed in the original literature search.

The second and third phases started with two consensus meetings held between the involved institutes (FCB and Aspetar). During the first meeting, the results of the electronic literature search were initially presented (XV) and discussed between the four authors (GR, RP, LT, and JAG) from FCB to determine what to cover in the first meeting between the two institutes that was held in Doha in July 2013. Each topic was discussed during the meeting. All expert opinions and assessments of the included terms were considered, and a consensus was reached. The document from the first meeting was summarized and sent to all of the participating authors (XV, JT, BH, GR, RP, LT, JAG, RW, and EW). One of them (XV) performed a second review of the literature from a manual search of references of relevant studies and review articles obtaining information that was then incorporated into a first draft of the classification system. The authors from both institutes reviewed this document, and a second meeting was scheduled. A time frame of 10 months was left between the two meetings to ensure an adequate evaluation. In this period, the draft was iteratively revised on the basis of the comments from all authors.

FCB and Aspetar held a second meeting in Barcelona in May 2014. All participants were asked to report any concerns about the terms included in the classification system, critiques, and personal opinions. The group reached a general agreement, and a final preliminary document was generated. This document was sent again to all the participants from the two meetings (XV, JT, BH, GR, RP, LT, JAG, RW, and EW), and six months were given to reach a final consensus. During this period, the draft repeatedly evolved until an agreement was reached and the participants approved the final document that was then sent to a FIFA Medical Centre of Excellence (Duke Sports Science Institute) to be evaluated by two other authors (WEG and EAG). Finally, the document was also sent to other professionals to obtain a broad and multidisciplinary feedback on the new classification system: an expert radiologist in MRI (XA), an expert in ultrasound (RB), an orthopedic surgeon specialized in muscle injuries (JCM), a researcher with extensive experience in sports medicine (KS), and an expert in muscle injuries (NM). Finally, the comments and suggestions from 7 authors (EAG, WEG, XA, RB, NM, JCM, and KS) were incorporated into the new MLG-R muscle classification system, which all authors approved in October 2015.

We used an innovative approach, employing the classification of malignant tumors (TNM) as a model (100) to organize our proposal, since a standard classification system improves communication between providers and allows to better exchange information and research across populations (100). Indeed, the Union for International Cancer Control (UICC) has published the UICC TNM classification of Malignant Tumors for over 50 years, constantly adapting it to the new knowledge in the field.

Finally, the most crucial novelty has been to make the ECM the cornerstone of our muscle injury classification system: the amount of injured ECM is quantified as an indicator of the loss of function of the muscle, and the associated clinical signs and symptoms.

Study II (Not part of the thesis)

In the second study, since the approach for the classification system was radically different from existing classification proposals, we published an educational letter describing how to classify an injury using the MLG-R proposal.

The article is structured as follows: first, an introduction on the importance of muscle injuries and their impact on team performance; then, an explanation of each letter of the MLG-R. A series of practical examples of muscle injuries were used with their corresponding radiological images, and they were classified using MLG-R.

Study III

Study Population

The series of injuries analyzed in this thesis came exclusively from the FCB medical department records, that provides medical assistance to FCB athletes, amateurs, and professionals from fifteen different sports. All of the information is recorded in a private software package developed by the FCB called COR (Conocimiento, Organización, y Rendimiento; in English, Knowledge, Organization, and Performance). This database contains all the FCB athletes' injury and illness data. All medical episodes are coded using The Orchard Sports Injury Classification System (OSICS) Version 10 (101, 102).

All male professional football players from the FCB (senior A and B and the two U-19 teams) with injuries that occurred between February 2010 and February 2020 were approached for eligibility. Finally, only players with hamstring muscle injuries (HMIs) were included in the study.

Our sample was homogenous since all cases came from the same club and players had the same medical resources, diagnostic criteria, rehabilitation programs, and RTP criteria (95).

Eligibility Criteria, Data Collection, and Extraction

To filter HMIs, we reviewed episodes coded as "Thigh Muscle strain/Spasm/Trigger Points" under the OSICS section. Initially, all episodes with symptoms compatible with an HMI were included and evaluated. Then, only injuries with a clinical presentation matching an HMI and confirmed by MRI (within 72h of the injury) were included in the final analysis. If the diagnosis was confirmed only by US, or MRI from the acute phase of the injury was not available, the injury was excluded from the final sample. In each case, a rehabilitation program aimed at RTP was performed by a team of physicians, following the club's clinical practice guidelines (103). Another eligibility criterion was that all complete medical information had to be available. Finally, players that needed a surgical treatment or experienced a reinjury during the rehabilitation were excluded.

RTP definition

The Return to Play (RTP) was defined as the moment in which a player returned to full, unrestricted practice with the team, or fully participated during games. It was recorded in the electronic medical records.

Study Period

As previously described, the ECIS study evaluates the incidence, prevalence, and new trends in football injuries. Muscle injuries are also influenced by new training/competition loads, schedule density, changes in the game, etc. However, this thesis does not aim to evaluate the seasonal incidence of injury. This thesis aims to evaluate the individual information related to an injury and its evolution. Instead of studying the natural time of an entire season, we studied injuries recorded from February 2010 to February 2020 to incorporate the maximum number of HMIs.

HMI Injury Inclusion Criteria

To be included as a confirmed case of HMI, the player had to present signs/symptoms of muscle injury during football practice. An MRI scan was mandatory within 72 hours after the event triggering the injury confirming the diagnosis. Finally, the player must have been excluded from at least one training session or match because of the injury.

Reinjury Definition

A reinjury is a muscle injury occurring during the rehabilitation process or within two months after RTP from an initial injury, affecting the same muscle and/or MTJ (62). Therefore, injuries affecting the same MTJ, its intramuscular tendon, or an associated fiber (even in a different location) will be considered a reinjury. For example, an initial injury could affect the proximal MTJ in the proximal third of the muscle belly. If in the following two months, a second injury affected the proximal MTJ in the middle third of the muscle belly, it was considered a reinjury. On the contrary, if the second injury affected the distal MTJ, it was not considered a reinjury.

Re-injuries were recorded in the medical records according to our previous definition.

Time-loss definition

Time-loss was defined as the time between the injury and the moment the player was allowed to train with the team and/or play for the team without restrictions.

MRI Protocol

MRIs were carried out with two different devices. Most of them (54) were performed at the FCB medical center using a 3.0T MRI system (Vantage Titan, Canon Medical Systems). The rest (22) were performed at an external medical center using another 3.0T MRI system (Magnetom VERIO, Siemens Medical Solutions). The same researchers evaluated all the MRI. Patients were positioned in the supine decubitus position, the examination focused on the injured limb, and the symptomatic area was marked with a cutaneous vitamin marker. A multi-purpose coil was used with speeder technology. This type of coil and technology allowed the acquisition of five sequences according to the standardized protocol for evaluating muscle injuries in the lower extremities. We evaluated Axial, Sagittal, and Coronal T2 Fat Sat: TR 5200, 5000, and 3700 ms; TE 44-60 ms; Eco train 7.5; SL 2.5-3.5 mm; in-plane resolution 0.9-1.4×0.88-0.97 mm2; and FOV 256x256, 192x272, and 288x320 mm. We also evaluated Axial and Coronal TSE T1: TR 900-980 ms; TE 11 ms; Eco train 7.5; SL 2.5-3.5 mm; in-plane resolution 0.71-0.9x0.71-0.9 mm2; and FOV 352x352 and 288x320 mm.

Image Review

A cross-sectional review of the MRI of each injury was independently performed by a musculoskeletal radiologist (SM) and a sports medicine physician (XV).

All injuries were classified using the MLG-R classification system (62). Both researchers were familiar with it and had years of experience working with muscle injuries and MRI images (104).

In the MLG-R classification system, category “M” stands for “mechanism”: direct (T) and indirect (I). Subcategories of category “I” were created to define indirect muscle injuries caused by stretching (S) and sprinting (P). Category “L” stands for “location”: proximal (P), middle (M), or distal third (D) of the muscle belly. A subindex describes the relationship of the injury to the proximal (P) or distal (D) MTJ. Category “G” stands for “grade”. The MLG-R classification system does not quantify edema. Edema characteristics are relevant in differentiating between grade 1 and grade 2 injuries. Grade 3 injuries are characterized by a quantifiable gap between fibers in craniocaudal or axial planes, with torn fibers in the muscle, the connective tissue, or both. If the fiber rupture affects the connective tissue, the superscript “r” is added to the grade. For injuries affecting the MTJ at two locations, we use the one located proximally to define the grade (i.e., code). Finally, a Grade 0 injury is a clinically suspected injury with a negative MRI. In these cases, the second letter describes the location of the pain in the muscle belly. Category “R” informs of the injury chronology. The initial injury would be R0, the first reinjury R1, and so on.

MRI images from each injury were reviewed three times in a patient-blinded study by the musculoskeletal radiologist (SM) and the sports medicine physician (XV). The first review was not performed independently to review the classification system before the MRI readings and agree on how to apply it. The second review was performed independently 3-8 months afterwards. Finally, a third review was performed and any discrepancies were discussed to agree on the classification.

Outcome

The primary outcome was RTP, measured in days. The independent variables or covariates derived from MRI images: injury locations at the tendon (free tendon, central tendon, or others), at the muscle belly (proximal, medial, or distal third), and with respect to the MTJ (proximal or distal); grade of injury (0, 1, 2, 3, or 3^r); reinjury (0, 1, or 2); and muscle injured (BFlh, BFsh, SMB, and SMT). We entered the variables in the models in binary format.

Statistical Analysis

We used three statistical models to validate the classification system and understand the factors determining the RTP: first, multiple linear regression as a baseline model; second, random forest; and third, eXtreme Gradient Boosting (XGBoost). This approach allowed us to check if different models led to the same conclusions.

We chose linear regression as it is the gold-standard model for analyzing RTP data, and it has been used in previous studies of hamstring injuries (105, 106).

Random forest is based on bagging and uses ensemble learning. It was used as a second model as it can efficiently handle non-linearities in the data; it does not tend to overfit, and it reduces the variance, leading to an improvement in accuracy in comparison to multiple linear regression (107). Finally, XGBoost offers increased accuracy and predictive power by using an ensemble of weak learners (108). We optimized the hyperparameters by conducting a grid search. We performed Leave-One-Out Cross-Validation (LOOCV) to assess the generalizability of the results and leverage as much as possible the information provided by each observation.

We computed Mean Absolute Error (MAE), Root Mean Squared Error (RMSE), and the coefficient of determination (R2) to determine the quality of the classification system. Moreover, we computed the Accumulated Local Effects (ALE) to understand the relative importance and contribution each feature in predicting the RTP (109, 110). Positive ALE increases the average RTP, while negative ALE decrease the average RTP. The alpha level was set at 0.05. All analyses were conducted in R 3.6.3 (111).

In addition, weighted and unweighted Cohen´s Kappa and the intraclass correlation coefficient (ICC) were used to assess the reliability of the MLG-R classification system. First, we quantified the diagnostic reliability between the two physicians (inter-observer reliability). Second, we measured the reliability of the diagnosis of each independent physician at two different points in time (intra-observer reliability).

5 ETHICAL APPROVALS

Ethical approval was not necessary for the study I because of its structure and the absence of data from players in the work.

The study III has been assessed and approved by the ethics committee of the "*Consell Català de l'Esport*" (Catalan Sports Council). The reference number 10/CEICGC/2020 was assigned to the study.

Generalitat de Catalunya
Comitè d'Ètica d'Investigacions Clíniques
de l'Administració Esportiva de Catalunya

DR. RAMON BALIUS MATAS,
ACTING AS SECRETARY OF THE ETHICS COMMITTEE
FOR CLINICAL RESEARCH
OF THE CATALAN SPORTS COUNCIL.

CERTIFIES

At the online meeting on 18th May 2020, the Ethics Committee agreed to favorably assess the project presented by Xavier Valle, Gil Rodas, Carles Monllau, Sandra Mechó, number 10/CEICGC/2020, entitled **"Muscle Injuries in Sports: A New Evidence Informed and Expert Consensus-Based Classification with Clinical Application"**

We note this favorable assessment for the appropriate purposes.

Generalitat de Catalunya
Consell Català de l'Esport
Av. Països Catalans, 40-48
08950 Esplugues de Llobregat

Dr. Ramon Balius Matas
Barcelone, 20th May 2020

In addition, it is an FCB policy to ask for authorized and informed consent from all players by signing the following document:

1 FC BARCELONA

Informed Consent for Routine Procedures and the Handling of Medical Documentation and Information.

I, ...(name), born on .... (date) and the holder of National Identity Card (DNI) number ...., in my capacity as athlete at Fütbol Club Barcelona

Voluntarily declare that:

1. I understand and have been informed of the following sections of the Code of Ethics in Sports Medicine drawn up by the International Federation of Sports Medicine:

   - The athlete's right to privacy must be protected.
   - In the event that information regarding the athlete's health is sought as a result of public interest or by the media, the athlete and their physician must decide together which information is to be made publicly available.
   - Within sports teams, the physician is responsible for the health of the athletes, along with the trainers and directors. The physician shall respect the confidentiality of the information; however, the athlete must authorize the sharing of information with the responsible parties, for the sole purpose of informing said parties as to whether the athlete's health may affect their participation in competitive events.

Consequently, I hereby authorize the physicians at Fütbol Club Barcelona's Sports Medicine Service to provide relevant information to the trainers regarding my health and the parameters of my physical condition, within the terms detailed above. I understand that any specific communication regarding my health will preferably take place with my consent.

2. I hereby give my CONSENT to allow Fütbol Club Barcelona's Sports Medicine Service to undertake, throughout the entirety of my relationship with Fütbol Club Barcelona, any routine procedures or tests that may be necessary in order to monitor and control my health or physical condition, including:

   - Medical visits
   - Physical and psychological health checks and medical examinations.
   - Blood and urine analyses, including determination of Omics biomarkers (genomic, transcriptomic, proteomic, and metabolomic profile analysis).
   - Anti-cloping controls
   - Vaccinations, including the flu and covid-19 vaccines.
   - Administration of medication, by medical indication.
   - Complementary examinations: ultrasound, X-rays, CT scans (without contrast), nuclear magnetic resonance (MRI scans, without contrast), scintigraphy (gamma scans), Holter monitoring, bone densitometry, electrocardiograms and echocardiograms.

- Functional assessment tests: effort-related, laboratory-based, body composition analysis, field tests and strengthrelated assessments. • Physiotherapy treatments
- Obtaining biological samples, which will be stored - with all due guarantees - in a biobank in accordance with Law 14/2007.

3. I have been informed that Fütbol Club Barcelona, as the party responsible for processing my personal data, shall process said data on the basis of the implementation of the contract and of both parties' fulfillment of their obligations. Specifically, Fütbol Club Barcelona shall process and store the biometric and health-related data obtained during the examinations and checks that are performed on me during my time at Fütbol Club Barcelona. This data shall be processed in order to: improve my sporting performance; prevent, diagnose and treat any injuries; personalize my nutrition and hydration regime; improve the quality of my sleep and rest; reduce fatigue and recovery time; monitor and personalize my training; and to carry out medical examinations and any other procedure or test designed to achieve the aforementioned aims and to improve my health, wellbeing and sporting performance as an athlete and that of my teammates in general. If a specific project requires the explicit consent of the affected party, FC BARCELONA shall request such consent.

The medical reports and statistics obtained by the medical team may be offered by FC BARCELONA to the sporting community (without including the athletes' personal data, wherever possible), in order to contribute to the improvement of the sport as a whole and to the conditioning of the athletes.

Personal data shall not be shared, sold, rented or otherwise made available in any way to any third parties, excepting suppliers and/or collaborators of FC BARCELONA who manage certain activities on behalf of the Club, and who shall not under any circumstances process the personal data for their own purposes.

Some of these suppliers and/or collaborators may be located outside the European union, and consequently your data may be processed outside the European Union or the European Economic Area. Under all circumstances, the Club shall ensure that the aforementioned processing of data is always protected by the appropriate guarantees, which may include:

a. Standard clauses approved by the El]

b. Third party certifications

FC BARCELONA shall retain your data throughout the entirety of the professional relationship and, under all circumstances, until the expiry of the applicable statute of limitations for any employment-related, criminal and civil proceedings or administrative sanctions that may apply, notwithstanding any data-blocking measures that may be taken.

Notwithstanding the above, I accept that all of the data related to my professional performance, including health-related data, may be processed by FC BARCELONA for research purposes and in order to improve the Club's technical and sporting methodologies, for an indefinite period of time and while said data remains useful. FC BARCELONA is firmly committed to anonymizing said data wherever possible; however, I understand that, given the public nature of certain information (particularly in relation to matches I may have played in and which have had an impact in the media or in terms of publicly available statistics), it may not be possible to fully anonymize all of the data in question.

The athlete may also access an informative document that describes, in greater depth and detail, the different types of data that FC BARCELONA shall (or may) process, along with the different purposes of their processing. The athlete can request this document by writing to FC BARCELONA's Data Protection Officer at dpo@fcbarcelona.cat.

I understand that I may exercise the right to access, rectify, oppose, suppress and limit the processing of my data, and to obtain a copy of said data, with regard to the processing carried out by FC BARCELONA, and that I may do so by sending a written request to c/Aristides Maillol s/n, 08028, Barcelona or by sending an email to proteccio.dades@fcbarcelona.cat. Likewise, I understand that I may also contact the Data Protection Officer at FC BARCELONA by sending an email to dpo@fcbarcelona.cat, if I feel that my personal data have not been processed in accordance with the stipulations of the legislation in force. If, after a reasonable period the Data Protection Officer has not provided a satisfactory response, I may contact the Spanish Data Protection Agency or the competent supervisory body, in accordance with the legislation in force.

Signed and authorized in Sant Joan Despi on

___ ________ ______

The athlete: Checked by: DNI: DNI:

6 STATISTICS

Study I

Because of the study´s structure, nature, and aim, no statistical analysis was needed.

Study III

Outcome

The primary variable was RTP, measured in days. The independent variables, or covariates, included in the models derived from MRI images were: injury location at the tendon (free tendon, central tendon, or other location); location at the muscle belly (proximal, medial, or distal third); MTJ injury location (proximal or distal), grade of injury (0, 1, 2, 3, or 3^r); reinjury (0, 1, or 2); and the muscle injured (biceps femoris long head (BFlh), biceps femoris short head (BFsh), SMB or SMT. We entered the variables in the models in binary format.

Statistical Analysis

We used three statistical models to validate the classification system and understand the factors determining the RTP. First, multiple linear regression as a baseline model; second, random forest; third, eXtreme Gradient Boosting (XGBoost). This approach was used to check if different models led to the same conclusions.

We chose multiple linear regression as it is the gold-standard model for analyzing RTP data, and it has been used in previous studies of hamstring injuries (105, 106). Random forest, based on bagging and uses ensemble learning, was used as a second model as it can efficiently handle non-linearities in the data, does not tend to overfit, and reduces the variance. These qualities of Random forest lead to an improvement in accuracy for multiple linear regression (107). Finally, XGBoost offers increased accuracy and predictive power by using an ensemble of weak learners (108).

We optimized the hyperparameters by conducting a grid search. We performed Leave-One-Out Cross-Validation (LOOCV) as a model validation technique to assess the generalizability of the results to leverage as much as possible the information provided by each observation. We computed Mean Absolute Error (MAE), Root Mean Squared Error (RMSE), and the coefficient of determination

(R2) as measures of the quality of the predictors. Moreover, we computed the Accumulated Local Effects (ALE) to understand the average relative importance and contribution of each feature in predicting the RTP (109, 110). Positive ALE contribute to a longer average RTP, while negative ALE decrease the average RTP. The alpha level was set at 0.05. All analyses were conducted in R 3.6.3 (111).

As a supplementary analysis, we re-ran the main analysis but including the pathomechanism, i.e., stretching or sprinting, to assess the relevance of this factor.

In addition, weighted and unweighted Cohen's Kappa and the intraclass correlation coefficient (ICC) were used to assess the reliability of the MLG-R classification systems. First, we quantified the diagnostic reliability between the two physicians (inter-observer reliability). Second, we measured the reliability of the diagnosis within each independent physician at two different points in time (intra-observer reliability).

7 RESULTS

Study I

The result from the first study is the proposal of a new classification system for muscle injuries, elaborated after the final consensus between the three institutes and the external experts involved in the project. As explained in the Methods section, the final proposal was developed after extensive literature reviews, agreements formed in meetings between the institutions, and agreements between the experts involved. The classification system can be seen in the Addendums section of this thesis within the original paper.

For this study, the hamstrings muscle group was used. The classification system includes 4 main categories related to parameters with clinical and prognostic relevance: mechanism (M), location (L), grading (G), and recurrence (R). For the classification system, we can therefore use the acronym MLG-R. Category M stands for direct and indirect muscle injuries. A subcategory of the Mechanism (M) was created to define stretching-type (subindex S) and sprinting-type (subindex P), among indirect hamstring muscle injuries. Category L (location) is subdivided into injuries located at the proximal, middle, or distal third of the muscle belly, with injuries further sub-classified according to the relationship with the MTJ. The criteria for the MRI measurements have been previously described in the literature (112). For the grading (G) category, the injury is evaluated on a T2-weighted MRI (a hyperintense signal is considered positive). The consensus was that an MRI should be performed within the first 72h following an injury. If more than one muscle is injured, the muscle with the greater area of signal abnormality or architectural distortion will be considered the primary site of injury, and grading criteria will be taken for that particular muscle. A recurrence (R) is defined as an injury of the same type and location as the index injury occurring during the first 2 months after RTP (74).

Study III

Of the 3875 injuries occurred during the study period, all episodes with symptoms compatible with an HMI were included and evaluated (Addendum section, original paper Figure 1). The patients and their injury characteristics can be seen in the Addendum section (Table 1).

Most of the hamstring injuries which affected the BFlh (n 54; 71,1%) were grade 3^r (n 50; 65,8%) and were located at the proximal third of the thigh (proximal MTJ) (n 33; 43,4%). Among all of the BFlh and SMT injuries located in the proximal third (n 41), 7 were located at the FT, 19 at the CT, and 15 at other locations of the MTJ.
When assessing the difference in the RTP by the severity of the injury (grade), the RTP was the longest for grade 3^r injuries (IQR=25,2), both in all muscle and in BFlh only (Addendum section, original paper, Figure 2). No significant statistical differences in RTP were detected between injuries of lower grades (Addendum section, original paper, Figure 2). The mean RTP of the BFlh injuries of grades 1, 2, and 3 were 11, 15, and 18 days respectively.
For grade 3^r BFlh injuries, there were no significant statistical differences in the RTP between different locations (Addendum section, original paper Figure 3). Injuries located at the proximal third and affecting the proximal MTJ (Pp) had a greater variance in the RTP, in comparison to injuries in other locations. The RTP for injuries located at the medial third affecting the proximal MTJ (Mp) and the distal MTJ (Md) was very similar. Likewise, no statistically significant differences (p=0.91) were found between injuries closer to the insertion, Dd, and Pp (Addendum section, original paper, Figure 3).
The analysis of the grade 3^r BFlh injuries located at the FT showed a median RTP time of 56 days, while the injuries located at the central tendon had a shorter RTP of 24 days (p=0.038) (Addendum section, original paper, Figure 4). The SMT injuries located at the FT had a worse prognosis (median RTP of 54,5 days) than those located at the central tendon (median RTP of 34 days). However, the differences were not statistically significant (p=0.43) (Addendum section, original paper, Figure 4). For the BFlh, the RTP after sustaining a complete MTJ gap was significantly longer (p=0.0087) in comparison to partial injuries (Addendum section, original paper, Figure 4). The imaging of partial and complete tendon injuries is provided in the (Addendum section, original paper, Supplementary files (Figure 4).
The three models (linear regression, random forest, and XGBoost) converged with respect to variable importance and accumulated local effects (Addendum section, original paper, Supplementary files, Table 1, and Figures 1-6). However, the XGBoost model yielded the best performance for all the metrics (Addendum

section, original paper, Table 2). MAE, RMSE, and R-Squared were 9,7884, 12,145, and 0,4847, respectively. In addition, we observed that the predictive power was higher in lower-grade than in grade 3 (Addendum section, original paper, Table 3). These results could not be compared with other classification systems as these performance measures were not reported (55, 113).

We observed that the grade of the injury was the most critical variable to determine the RTP, followed by the MTJ location (FT, CT, or other). When looking at the ALE, we identified FT injuries as the ones with the longest RTP (Supplementary files, Figure 6). Moreover, grade 3^r was identified as the second most relevant factor for long RTP, followed by re-injuries (Addendum section, original paper, supplementary files, Figure 6).

The mechanism of injury (sprinting or stretching) might also play a relevant role in severity and, therefore, in the RTP. To assess the impact of this factor in our cohort, we re-ran the main analysis and included the mechanism of injury. We identified 63 injuries caused by sprinting and 13 by stretching, with an average RTP of 30,8 and 19,5, respectively (Appendix, Table 1). Most of the injuries caused by sprinting affected the BFlh (53 out of 63, 84%),%) while the SMB was the muscle most frequently affected by stretching (11 out of 13, 84%) (Appendix, Table 2). When examining grade 2 and grade 3^r injuries affecting the BFlh, we found that 47 out of 48 cases (98%) were caused by sprinting, presenting an average RTP of 32 days (Appendix, Table 3). Since BFlh grade 3^r injuries present a high burden to the patient, we compared the RTP by location and mechanism of injury. We observed that injuries affecting the BFlh at Md caused by sprinting presented the highest RTP (41,5 days). Nonetheless, counts were low except for injuries at Pp caused by sprinting, which affected 17 patients with an average RTP of 39,5 days (Appendix, Table 4).

Proximal injuries have been identified as being more complex and having a poorer prognosis. When looking at Pp injuries of BFlh or SMT grade 3^r, we identified 23 individuals where injury had been caused by sprinting, and only 2 where injury had been caused by stretching, with average RTP of 40,5 and 38 days, respectively (Appendix, Table 5). Finally, we observed that Mp injuries of the BFlh and SMT with grade 3^r caused by stretching had an excellent prognosis, with an RTP of 6 days (n=3). On the contrary, Mp injuries of the BFlh and SMT with grade 3^{r} caused by sprinting had an RTP of 32,3 days (n 10) (Appendix, Table 6).

In order to assess the effect of sprinting and stretching, we re-ran the XGBoost model, including the mechanism. We observed that injuries caused by the stretching mechanism were associated with a lower RTP, while injuries caused by the sprinting mechanism had a slightly worse prognosis (Appendix, Figure 1).

Finally, for inter- and intra-observer reliability, Cohen’s Kappa and the intraclass correlation coefficient (ICC) showed an excellent level of agreement between the different measurements (Addendum section, original paper, Supplementary files, Table 2).

8 DISCUSSION

This thesis derived from an assignment from the FCB medical department to design a classification system as part of its muscle injury guide (95). A group of experts, mainly from ASPETAR and FCB, and the co-authors of the first article included in this thesis agreed on the need to develop a muscle injury classification system, since the ones existing at that time were not satisfactory. The main suggestions were to reduce subjectivity and discrepancies in terminology, and to highlight the importance of differentiating between the injuries affecting the muscle and the ones affecting the tendon (biological time). Subsequently, we focused on ECM damage.

Important aspects of any classification system are the use of clear, non-ambiguous, and least-subjective terminology, and the achievement of the highest level of consensus possible among experts (62). There are different terms to describe muscle injuries; however, they lack a clear definition and consensus. not even the term fascia, used to refer to part or the whole MTJ structure (114). All these terms describe the location of the injury in relation to the MTJ anatomy and/or the damage to the muscle/MTJ. The term myofascial, for example, is used in literature to define a particular injury location with a different clinical evolution and prognosis (63, 78, 86, 87, 92, 115-121). Other criteria defining a myofascial injury, like the extent of the lesion, are not described in the literature. This also happens in the case of terms like peripheral (78), myoaponeurotic (122), and epimysial (63, 123, 124), for example. Finally, a classification system requires clear and generally accepted definitions to allow effective communication between healthcare providers and researchers (125, 126). For example, we avoided terms such as “strain” and “tear” to have a more precise classification system.

Once developed, we compared our MLG-R muscle injury classification system with the two most commonly used systems: the Munich and the BAMIC.

First, both the MLG-R and the Munich systems classify injuries as direct or indirect, according to the mechanism. However, the latter subdivides indirect injuries in functional (overexertion or neuromuscular) and structural (55). The BAMIC system is limited to indirect injuries, subclassified in myofascial, myotendinous, or intratendinous (92).

Unlike the Munich system, ours does not aim to incorporate non-structural disorders. Several works highlighted that functional disorders related to muscle injuries need further investigation (127-129). The diagnosis of these muscle disorders is not well understood, and this makes it difficult to acquire reliable epidemiological data. Moreover, time loss related to functional disorders reported in some series with football players is high (64, 91). However, we cannot discard the influence of several external factors, mainly the interest of individual players on time loss.

Exercise-Induced Muscle Damage (EIMD) as delayed-onset muscular soreness (DOMS) is incorporated in the Munich and other previous systems (55, 130), but not in the BAMIC (92). We did not include DOMS as a muscle injury because we considered it more as an strength adaptive process (131-136). While histological disturbances may be present, their origin appears to be related to an intense activity for which the muscle is unprepared (135, 137).

To grade structural injuries (minor, partial, moderate, subtotal, complete, or tendon avulsion), the Munich system uses similar general histological/anatomical criteria as previous classical imaging systems (94) (55). The BAMIC system grades instead structural injuries on the basis of their extension visualized by MRI. Specifically, it evaluates the amount of fiber disruption, the craniocaudal length (CCL), and the CSA. The cutting points for every grade are similar to the ones used in other systems (130, 138, 139), and they are more based on a "comfortable exact numeric value" than on previous research. Finally, the MLG-R system classifies injuries in two groups (direct or indirect) and four grades (0 to 3), the reader can find the detailed criteria for the different grades in the study I. Grade 0 injuries are clinically apparent muscle injuries with a negative MRI (62). Injuries are defined as grade 1 or 2 when edema is present and according to MRI characteristics, but not extension. This is based on the biological time for healing (140). Finally, when a fiber disruption is visible through MRI, injuries are defined as grade 3. Indeed, the time needed to heal when there is a fibre disruption is higher than for oedema as has been proved in the literature (61). The MLG-R system also subclassify grade 3 injuries by adding the superscript "r" if there is quantifiable damage to the connective tissue (141), since the time to heal the muscle tissue is shorter than the time needed for connective tissue.

The relationship between the extension of the damage evaluated by the MRI and RTP has been previously studied (60, 105) with inconsistent results, possibly because there was no differentiation between the tissues affected, which we demonstrated to be the most critical factor for prognosis (141). In a study by Moen et al. (105), for example, hamstring were classified in four grades: "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, and grade (3): total muscle or tendon rupture. When no abnormalities were found, we regarded this as a grade 0 injury" (105).

Although a bigger CSA is thought to cause more damage to the ECM, we consider this assumption too simplistic, since the distribution of the connective tissue is not homogenous or symmetrical. Indeed, the ECM goes from a higher to a lower density structure with an asymmetric distribution in the muscle belly (142). Therefore, depending on the location, the amount of connective tissue injured could be different even in two injuries with a CSA of the same size. Finally, the evaluation of the CSA should be done separately for the muscle and the tendon. We also considered splitting grade 3 injuries into subgrades depending on the CSA extension like in previous systems (92, 105, 130, 138, 139). However, to decide the cutting points, we would need a bigger sample.

The Munich system (55) does not differentiate if the injured tissue is muscle or tendon, and does not describe the relationship of the injury with the MTJ anatomy. The BAMIC system (92) does not differentiate between injured tissues either, but it classifies injuries into myofascial, myotendinous, and intratendinous, according to their relationship with the MTJ anatomy. However, there are no defined criteria for such classification, but it purely depends on the opinion of the professional.

The importance of injuries affecting the connective tissue has been assessed in previous literature. It has been shown that time of recovery is longer for them than for muscle injuries, and the treatment and rehabilitation are more extensive (86, 113, 143). The BAMIC group also highlights these aspects, even if it does not study injuries affecting the connective tissue not only as intratendinous injuries but in other parts/manners of the MTJ, also having effect on the RTP (113).
A study using the BAMIC system (114) included 65 hamstring injuries in 44 athletes from track and field disciplines: 28 males (63,6%) and 16 females

(36,4%). Of the 65 injuries, 21 were grade 0 (clinically apparent muscle injuries but with negative MRI), still not well understood: they could either be minimum muscle injuries not detected by an MRI, or injuries affecting tissues other than muscle. Therefore, only 44 grade 2 and 3 injuries were analyzed. Of these, 43,1% were located in the BFlh, 6,2% in the ST, 10,8% in the SB, and 1,5% in the BFsh. In 6,2% of the cases, there were multiple muscle injuries. In the study III of this thesis, 71,1 % of the muscle injuries were located in the BFlh, 15,8% in the SB, 11,8% in the ST, and 1,3 % in the BFsh. These differences could be due to several factors, like sample size, gender, and sport.

In the Munich and BAMIC systems, RTP could not be compared between grades because of the lack of differentiation between the tissues affected. However, both systems agree that injuries affecting the connective tissue and higher-grade injuries need a longer RTP time (113, 141).

In the BAMIC study (114), there were no significant differences in RTP between grades 1 and 2 or between classifications (myofascial and myotendinous). There was also no difference in RTP or risk of reinjury depending on the injury location (proximal, central, or distal) (113).

Hamstring reinjury rates have been reported to range from 12% to 4-5 times this value (144); however, they are usually around 15–20% (113). According to the BAMIC system, the link between the extent of the injury and the risk of reinjury is inconclusive (61, 145, 146), possibly because the system does not distinguish between the tissues affected, and injuries are quantified quantitatively rather than qualitatively.

In the Munich study (56), the percentage of reinjuries was 13%. There was no significant association between the injury classification and the risk of reinjury: the percentage of reinjuries was 13% in the case of minor injuries; 12% in the case of partial/moderate muscle tears; and 20% in subtotal/complete muscle injuries/tendinous avulsions (90). In the BAMIC study, the percentage of reinjuries was 18,5%, and the grade of the injury was not associated with the risk of reinjury. Also, no difference in reinjury rate was found according to injury location in relation to the MTJ (proximal, central, or distal) (113). However, having an injury located at the intratendon was associated with a higher risk of recurrence. Finally, in the sample we analyzed with the MLG-R system, the percentage of reinjuries was 11,8%; 2 injuries were grade 2, and 7 were grade 3^r. All the grade 3^r injuries were located either at the proximal third around the fibers of the proximal MTJ (Pp), or at the distal third around the fibers of the distal MTJ (Dd), closer to the origin/insertion points. Therefore, we concluded that a higher risk of reinjuries occurs when injuries affect the MTJ.

Initially, we showed that stretching injuries had a better prognosis and a lower RTP, so we included the mechanism of injury (stretching or sprinting) as a classification factor. However, we then decided to exclude this item from the final MLG-R classification system since it did not present enough heterogeneity (most stretching injuries were located in the SMB and most sprinting injuries in the proximal area of the BFlh). Also, we showed that this item had very little prognostic value in comparison to the others, while adding complexity to the classification in terms of interpretability, ease of use, and computational complexity. Finally, to better understand the mechanism of hamstring injuries and their interaction with other prognostic factors and reduce the burden on the player, further research must be conducted.

Several studies show that the RTP for direct injuries is shorter than the one for indirect injuries (147, 148). In a direct injury, the damaging force is external, resulting in a compression of the muscle tissue. This results in swelling/rupture of the muscle fibers, with a subsequent inflammatory/bleeding event at the location of the trauma (4). The consequences at the site of the impact can range from a localized muscle edema to an intramuscular hematoma, depending on the force of the trauma and the contraction level of the muscle at the time of impact (149-151). The shorter RTP time in this type of injury might be due to the fact that the ECM is preserved; therefore, the primary mechanism of transmission of the muscle force is minimally affected, and symptoms are limited to the inflammatory/bleeding event in the muscle tissue. On the contrary, an indirect injury is located at the MTJ (11), and the force responsible for the damage is transmitted through the ECM from the sarcomere to the connective tissue 3D structure. The severity of the injury depends on the location of the damage in the ECM. The closer to the insertion, the thicker the ECM is, leading to a more severe injury, with more signs/symptoms and requiring a longer RTP time (141). Finally, a deep knowledge of the MTJ anatomy is key to understand muscle injuries (141).

As A. R. Gillies said: “skeletal muscle is primarily contractile material. However, because muscle is a composite tissue of connective tissue, blood vessels, and nerves, as well as contractile material, these “minor tissues” (in terms of relative mass) may strongly influence muscle function” (152).

The main factor determining the time needed for the RTP is the location and extension of the ECM injury. Therefore, the focus should be shifted to the connective tissue structures of the muscle-tendon unit. However, the knowledge on the functional properties and geometry of muscular ECM is minimal (152-154). The three layers of ECM (endomysium, epimysium, and perimysium) are not individual layers covering the muscle, but they form a three-dimensional network with complex geometry and multiple connections (154). Therefore, the description of ECM injuries should be focused on evaluating the extension and location with regards to the MTJ anatomy and not the layer of the ECM affected. A correct description and diagnosis of the injury allow us to identify and quantify which tissues are affected and the extension of the injury. We should consider classifying injuries as connective or myoconnective, instead of just talking about muscle injuries, to acknowledge the vital role of the ECM in the diagnosis and prognosis (155). Finally, identifying the tissue affected in an injury is essential for reaching the correct prognosis, identifying the healing time, and achieving a proper rehabilitation, reducing the risk of reinjury. We proved that the MLG-R system is able to identify the tissue affected in an injury.

9 STRENGTHS AND LIMITATIONS

The main limitations of our system are that the sample size, it was from one institution (FCB), and only included male athletes playing one sport. Therefore, testing the classification system in multiple centers with different sports is necessary to increase the knowledge about muscle injuries.

Another limitation of the MLG-R system is its complex nomenclature, which could reduce its appeal among the sports community (94). Indeed, although the use of our classification system is easy to understand, it requires a deep knowledge of muscle anatomy (156). However, a learning curve is always necessary when starting to use a new classification system, so it does not really limit the use of ours.

Finally, more parameters may play a role in the prognosis and risk of reinjury and are worth considering in future studies: the level of pain at the time of the injury, the time needed to walk pain-free after a hamstring injury, the percentage of strength loss compared to the contralateral muscle, or a previous ipsilateral test. Additionally, although we inspected the prognostic value of the mechanism of injury (stretching or sprinting), its role and relevance in the RTP still need to be determined.

The main strength of the MLG-R classification system is that it is the first one incorporating reinjury status into the grading of muscle injuries (94). Moreover, it is based on research and experience of clinical experts in the field from 3 institutes, and offers a detailed definition of the grading levels, with prognostic value and easy clinical application for physicians, physiotherapists, trainers, and coaches. By filling out the four letters, our classification system gives a full description of an injury and its evolution: how it occurred where it is located (its relationship with the MTJ), its grade (amount of connective tissue affected), and its chronology (first episode or reinjury).

We also demonstrated that the MRI-based MLG-R classification system provides an accurate prognosis on hamstring injuries in professional athletes, and that the main determinant for RTP after a hamstring injury is the connective tissue affected. Another strength is that the results came from a homogeneous sample of professional football players with the same resources, philosophy for diagnosis, rehabilitation, and RTP criteria. Finally, all the players were followed up for at least one season after the injury, allowing us to monitor reinjuries or new injuries in the same region.

10 FUTURE PERSPECTIVE

Our system is flexible and open: it can be easily adapted to incorporate further relevant knowledge for the prognosis and diagnosis of different muscle groups.

The results presented in this thesis have important implications for future research in the field of muscle injury. First, they highlight the importance of differentiating between tissues and evaluating ECM damage in future muscle injury classification systems. Also, they show that the biological time to heal different tissues (muscles and tendons) must be considered to determine the RTP time when designing rehabilitation protocols.

11 CONCLUSIONS

Writing a thesis is a crucial step in professional life and entails important moments for the author. For a thesis, as for life in general, you can set a plan, but then you may reach your goal through unanticipated paths. In particular, writing this thesis took me longer than expected because of several factors: the process of reviewing the literature; the inclusion of several institutions plus external experts in the design of the system; and the slow process of publishing the papers (especially during the COVID-19 pandemic). However, the unexpected length of the journey eventually became an advantage, as we had the chance to better understand our goal and even improve it.

STUDY I

We obtained an evidence-informed and expert consensus-based classification system for muscle injuries. With our MLG-R system, we can describe the injury mechanism (M), location (L), and grade of severity (G), and the number of reinjuries (R). This way, we minimize the subjectivity of the injury description. We demonstrated that our MLG-R muscle injury classification system is easy to apply, although a deep knowledge of muscle anatomy is required. It is flexible and open, allowing the incorporation of any further knowledge relevant to prognosis or diagnosis, and it is the first system incorporating reinjury status. In particular, reinjuries influence the prognosis and must be taken in account for the RTP. Therefore, incorporating reinjury status helps to understand the history and foresee the evolution of the original injury.

STUDY III

We showed that the injury grade is the most important variable to determine the RTP, followed by location with respect to the MTJ. In our sample, 50 (65.8%) of the 76 injuries are grade 3^{r}, and we refer to them as muscle injuries even if, in most cases, they affect the MTJ.

From the different grades, the main determinant for RTP is the damage to the connective tissue structures of the muscle, grade 3^{r}. This finding supports the concept that the ECM and its role in force generation and transmission are key for the signs, symptoms, and prognosis of muscle injuries.

In particular, we observed that RTP is greater for injuries affecting the BFlh/ST FT than for injuries located at the central tendon. This reinforces the idea that the more proximal the location of an injury, the higher the RTP. Moreover, we found that RTP is grater for BFlh injuries with complete gap than for BFlh injuries with partial gap. This further proves that the greater the CSA of the intramuscular tendon, the higher the RTP. Because of these observations, we designed our system with the main aim to evaluate the ECM damage.

Finally, the Cohen's kappa and the intra-class correlation coefficient showed an excellent level of agreement between the different measurements, and a strong interobserver reliability.

In conclusion, we show that our novel muscle injury classification system serves to validate and understand the clinical prognosis of hamstring injuries, with several advantages in comparison to previous systems.

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13 APPENDIX

Table 1: RTP for stretching and sprinting injuries

Sprint/Stretc	N	Average RTP	SD RTP
Sprint	63	30.8	16.4
Stretch	13	19.5	17.2

Table 2: RTP for stretching and sprinting SM, ST, and BFlh injuries (all included)

Muscle_injur	Sprint/Stretc	N	Average RTP	SD RTP
BFlh	Sprint	53	30	16.5
BFlh	Stretch	1	20	NA
BFsh	Sprint	1	21	NA
SMB	Sprint	1	29	NA
SMB	Stretch	11	16.2	14.5
SMT	Sprint	8	37.8	16.5
SMT	Stretch	1	56	NA

Table 3: RTP for stretching and sprinting BFlh grade 2 or 3^r injuries

Sprint/Stretc	N	Average RTP	SD RTP
Sprint	47	32	16.5
Stretch	1	20	NA

Table 4: RTP for stretching and sprinting BFlh I D_d 3r injuries and BFlh P_p 3^r injuries

Sprint/Stretc	Location	N	Average RTP	SD RTP
Sprint	Dd	5	35.2	10.9
Sprint	Dp	1	29	NA
Sprint	Md	4	41.5	14.7
Sprint	Mp	7	37.7	12.2
Sprint	Pp	17	39.5	17.2
Stretch	Pp	1	20	NA

Table 5: **RTP for stretching and sprinting BFlh+SMT Pp 3r injuries**

Sprint/Stretc	Location	N	Average RTP	SD RTP
Sprint	Pp	23	40.5	16.2
Stretch	Pp	2	38	25.5

Table 6: **RTP for stretching and sprinting Mp and Md injuries**

Sprint/Stretc	Location	N	Average RTP	SD RTP
Sprint	Md	7	29.9	18.3
Sprint	Mp	10	32.3	14.1
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14 ADENDUMS (PAPERS)

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New Evidenceensus- Based Application

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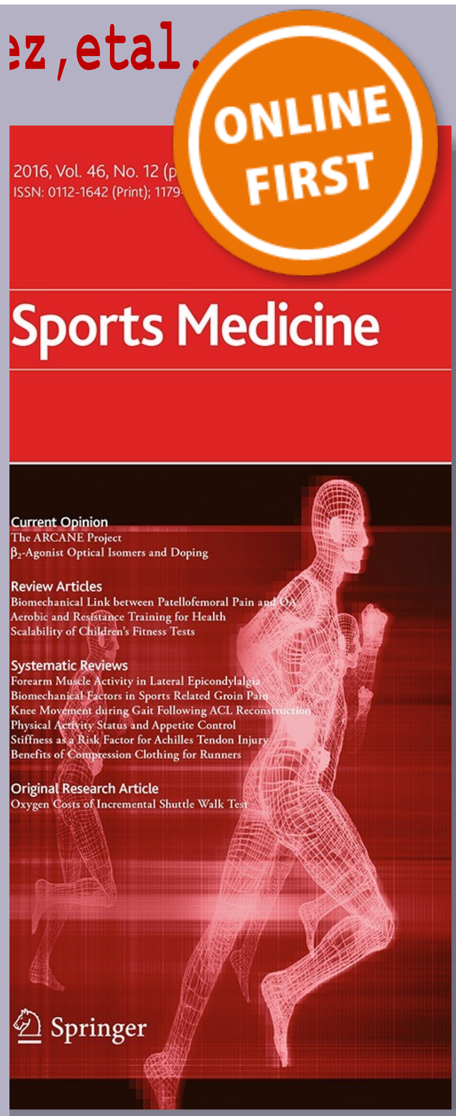

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LEADING ARTICLE

Muscle Injuries in Sports: A New Evidence-Informed and Expert Consensus-Based Classification with Clinical Application

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Abstract Muscle injuries are among the most common injuries in sport and continue to be a major concern because of training and competition time loss, challenging decision making regarding treatment and return to sport, and a relatively high recurrence rate. An adequate classification of muscle injury is essential for a full understanding of the injury and to optimize its management and return-to-play process. The ongoing failure to establish a classification system with broad acceptance has resulted from factors such as limited clinical applicability, and the inclusion of subjective findings and ambiguous terminology. The purpose of this article was to describe a classification system for muscle injuries with easy clinical application, adequate grouping of injuries with similar functional impairment, and potential prognostic value. This evidence-informed and expert consensus-based classification system for muscle injuries is based on a four-letter initialism system: MLG-R, respectively referring to the mechanism of injury (M), location of injury (L), grading of severity (G), and number of muscle re-injuries (R). The goal of the classification is to enhance communication between healthcare and sports-related professionals and facilitate rehabilitation and return-to-play decision making.

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Key Points

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The article describes a new evidence-informed and expert-consensus classification for muscle injuries.

The information contained under the initialism MLG-R (mechanism, location, grading, and reinjury) represents the most valuable information with clinical application.

The new classification should improve communication between health- and athlete-related professionals regarding muscle injuries.

1 Introduction

Muscle injuries are very common in soccer [1], rugby [2], American Football [3–5], Australian Football [6, 7], and track and field [8, 9]. The incidence of muscle injury may be as high as 31% in soccer and 28.2% in track and field [1, 9]. The muscles most commonly involved are biarticular with a complex architecture and containing a high proportion of fast-twitch fibers [1]. Ninety percent of injuries are caused by either excessive strain or contusion [10, 11]. In professional soccer, between 92 and 97% of all muscle injuries are located in the lower extremity: hamstrings (28–37%), quadriceps (19–32%), adductors (19–23%), and calf muscles (12–13%) [1, 12]. A European elite soccer team can anticipate up to 15 muscle injuries per season resulting in up to 223 days of training absence (27% of total time loss) and players missing 37 matches [1]. However, determining when a player is ready to return to play (RTP) following muscle injury is challenging because the recovery from injury is highly variable [13, 14]; premature RTP may be a factor in the observed high re-injury rates (12–43%) and prolonged time loss [1, 13, 15–19]. Significantly, professional soccer teams with lower season injury rates have a better performance in their national and international competitions [20, 21]. Therefore, muscle injuries are a major concern in sports medicine.

The severity of an injury can be determined by both direct and indirect means (i.e., clinically, through imaging studies, and through blood tests) [22]. Given that histological analysis of injured muscle tissue is not feasible as a routine diagnostic test, the description of injury severity is typically based on signs and symptoms, information about the mechanism of injury, and imaging studies. The mainstay for diagnosis and classification of muscle injuries has been a thorough history and physical examination, assisted by ultrasound and magnetic resonance imaging (MRI) studies. Several grading and classification systems for muscle injuries [23–33], specific muscles [34–36], or muscle groups [37, 38] have been published [39]. Some of these classification systems have been based on either clinical [23, 24] or imaging studies [25–27, 30], while others are based on a combination of clinical and imaging assessment [31, 32].

One of the recent combined classification approaches is the Munich consensus statement [31], which has been tested for validity [40]. In the validation study, it was concluded that the proposal was better for 'structural' compared with 'functional' injuries [40]. British Athletics has also proposed a muscle injury classification system, which has demonstrated reproducibility and consistency [41]. Their classification system recognises that injuries extending into the tendinous portion are associated with longer time loss and increased recurrence rate [41]. However, both of these classification systems use ambiguous terms, such as 'myofascial' by British Athletics and 'functional' in the Munich consensus. This may prevent universal use of both classifications.

An ideal classification system should include non-ambiguous terms, be easily applied, and describe objective findings that are clearly demonstrable [42]. Furthermore, a muscle injury classification system with real clinical value for clinicians, trainers, and athletes should have prognostic validity [43]. As a result, establishing a classification system exclusively based on clinical or imaging study data is challenging [39] and as such there is still not universal agreement on the utility and clinical application of the available classification systems [39, 42, 44].

The purpose of the present article was to describe a classification system for muscle injuries with easy clinical application, adequate grouping of injuries with similar functional impairment, and potential prognostic value.

2 Methodological Aspects

2.1 Procedures

An evidence-informed and expert consensus-based study was used. The methodology employed in the present research was based on previous publications related to consensus statements in medicine [45–47]. Three different centers (FC Barcelona Medical Department, Aspetar, and Duke Sports Science Institute) from three different continents (Europe, Asia, and North America), all with a high volume of muscle injuries and extensive experience in elite sports medicine were involved. The study was designed in three phases: (1) identify the existing evidence related to risk and prognostic factors for muscle injuries; (2) discuss these factors between two of the centers and establish a consensus based on the quality of studies in combination with experts' experience; and (3) elaborate the final classification. One of the authors (XV) first performed an electronic literature search to identify the risk and prognostic factors. The PubMed (MEDLINE) database was used to identify the relevant clinical studies in muscle injuries. The following search terms were employed and restricted to the English language: (muscle injury OR muscular injury OR muscle injuries OR muscular injuries OR muscle lesion OR muscular lesion OR muscle lesions OR muscular lesions OR muscle strain OR muscular strain OR muscle strains OR muscular strains OR muscle damage OR muscular damage) AND [(classification OR classifications OR rating OR grading OR severity) OR (risk factor OR risk factors OR prognostic factor OR prognostic factors OR predisposing OR predisposition)]. To be considered, articles were required to be original clinical research, but review articles were used to manually search for references potentially missed in the original literature search.

Two consensus meetings were held between two of the involved institutions (FC Barcelona and Aspetar). The results of the electronic literature search were initially presented (XV) and discussed between the four authors (GR, RP, LT, JAG) from FC Barcelona to determine the terms to bring to the first meeting. The first meeting of the two institutions was held in Doha in July 2013. Each topic was openly discussed during the meeting. All expert opinion and assessment of the included terms were taken into consideration and a first consensus position determined. The document from the first meeting was summarized and sent to all the authors involved in the meeting (XV, JT, BH, GR, RP, LT, JAG, RW, EW). A second review of the literature based on a manual search of references in the list of relevant studies and review articles was performed by one of the authors and the information extracted (XV). The information was then incorporated into a first draft of the classification system. This document was then reviewed by the authors from both institutions and a second meeting was scheduled. A time frame of 10 months was left between the two meetings to ensure adequate time for evaluation of the classification prior to the second meeting. Between the first and second meeting, the draft was developed iteratively based on comments from all authors.

A second meeting was held in Barcelona in May 2014 between the two institutions. All participants were given the opportunity to report concerns with the terms considered for the classification, and to critique and give personal opinion on the topic. A group agreement was achieved and a final preliminary document generated from this second meeting. This document was again sent to all participants at the two meetings (XV, JT, BH, GR, RP, LT, JAG, RW, and EW) and a time frame of 6 months given before the final consensus. During this period of 6 months, the draft evolved iteratively until agreement was achieved, and a final document was then approved by all involved participants. This final document was then sent to a FIFA Medical Centre for Excellence (Duke Sports Science Institute) to be evaluated by two authors (WEG and EAG). As a last stage, the final document was also sent to other professionals to provide a broad and multidisciplinary feedback on the new classification system: an expert radiologist in MRI (XA), an expert in ultrasound (RB), an expert and recognized orthopedic surgeon with a special interest in muscle injuries (JCM), a researcher with extensive experience in sports medicine investigation (KS), and another international expert in muscle injuries (NM). The comments and suggestions from these six authors (EAG, WEG, XA, RB, NM, JCM, KS) were incorporated into the final muscle classification, which was approved by all authors in October 2015.

2.2 Terms and Concepts Reviewed

A summary of the terms and concepts discussed in the meetings to be incorporated into the new classification is shown below.

2.2.1 Mechanism of Injury: Direct or Indirect

Classically, muscle injuries have been classified as direct or indirect [10, 48–50]. In the hamstring, indirect injuries are considered as being either a sprinting or stretching type, with a relationship between the injury mechanism, localization, and prognosis [51, 52]. Indirect muscle injuries are typically located close to a myotendinous junction (MTJ) [49, 51, 53–58], proximally or distally, or within an intramuscular tendon [37, 56, 59–62]. They have also been described on ultrasound and MRI as involving the periphery of a muscle (i.e., epimysium, fascia) [63, 64]. The age of the patient has been also shown to influence the location of muscle injuries [65].

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Conversely, direct injuries are located where the contact occurs. Direct muscle injuries have been graded based on clinical signs [36]. If the muscle is contracted when the impact happens, the energy is best absorbed and consequently less histological damage is observed [11, 66, 67]. The size of direct muscle injuries is not well correlated with clinical signs and functional impairment [68], and such injuries usually have a better evolution with a shorter time to recovery in comparison to indirect injuries [69].

2.2.2 Connective Tissue Organization

The structure of the extracellular matrix (ECM) has been classically described in three layers: endomysium, perimysium, and epimysium. Currently, the ECM is considered a complex and interconnected structure [70–72], where ''muscle fibers are embedded within a matrix of ECM that forms discrete layers that are mechanically interconnected'' [73]. In this model, force generated by actin-myosin interaction is transmitted to the ECM and subsequently to the net of connective tissue. Focal ECM or muscle fiber injuries are reported to have negligible functional significance owing to the mechanical redundancy built into the ECM [73]. This connective tissue net structure and its role in force generation and transmission is a key factor in the signs, symptoms, and prognosis of muscle injuries [74]. In other words, the more ECM is injured the worse the prognosis [75–77].

Because of the important role of the ECM in clinical symptoms and severity of muscle injuries, an important component of the classification system is based on the evaluation of the amount and severity of the ECM damage. The amount of damage to the ECM depends on the mechanism of injury (direct or indirect) [78], the injury relationship with the MTJ (proximal or distal to the MTJ insertion; the more proximal to the MTJ insertion the injury is located, the greater the amount of damage to the ECM) [75], the percentage of the muscle cross-sectional area (CSA) (as defined by Slavotinek [79]) affected by the injury (degree of injury), and the presence of tendon involvement [76].

2.2.3 Prognostic Factors

There was a complete group consensus to include prognostic factors to the classification. Although some studies have based the prognostic factors on imaging studies, the group decided to design a classification that considers the inclusion of clinical and imaging characteristics as potential prognostic factors according to our experience and the available studies [37, 43, 80].

Regarding clinical characteristics, in a direct muscle injury, the force producing the injury is externally applied and the muscle damage occurs as a result of compression between the external force and the bone. This injury tends to be more superficial in contracted muscles and deeper when the muscle is relaxed at the time the trauma happens [11]. There are animal model studies regarding direct injury that show a deficit in contractile function, although the authors mention that ''extrapolating the relationship between injury severity and functional loss to clinical situations is also limited since contractility was measured during maximal tetanus in an anesthetized animal'' [81].

In indirect injuries, the force creating the injury is transmitted through the ECM [82]. The closer the injury location is to the MTJ attachment the greater the amount of ECM that will be injured and the more severe the clinical impairment [75]. The mechanism of hamstring muscle injury can also be related to injury location. Stretching injuries more often affect the proximal semimembranosus, in either the muscle or tendon tissue [51, 83]. Although it has been previously reported that proximal muscle injuries are associated with longer rehabilitation periods [51], this has not been confirmed in recent studies [13, 62, 84]. Other signs and symptoms used as prognostic factors are the time needed to walk pain free after a hamstring injury or specific functional characteristics. Injuries requiring more than 24 h before pain-free walking have been related to an expected time loss greater than 3 weeks [43]. For functional characteristics, active knee range of motion deficit after a hamstring injury may be a valid parameter to grade the injury severity and the expected recovery time in elite athletes [18, 37, 85]. The level of evidence for the influence of time to walk pain free and have an active knee range of motion on the prognosis of hamstring muscle injuries is still low.

Regarding imaging characteristics, MRI or ultrasound has been used to establish a relationship between evolution of the injury and type, location, tendon involvement, and extent of the injury [1, 13, 16, 17, 19, 37, 51, 62–64, 80, 83, 86–94]. Although imaging studies have good diagnostic value, their usefulness in predicting RTP using edema as a marker for injury is limited [95]. In the acute phase of injury, most of the existing evidence regarding prognostic value of imaging studies (mainly MRI based) is related to hamstrings and rectus femoris muscles [16, 90, 96]. These studies have tried to establish an association between different imaging measurements and time loss. Slavotinek reported that the percentage of the cross-sectional area (% CSA), the craniocaudal length, and the injury volume were the MRI parameters associated with time loss [79]. These parameters provide prognostic information owing to their relationship with the amount of disrupted fibers and the degree of dysfunction, and thereby suggest time to recovery. The strongest association with return to sport was related to the craniocaudal length adjacent to the MTJ [79]. It has also been observed that there is less time loss in patients with the clinical suspicion of a hamstrings injury but negative MRI [13, 16, 17, 62, 64, 80, 97]. There is also evidence regarding imaging-based prognostic factors from other muscles.

In rectus femoris injuries, it has been shown in MRI and ultrasound studies that when the central tendon is disrupted the recovery duration is longer [63, 98, 99]. The soleus muscle has also been investigated [94], reporting the prognosis and RTP according to injury location in the soleus muscle. The authors found that injuries in the central aponeurosis had a longer recovery time than injuries in the lateral and medial aponeurosis and myofascial sites [94]. Hence, in addition to the musculotendinous injury being a site of relevant pathology, the intramuscular tendon may be injured [76], with a variety of appearances on MRI. There is some evidence that these injuries require a prolonged rehabilitation time and may have higher recurrence rates [76]. As a result, it is important to recognize the tendon component of a muscle injury and its role in prognosis [41].

In summary, several parameters related to the extent of muscle injury and tendon involvement are potentially associated with duration of time loss from competition. These parameters may guide clinicians during the management of these injuries and therefore should be incorporated into a muscle injury classification system.

3 New Classification System

The new classification system proposed for muscle injuries was elaborated after the final consensus between the three institutions and is summarized in Table 1. For the purpose of this article, the hamstrings muscle group will be considered. The classification includes four main categories related to parameters with clinical and prognostic relevance: mechanism of injury (M), location of injury (L), grading of severity (G), and number of muscle re-injuries (R). The classification can be therefore abbreviated as MLG-R (Table 1). Category M stands for direct and indirect muscle injuries. Subcategories of the mechanism (M) category were created to define stretching type (subindex S) and sprinting-type (sub-index P) indirect hamstring muscle injuries (Table 1). Category L (location) was subdivided into injuries located at the proximal, middle, or distal third of the muscle belly, with injuries further subclassified according to the relationship with the MTJ (Table 1). For the purpose of this article, muscle belly is defined according to Askling criteria but considering three portions (proximal, middle, and distal) instead of two [100]. The criteria for the MRI measurements have been previously described [79]. For the grading (G) category, the injury is evaluated on T2-weighted MRI (the presence of a hyperintense signal is considered positive), and the consensus was that an MRI should be performed between 24 and 48 h following injury. If more than one muscle is injured, the muscle with the greater area of signal abnormality or architectural distortion will be considered the primary site of injury and grading criteria will be taken for that particular muscle. Only the presence or absence of edema is recorded for grades 1 and 2 (Table 1); no differentiation is made between different volumes of edema. A recurrence (R) is defined as an injury of the same type and location as the index injury occurring during the first 2 months after return to full competition [1].

Injuries affecting the same MTJ, its intramuscular tendon or fibers associated with it (even in a different location), will also be considered a re-injury. As an example, if the first injury of the long head of biceps femoris affects the proximal MTJ in the proximal third of the muscle belly and another injury occurs within the next 2 months but located in the middle third of the muscle belly in fibers related to the proximal MTJ, this would be considered a re-injury. By contrast, if the second injury is located around or affecting the distal MTJ (a different MTJ from the initial injury), it would not be considered a re-injury. In other words, a reinjury is the occurrence of a muscle injury affecting the same muscle and MTJ as the initial injury. Figures 1, 2, 3, 4 and 5 show examples of muscle injuries classified using the MLG-R system.

4 Discussion

The principal purpose of this article was to propose a classification system for muscle injuries capable of describing the injury, with useful clinical application, a

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quick learning curve, and the potential to provide prognostic value. Based on existing evidence and our group's clinical experience, we considered that the mechanism of injury (M), injury location (L), MRI-based grading (G), and previous muscle injuries (R) as the most important factors to be included. Although this classification was designed with the aim of being applied to any muscle group, it initially described injuries to the hamstring muscles (Table 1). Subsequent studies will be conducted to report modification of this classification system to include other muscle groups and validate its content.

An important aspect of any consensus classification is the use of clear, non-ambiguous, and least-subjective terminology and also that the concepts included account for the highest level of consensus among experts. 'Myofascial' is a term widely used, representing a different injury location with a different clinical evolution and prognosis [27, 30, 63, 64, 98, 99, 101–105]. The term myofascial is ambiguous, and other terms such as 'peripheral' [63], 'myoaponeurotic' [106], 'epimysial' [55, 64, 107], or 'distal aponeurosis' have been suggested [90, 108]. The uniform definition and appropriate use of all these terms remain difficult but necessary for effective communication between healthcare providers and researchers [109, 110]. A recent article has suggested a classification for the fascia, defining its terminology, and describing its function and histological features [109]. As a result of this complexity, this classification describes the anatomical location of the injury and its relationship with the MTJ so that the term fascia is no longer needed, thereby avoiding terminological confusion.

One of the concepts that we analyzed and discussed in the present consensus was the definition of functional or non-structural disorders that was suggested in another classification system [31]. We believe non-structural or

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Table 1 Summary of the muscle classification system

Mechanism of injury (M)	Locations of injury (L)	Grading of severity (G)	No. of muscle re-injuries (R)
Hamstring direct injuries			
T (direct)			
	P Injury located in the proximal third of the muscle belly	0–3	0: 1st episode
	M Injury located in the middle third of the muscle belly		1: 1st reinjury
	D Injury located in the distal third of the muscle belly		2: 2nd reinjury …
Hamstring indirect injuries		0–3	
I (indirect) plus sub-index s for stretching type, or sub-index p for sprinting type	P Injury located in the proximal third of the muscle belly. The second letter is a sub-index p or d to describe the injury relation with the proximal or distal MTJ, respectively		0: 1st episode
	M Injury located in the middle third of the muscle belly, plus the corresponding sub-index		1: 1st reinjury 2: 2nd reinjury …
	D Injury located in the distal third of the muscle belly, plus the corresponding sub-index		
Negative MRI injuries (location is pain relat ed)		0–3	
N plus sub-index s for indirect injuries stretching type, or sub-index p for sprinting type	N p Proximal third injury		
	N m Middle third injury		0: 1st episode
	N d Distal third injury		1: 1st reinjury
			2: 2nd reinjury …
Grading of injury severity			
0	When codifying indirect injuries with clinical suspicion but negative MRI, a grade 0 injury is codified. In these cases, the second letter describes the pain locations in the muscle belly		
1	Hyperintense muscle fiber edema without intramuscular hemorrhage or architectural distortion (fiber architecture and pennation angle preserved). Edema pattern: interstitial hyperintensity with feathery distribution on FSPD or T2 FSE? STIR images		
2	Hyperintense muscle fiber and/or peritendon edema with minor muscle fiber architectural distortion (fiber blurring and/or pennation angle distortion) ± minor intermuscular hemorrhage, but no quantifiable gap between fibers. Edema pattern, same as for grade 1		
3	Any quantifiable gap between fibers in craniocaudal or axial planes. Hyperintense focal defect with partial retraction of muscle fibers ± intermuscular hemorrhage. The gap between fibers at the injury's maximal area in an axial plane of the affected muscle belly should be documented. The exact % CSA should be documented as a sub-index to the grade		
r	When codifying an intra-tendon injury or an injury affecting the MTJ or intramuscular tendon showing disruption/retraction or loss of tension exist (gap), a superscript (r) should be added to the grade		

CSA cross-sectional area, FSE fast spin echo, FSPD fat saturated proton density, MRI magnetic resonance imaging, MTJ myotendinous junction, STIR short tau inversion recovery

functional disorders should not be incorporated into our new muscle injury classification system at this moment. As other authors have pointed out, functional disorders related to muscle injuries require further investigation to be better understood [31, 42, 111]. The diagnosis of muscle distortion is not yet well understood and remains subjective, which makes the acquisition of solid epidemiological data difficult. The time loss related to functional disorders reported in some series is high [13, 40], but the influence of several external factors on this time loss cannot be discarded. Interestingly, Malliaropoulos et al. have reported a functional classification for posterior thigh muscles [37], including information on the ECM damage [73]. Unfortunately, this functional grading system has not been extensively used nor has it been explored for other muscle groups. Furthermore, delayed-onset muscular soreness should not be incorporated as a muscle injury because delayed-onset

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muscular soreness may be more of an adaptive process than an injury per se [112–117]. While histological disturbances might be present, their origin appears related to intense activity for which the muscle is unprepared [116, 118].

The present classification does not include terms such as 'strain' or 'tear' to avoid misunderstanding. We believe the

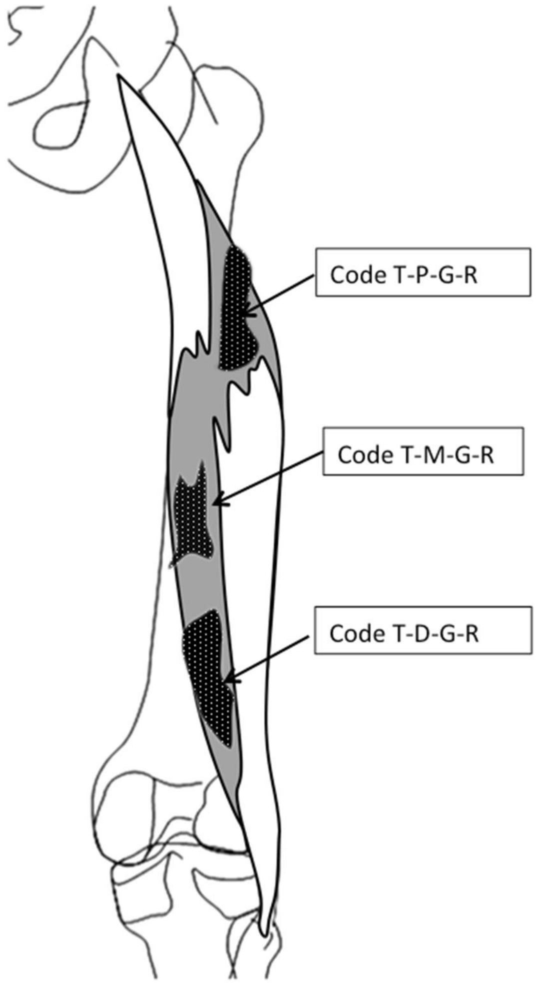

Fig. 1 Examples of codifications for biceps femoris long head (BFlh) direct injuries. T-P-G-R a BFlh direct injury located at the proximal third of the muscle belly, plus the corresponding grade and number of re-injuries. T-M-G-R a BFlh direct injury located at the middle third of the muscle belly, plus the corresponding grade and number of reinjuries. T-D-G-R a BFlh direct injury located at the distal third of the muscle belly, plus the corresponding grade and number of re-injuries

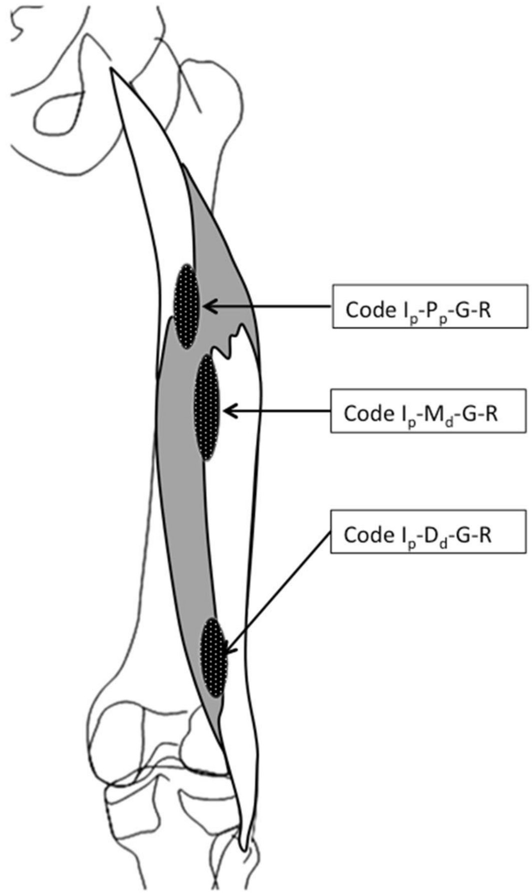

Fig. 2 Examples of codifications for biceps femoris long head (BFlh) indirect injuries, sprinting type. I_p-P_p-G-R a BFlh indirect injury sprinting type located in the proximal third of the muscle belly and related to fibers from the proximal myotendinous junction (MTJ), plus the corresponding grade and number of re-injuries. I_P-M_d-G-R a BFlh indirect injury sprinting type located in the middle third of the muscle belly and related to fibers from the distal MTJ, plus the corresponding grade and number of re-injuries. I_P-D_d-G-R a BFlh indirect injury sprinting type located in the distal third of the muscle belly and related to fibers from the distal MTJ, plus the corresponding grade and number of re-injuries

terms direct/indirect can be used to refer to the mechanism of injury. The location of the injury has been considered an important factor for the present classification. As a consequence, a thorough knowledge of the muscle's anatomy and especially their MTJ and intramuscular tendons is needed to correctly use the present muscle injury classification. Fiber disruption at the MTJ has proven to be a strong prognostic factor for longer recovery in studies where the RTP decision making was not blinded for the MRI results [63, 98, 99]. Several questions regarding how to deal with intramuscular tendon disruptions in regard to their treatment or rehabilitation programs have been considered by some authors [98]. As previously mentioned, recent studies have concluded that injuries affecting the intramuscular tendon in hamstring and quadriceps are associated with a longer time loss and may necessitate modification of the type of treatment used [76].

The present classification has incorporated an MRIbased grading system. The classification has incorporated the % CSA to grade indirect muscle injuries in an attempt to quantify the structural damage in an objective and reliable manner [96]. Given the three-dimensional disposition of the ECM, the important factor is not the length but the percentage of ECM disrupted relative to the total in the transverse plane. While the volume injured would represent the same injury degree, % CSA is believed to be an easier parameter to obtain from the MRI. Injuries are graded as the relationship between the injury's maximal anteroposterior and transverse area in the axial plane, and the muscle's CSA at the same point [17, 62, 64, 79]. This ability to grade ECM damage needs to be demonstrated in further research. However, the relationship between extension and severity of the injury is not a new idea [98]. Several authors have used the MRI to grade muscle injuries and evaluate injury severity and rehabilitation time in football players, or to create an MRI-based scoring scale predictive of return to sports using the percentage of CSA [13, 38, 40].

One of the pitfalls of any grading system is to avoid subjective information. It was one of our purposes to create a grading item that could classify injuries based on a quantifiable parameter (exact % CSA) based on the principle

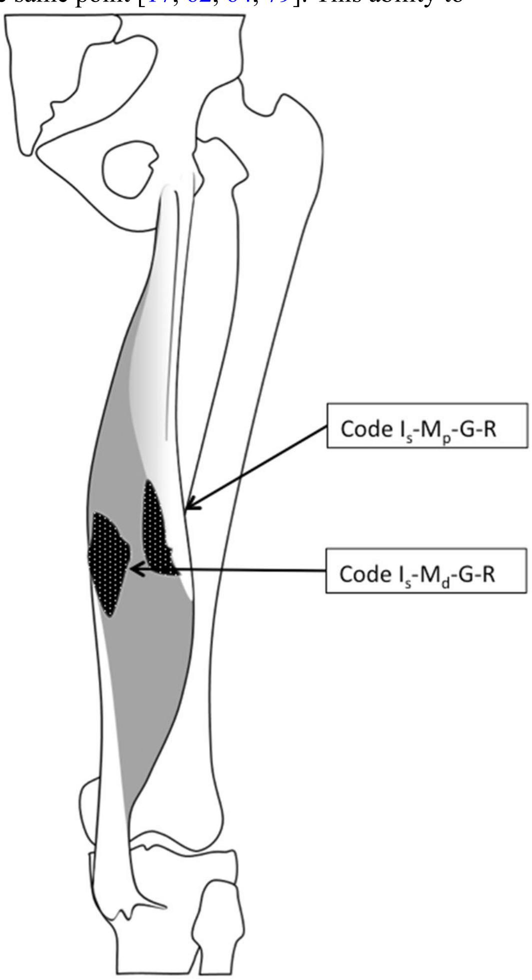

Fig. 3 Examples of codifications for semimembranosus (SM) indirect injuries, stretching type. I_s-M_p-G-R a SM indirect injury stretching type located at the middle third of the muscle belly and related to fibers from the proximal myotendinous junction (MTJ), plus the corresponding grade and number of re-injuries. I_s-M_d-G-R a SM indirect injury stretching type located at the middle third of the muscle belly and related to fibers from the distal MTJ, plus the corresponding grade and number of re-injuries

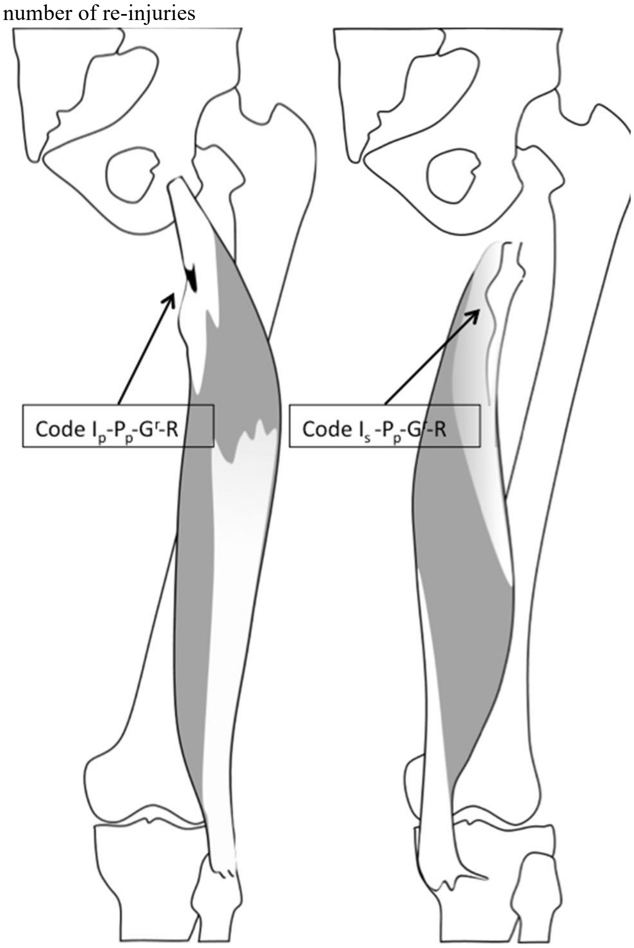

Fig. 4 Examples of codifications for indirect biceps femoris long head (BFlh) and semimembranosus (SM) injuries with tendon gap, retraction, or loss of tension. I_p-P_p-G^r-R a BFlh indirect injury sprinting type located at the proximal third of the muscle belly and related to fibers from the proximal myotendinous junction (MTJ), plus the corresponding grade describing the tendon extension and number of re-injuries. I_s -P_p-G^r-R a SM indirect injury stretching type located at the proximal third of the muscle belly and related to fibers from the proximal MTJ, plus the corresponding grade describing the tendon extension and number of re-injuries

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that the more connective tissue is damaged, the greater the functional impairment and the worse the prognosis [75–77]. The ultimate goal of the damage quantification (% CSA) would be to evaluate the injury severity as time loss [13, 43], and as a marker of strength impairment [116]. The use of this objective grading system in a large sample will help better define the grades based on its prognostic value, and whether or not the prognosis can be estimated as a continuous variable, or by use of a cut off point of % CSA. Special mention should be made for grade 0 injuries, which represent clinically evident muscle injuries with negative MRI. This grading category has been adopted because it represents a group of injuries with a better prognosis but which still have unclear and debatable significance [31, 40, 42, 119].

Re-injury was one of the parameters of the present classification system where an easier consensus was reached. Re-injury is an important predictor for a longer recovery period compared with first-time injury

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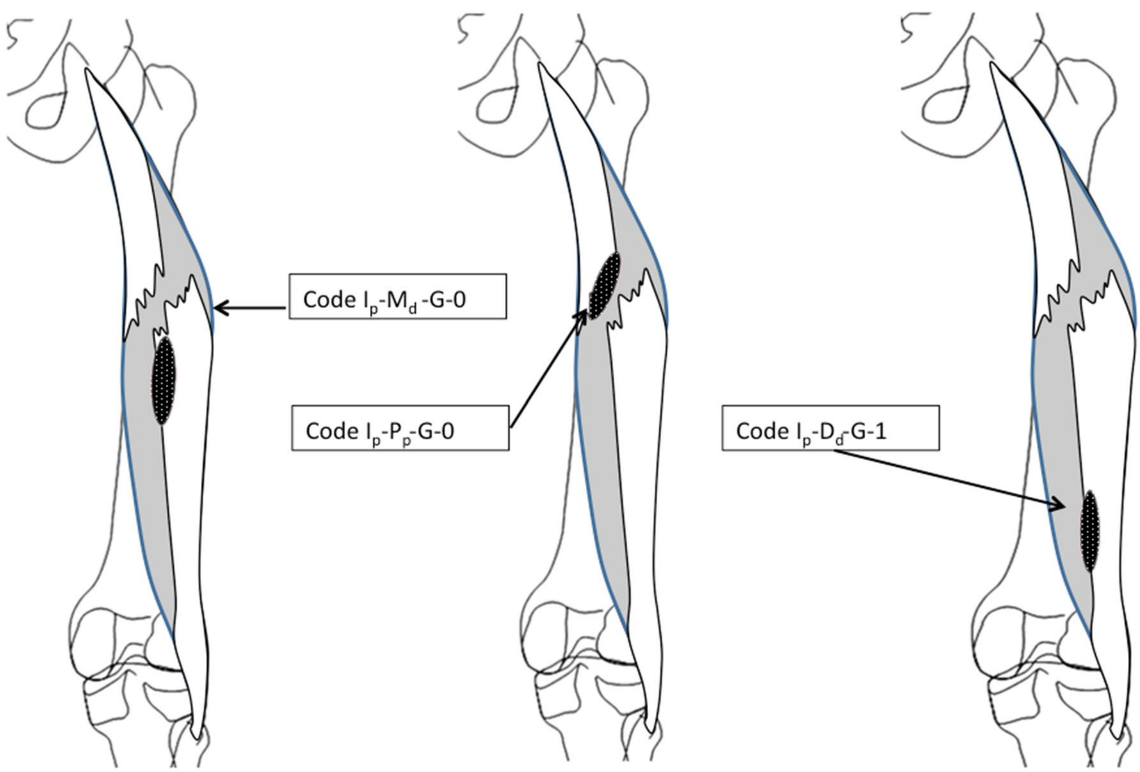

Fig. 5 Example of codification for re-injuries. I_p-M_d-G-0 a first episode biceps femoris long head (BFlh) indirect injury sprinting type located at the middle third of the muscle belly and related to fibers from the distal myotendinous junction (MTJ), plus the corresponding grade and number of re-injuries (0). If a second episode happens in the next 2 months in the same muscle, I_p-P_p-G-0 a BFlh indirect injury sprinting type located at the proximal third of the muscle belly and related to fibers from the proximal MTJ, plus the corresponding grade and number of re-injuries (0). I_p-D_d -G-1 a BFlh indirect injury sprinting type, located at the distal third of the muscle belly and related to fibers from the distal MTJ, plus the corresponding grade and number of re-injuries (1)

[1, 13, 29, 68, 115]. Therefore, this parameter should be included in the classification of muscle injuries.

Areas of further research to improve this classification system would include the clarification of the role of pain location, distance to insertion, or time to walk pain free in muscle injuries. The incorporation of the percentage of strength loss compared with the contralateral muscle or a previous ipsilateral test may also be considered in the future. In addition, the incorporation of the type of muscle involved may be considered given the fact that injuries of muscles with complex intramuscular tendon anatomy can be more challenging [102]. Finally, the present classification needs to be validated, and further prospective studies should help determine its prognostic value [119].

The present classification system has some limitations. First, this is only a theoretical model that still needs to be validated. Second, part of the information contained in the classification originated from the literature search is mostly related to research conducted for hamstring and rectus femoris injuries. Its applicability to other muscle groups needs to be further investigated. Third, the grading category is based on tendon injury, edema presence/absence, and architectural distortion or gap quantification, but not on edema quantification. There are currently no objective data yet to establish a cut-off point for the degree of muscle injury with a good prognostic value. Therefore, all injuries with a measureable gap would be coded as grade 3 and the corresponding % CSA would be added as a sub-index. A future aim would be to objectively establish the degrees of muscle injury with better prognostic value.

However, the present classification also has some strengths. This classification system is based on the currently available research and experience of clinical experts from three institutions with experience in a assessing a high volume of muscle injuries. We believe another strength is the detailed definition of the grading levels and its potential prognostic value and easy clinical application for health-related professionals (i.e., physicians, physiotherapists, and trainers). The classification can help to improve clear communication between healthcare and sports-related professionals and assist them in the decision making regarding rehabilitation protocols and RTP [93, 120–128]. In addition, we believe it is a flexible and open system, allowing future adaptation to incorporate any subsequent knowledge shown to be relevant to prognosis or diagnosis.

5 Conclusions

This evidence-informed and expert consensus-based classification system for muscle injuries is based on an initialism system: MLG-R. It describes the mechanism of injury (M), location of injury (L), grading of severity (G), and number of muscle re-injuries (R). The classification may help to improve communication between healthcare and sports-related professionals and assist in the decision making regarding rehabilitation protocols and RTP. Validation studies are required to establish the veracity and utility of this system by describing its prognostic value.

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Compliance with Ethical Standards

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Conflict of interest Xavier Valle, Eduard Alentorn-Geli, Johannes L. Tol, Bruce Hamilton, William E. Garrett Jr., Ricard Pruna, Lluı´s Til, Josep Antoni Gutierrez, Xavier Alomar, Ramo´n Balius, Nikos Malliaropoulos, Joan Carles Monllau, Rodney Whiteley, Erik Witvrouw, Kristian Samuelsson, and Gil Rodas declare that they have no conflicts of interest directly related to the content of this article.

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SCIENTIFIC LETTER

The MLG-R muscle injury classification for hamstrings. Examples and guidelines for its use

Clasificación de lesiones musculares MLG-R para los isquiotibiales. Ejemplos y directrices de uso

Introduction

Muscle injuries are very common in sport.[1–3] In soccer, the most popular sport in the world, the majority of muscle injuries are located in the lower extremity (92–97%); hamstrings (28–37%), quadriceps (19–32%), adductors (19–23%), and calf muscles (12–13%),[1] all of them are biarticular muscles, with a complex architecture and containing a high proportion of fast-twitch fibers.[1]

Football teams have important budgets and spend great amounts of money to win titles; it has been proved that injuries had a significant influence on performance in male professional football,[4] but muscle injuries seem to keep growing.[5] The reason to this is multivariable: there is no consensus regarding hamstring muscle injuries (HMIs) return to play (RTP) criteria in the literature,[6] the time for recovery is highly variable,[7] the increased physical demands during games,[8] or the influence of congested period of games on players health.[9]

During the last years several proposals for classification and grading muscle injuries have been published.[10–12] The FC Barcelona medical department with the collaboration of two important institutions in sports medicine and several experts in the field, have developed the MLG-R proposal, with the hamstrings group as a model.[13]

A good classification system is necessary, which allows to have reliable epidemiological data, which are the base to improve our knowledge about muscle injuries; better knowledge leads to better therapeutic options, prognosis, RTP criteria or lower reinjury rates.

MLG-R description and goals of the paper

The MLG-R proposal is a four-letter initialism system (MLG-R), respectively referring to the mechanism of injury (M), location of injury (L), grading of severity (G), and number of muscle re-injuries (R). The aim of the proposal was to describe a classification system for muscle injuries with easy clinical application, adequate grouping of injuries with similar functional impairment, and potential prognostic value (which still need to be proved). To achieve classification objectives, the study was designed in three phases: (1) identify the existing evidence related to risk and prognostic factors for muscle injuries; (2) discuss these factors between two of the institutions and establish a consensus based on the quality of studies in combination with experts' experience; and (3) elaborate the final classification.[13]

The extracellular matrix (ECM) has been classically described in three layers: endomysium, perimysium, and epimysium[14]; in our opinion ECM plays a key role in muscle injuries clinical symptoms and severity, because of that, we could say that the main aim of the proposal is oriented to evaluate how much ECM is being affected by the injury. The amount of damage to the ECM is influenced by the mechanism of injury (direct or indirect),[15] the injury relationship with the MTJ (more proximal or distal to the MTJ insertion),[16,17] the percentage of the muscle cross-sectional area (CSA)[18] affected by the injury (degree of injury), and the presence of tendon involvement.[19] To correctly use the MLG-R proposal a deep knowledge about muscles anatomy and its MTJs will be needed.

The fill out of the first letter will be easy, Table 1. For a long-time muscle injuries were classified as direct (T as first letter in the proposal) or indirect (I)[20]; the size of direct muscle injuries is not well correlated with clinical signs and functional impairment,[21] and such injuries usually have a better evolution with a shorter time to recovery in comparison to indirect injuries.[15] In our opinion, this is because the injury is the consequence of an external compression causing mainly a damage to the contractile fibers of the muscle, however the connective tissue remains well preserved in most of the cases, therefore the muscle function is less affected. When an indirect muscle injury occurs the damaging force is created and transmitted through the muscle connective tissue causing an injury to the connective tissue itself or in the borders between the connective tissue and the contractile fibers, this type of injury is worse tolerated causing more functional impairment.[15]

The second letter will give the information about the anatomical location of the injury, at the proximal (P), middle (M) or distal (D) third of the thigh, and what is even more important, the subindex describing if the injury is located

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Table 1 Summary of the new classification system.

Mechanism of injury (M)	Locations of injury (L)	Grading of severity (G)	Number of muscle re-injuries (R)
Hamstrings direct injuries			
T (direct)	**P** Injury located in the proximal third of the muscle belly	0–3	0 1st episode
	M Injury located in the middle third of the muscle belly		1 1st re-injury
	D Injury located in the distal third of the muscle belly		2 2nd re-injury, and so on.
Hamstrings indirect injuries			
I (indirect) plus subindex s for stretching-type, or subindex p for sprinting-type.	**P** Injury located in the proximal third of the muscle belly. The second letter is a subindex p or d to describe the injury relation with the proximal or distal MTJ respectively.	0–3	0 1st episode
	M Injury located in the middle third of the muscle belly, plus the corresponding subindex.		1 1st re-injury
	D Injury located in the distal third of the muscle belly, plus the corresponding subindex.		2 2nd re-injury, and so on.
Negative MRI injuries (location is pain related)			
N plus subindex s for indirect injuries stretching-type, or subindex p for sprinting-type.	**N** p proximal third injury **N** m middle third injury **N** d distal third injury	0–3	0 1st episode 1 1st re-injury 2 2nd re-injury, and so on.
Grading of injury severity			
0	When codifying indirect injuries with clinical suspicion but negative MRI, a Grade 0 injury is codified. In these cases the second letter describes the pain locations in the muscle belly.		
1	Hyperintense muscle fibers edema without intramuscular hemorrhage or architectural distortion (fiber architecture and pennation angle preserved). Edema pattern: interstitial hyperintensity with feathery distribution on FSPD or T2 FSE + STIR images.		
2	Hyperintense muscle fibers and or peritendon edema with minor muscle fibers architectural distortion (fiber blurring and/or pennation angle distortion) ± minor intermuscular hemorrhage, but no quantifiable gap between fibers. Edema pattern, same as for grade 1.		
3	Any quantifiable gap between fibers in craniocaudal or axial planes. Hyperintense focal defect with partial retraction of muscle fibers ± intermuscular hemorrhage. The gap between fibers at the injury's maximal area in an axial plane of the affected muscle belly should be documented. The exact %CSA should be documented as a subindex to the grade.		
r	When codifying an intra-tendon injury or an injury affecting the MTJ or intramuscular tendon showing disruption/retraction or loss of tension exist (gap), a superscript (r) should be added to the grade.		

around fibers from the proximal (p) or distal (d) MTJ.[13] In injuries located more distal to the MTJ origin, less amount of connective tissue will be damaged.[16] As we mentioned before, a deep knowledge about the muscle, specially about the MTJ anatomy is needed, because you can have an injury located in the distal third of the thigh but affecting fibers from the more distal part of the proximal MTJ tendon, and the prognosis will be totally different than a distal third injury located around fibers of the distal MTJ.

The third letter is the grade of the injury, and it is defined by several radiologic features; the interstitial edema presence or absence (T2 feathery hyperintensity), architectural fibers distortion (muscular fiber blurring, gap between muscular fibers, loss of pennation angle), injury of the connective tissue (T2 hyperintensity and tears), intramuscular hematoma and intermuscular fluid.[13]

Grades 1 and 2 are defined by edema presence, no quantification, and its characteristics (Table 1). The grade

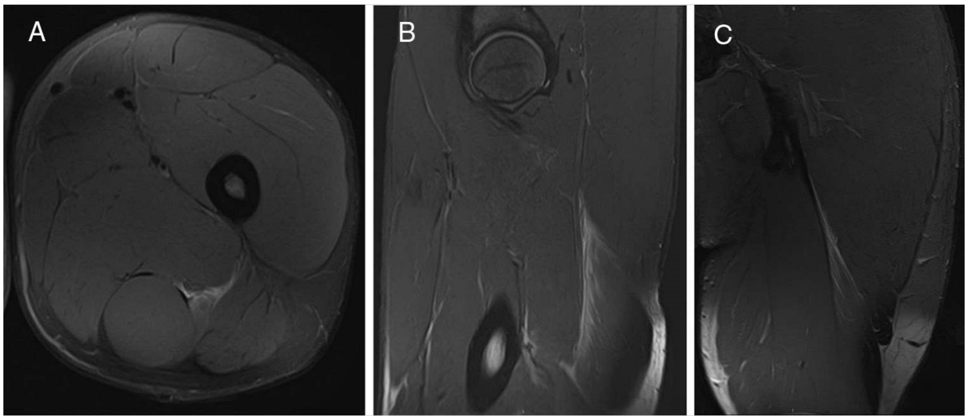

Figure 1 Biceps femoris long head (BFlh) indirect injury (I), located at the proximal third of the thigh (P) and affecting the proximal MTJ (P_p). There is hyperintense focal defect with partial retraction of muscle fibers ± intermuscular hemorrhage (G_3). This is a first episode (R_0). A: Axial T2 weighted fat saturated image showing MTJ destructured with interstitial edema and intermuscular fluid. B: Sagittal T2 weighted fat saturated image showing hyperintense focal defect with partial retraction of muscle fibers. C: Coronal T2 weighted fat saturated image showing intermuscular hemorrhage. Final codification: I P_p G_3 R_0.

3 use the %CSA to evaluate the amount of injury, for that we use the axial MR slice where we see the biggest area of injury, and we obtain the quotient between this region and the global area of the muscle belly at this level[18]; it will be documented as a subindex in the grade.

It has been reported that muscle injuries affecting the intramuscular tendon require a prolonged rehabilitation time and may have higher recurrence rates.[16,19] Because of that, in our proposal, tendon injuries will be recorded as a superindex in the third letter (Grade); if an intratendon injury or an injury affecting the MTJ or intramuscular tendon showing disruption/retraction or loss of tension exist (gap), a superscript (r) should be added to the grade.

The fourth letter fill out will describe if we are talking about a first episode of muscle injury, or a reinjury, and if this is the case, the number of reinjury.

The aim of this paper is to describe how is the process to use the MLG-R proposal is. For that we will codify injuries using several examples of muscle injuries in hamstrings to describe the process. The full description of the MLG-R proposal and the meaning of each letter has been described in a previous paper[13]; it is also summarized in the Table 1 in this paper.

Examples of injuries and codification

Figs. 1 and 2, BFlh proximal MTJ injuries.

Fig. 3, BFlh distal MTJ.

Figs. 4 and 5, semimembranosus proximal and distal MTJ injuries.

Fig. 6, semitendinosus proximal MTJ injury.

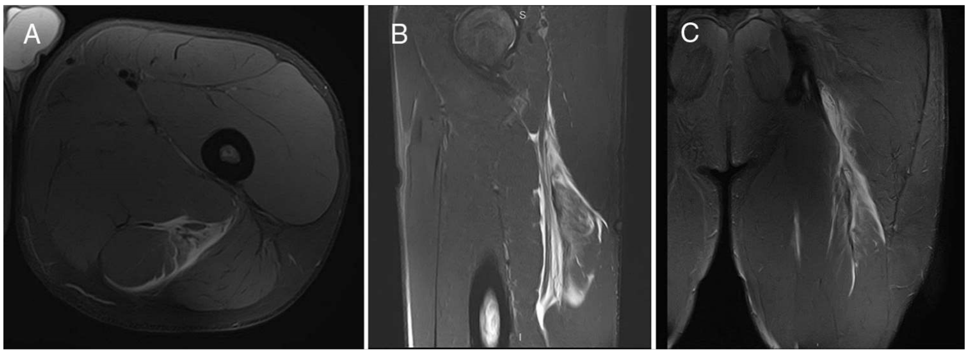

Figure 2 Biceps femoris long head (BFlh) indirect injury (I), located at the proximal third of the thigh and affecting the proximal MTJ (Pp). There is quantifiable gap between muscle fibers in craniocaudal and axial planes; hyperintense focal defect with retraction and intermuscular hemorrhage (G3); there is also a clear transversal free tendon injury tendon showing disruption, retraction and loss of tension, superscript r (Gr3). This is a first episode (R0). A: Axial T2 weighted fat saturated image showing intermuscular hemorrhage surrounding the sciatic nerve, and a free tendon rupture and injury of the semitendinosus MTJ whit interstitial edema. B: Sagittal T2 weighted fat saturated image showing loss of the pennation angle and intermuscular fluid. C: Coronal T2 weighted fat saturated image showing central tendon loss of tension. Final codification: I Pp Gr3 R0.

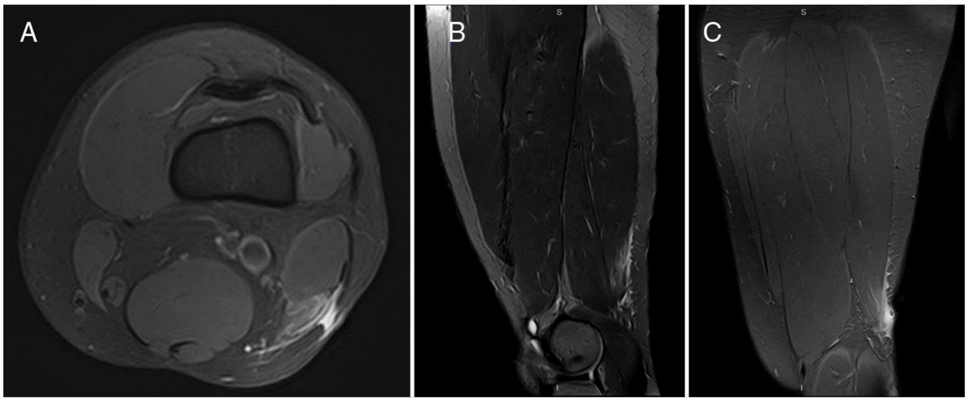

Figure 3 Biceps femoris long head (BFlh) indirect injury (I), located at the distal third of the thigh and affecting the distal MTJ (Dd). There is hyperintense focal defect with partial retraction of muscle fibers ± intermuscular hemorrhage (G3); the tendon is affected but there is not disruption/retraction or loss of tension exist (no r superscript). This is a first episode (R0). A: Axial T2 weighted fat saturated image showing distal tendon injury and interstitial edema of the BFlh. B: Sagittal T2 weighted fat saturated image showing tendon injury but without retraction or loss of tension, therefore no superscript (r) should be added to the grade. C: Coronal T2 weighted fat saturated image showing interstitial muscular edema. Final codification: I Dd G3 R0.

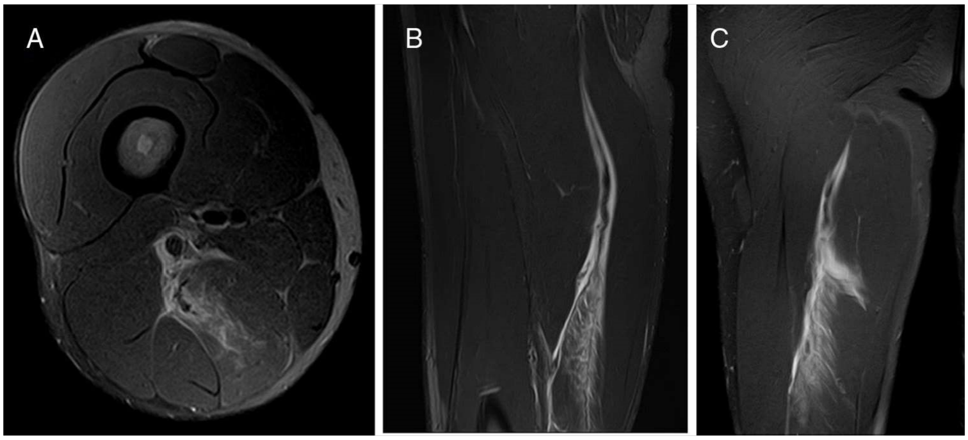

Figure 4 Semimembranosus (SMB) indirect injury (I), located at the proximal third of the thigh and affecting the proximal MTJ (M/Pp). There is quantifiable gap between muscle fibers in craniocaudal and axial planes; hyperintense focal defect with retraction and intermuscular hemorrhage (G3); there is also a clear transversal/longitudinal? tendon injury tendon showing disruption, retraction and loss of tension, superscript r (Gr3). This is a first episode (R0). A: Axial T2 weighted fat saturated image showing MTJ disruption whit interstitial edema; there are chronic changes affecting the tendon. B: Sagittal T2 weighted fat saturated image showing tendon loss of tension, and interstitial edema. C: Coronal T2 weighted fat saturated image showing again the tendon loss of tension and loss of the muscle fibers pennation angle. Final codification: I M/Pp Gr3 R0.

Discussion

Having reviewed the most relevant muscle injury classification systems we can see some differences between them. The proposal from Chan[10] was the first including the injury's anatomical location using the connective tissue and the injury patterns to describe a muscle injury; both were important improvements, specially including the connective tissue anatomy to describe the injury location. The problem in terms of describing the injury patterns is common to other proposals, there is a lack of consensus about the terminology, which means a great subjectivity when injuries have to be described. A key point in any classification should be the use of clear, non-ambiguous terminology. ''Myofascial'' is a term widely used, representing a particular injury location with a different clinical evolution and prognosis,[16,17,22] but it is an ambiguous term, and other expressions such as ''peripheral''[23] or ''myoaponeurotic''[24] have been suggested and used to describe similar injuries. To avoid this subjectivity, the MLG-R proposal is to describe the anatomical location of the injury and its relation to the MTJ, injuries located more ''peripheral'' to the MTJ insertion will have a better prognosis.

The Munich consensus[11] was a great effort trying to include all types of muscle injuries, offering a wide range of possibilities to classify and grade them. The inclusion of

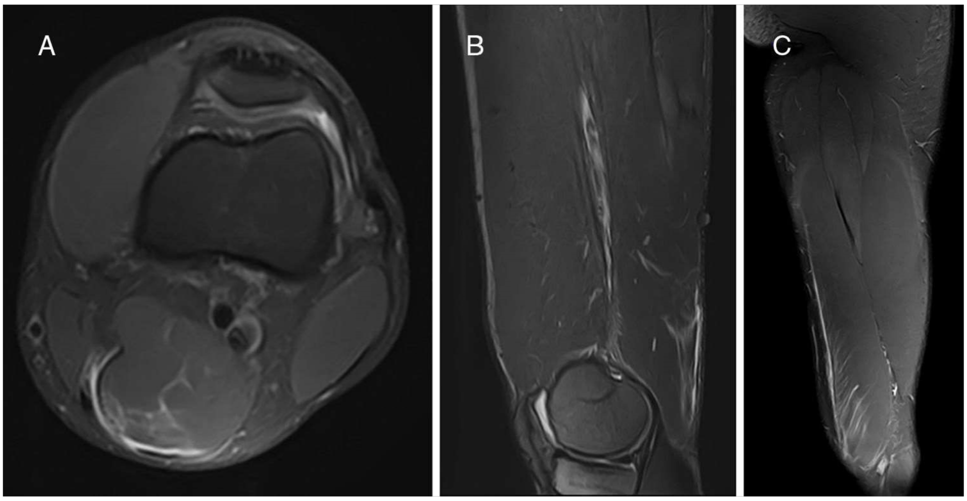

Figure 5 Semimembranosus (SMB) indirect injury (I), located at the distal third of the thigh and affecting the distal MTJ (Dd). There is quantifiable gap between muscle fibers in craniocaudal and axial planes; hyperintense focal defect with retraction and intermuscular hemorrhage (G3). This is a first episode (R0). A: Axial T2 weighted fat saturated image showing MTJ destructuration. B: Sagittal T2 weighted fat saturated image showing MTJ destructuration without loss of tension. C: Coronal T2 weighted fat saturated image showing interstitial edema. Final codification: I Dd G3 R0.

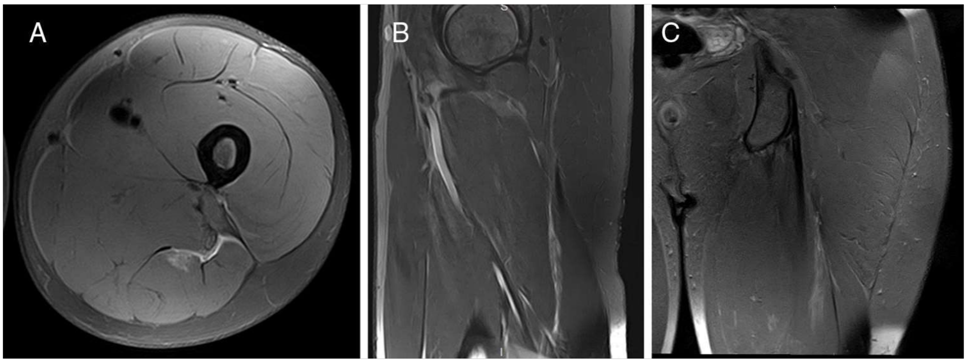

Figure 6 Semitendinosus (SMT) indirect injury (I), located at the proximal third of the thigh and affecting the proximal MTJ (Pp). There is quantifiable gap between muscle fibers in craniocaudal and axial planes; hyperintense focal defect with retraction and intermuscular hemorrhage (G3). This is a first episode (R0). A: Axial T2 weighted fat saturated image showing muscle fibers destructuration and intermuscular fluid. B: Sagittal T2 weighted fat saturated image showing the MTJ injury with small muscle fibers gap. C: Coronal T2 weighted fat saturated image showing interstitial edema. Final codification: I Pp G3 R0.

delayed onset muscular soreness (DOMS) as a muscle injury is quite controversial. Several publications have proved that DOMS is an adaptive process far from being considered a muscle injury, even when histologically some features are similar in both diagnosis.[25] While histological disturbances might be present, their origin appears related to intense activity for which the muscle is unprepared.[25] Also the definition of functional or non-structural disorders, as other authors have pointed out, functional disorders related to muscle injuries require further investigation to be better understood.[26] It should be taken into account that the diagnosis of muscle distortion is not yet well understood and remains subjective, which makes the acquisition of solid epidemiological data difficult.

Although one of the main goals of our proposal was to enhance communication between healthcare and sports-related professionals by avoiding the use of confusing terminology, the MLG-R proposal has been criticized because of the complexity of nomenclature used, which can cause limited attractiveness for its use amongst the sports community.[27] As it has been proved in the previous examples, the use of our classification proposal is very easy to understand and acquire, although a deep knowledge of muscle anatomy is required for the proper use of the classification. With the fill out of the four letters, the classification proposal includes: a description of the injury with information about how it occurs, where the injury anatomically located is, and its relationship with the myotendinous junction (MTJ) of the muscle. The previous items will offer a description about how severe the injury is by quantifying the amount of connective tissue affected, and then we will add the chronology of the injury (first episode o reinjury), offering a full description of the injury and its timing evolution.

The MLG-R classification system has being recognized as the first to incorporate the re-injury status into the grading of muscle injuries[27]; re-injuries are known to cause significant longer absences,[1] therefore to have influence in prognosis and be taken in account for the RTP. To incorporate the re-injury status offers important information about the injury, helping to understand the history and to better foresee its evolution.

The grading category, is based on the muscle injury radiological features. All these features are globally evaluated and the quantification of edema is not a parameter taken into account. The most important thing is to evaluate the connective tissue injured.

There is currently no objective data to establish a cut-off point for the grade of muscle injury with a good prognostic value. Therefore, all injuries with a measureable gap would be coded as grade 3 and the corresponding % CSA would be recorded and added as a sub-index, in order to evaluate in the future is changes at this point are needed, and more grades established.

The definition of re-injury is any indirect muscle injury affecting the same MTJ, its intramuscular tendon or fibers associated with it (even in a different location) during the next two months after the RTP.[13] It is important to establish the period of time when it can be considered a reinjury, it is well known that most reinjuries occur during the first 2–3 months after RTP then they decrease drastically. As an example, if the first injury of the long head of biceps femoris affects the proximal MTJ in the proximal third of the muscle belly and another injury occurs within the next 2 months but located in the middle third of the muscle belly in fibers related to the proximal MTJ, this would be considered as a re-injury. By contrast, if the second injury is located around or affecting the distal MTJ (a different MTJ from the initial injury), it would not be considered a re-injury.

The MLG-R is not the best and it will not be the last proposal, but its strongest point is to be a flexible and open system, allowing future adaptation to incorporate any subsequent knowledge shown to be relevant to prognosis or diagnosis. Our final aim is to create a better and more accepted proposal in the future.

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ORIGINAL RESEARCH ARTICLE

Return to Play Prediction Accuracy of the MLG-R Classification System for Hamstring Injuries in Football Players: A Machine Learning Approach

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Abstract

Background and Objective Muscle injuries are one of the main daily problems in sports medicine, football in particular. However, we do not have a reliable means to predict the outcome, i.e. return to play from severe injury. The aim of the present study was to evaluate the capability of the MLG-R classification system to grade hamstring muscle injuries by severity, offer a prognosis for the return to play, and identify injuries with a higher risk of re-injury. Furthermore, we aimed to assess the consistency of our proposed system by investigating its intra-observer and inter-observer reliability.

Methods All male professional football players from FC Barcelona, senior A and B and the two U-19 teams, with injuries that occurred between February 2010 and February 2020 were reviewed. Only players with a clinical presentation of a hamstring muscle injury, with complete clinic information and magnetic resonance images, were included. Three different statistical and machine learning approaches (linear regression, random forest, and eXtreme Gradient Boosting) were used to assess the importance of each factor of the MLG-R classification system in determining the return to play, as well as to offer a prediction of the expected return to play. We used the Cohen's kappa and the intra-class correlation coefficient to assess the intra-observer and inter-observer reliability.

Results Between 2010 and 2020, 76 hamstring injuries corresponding to 42 different players were identified, of which 50 (65.8%) were grade 3^r, 54 (71.1%) affected the biceps femoris long head, and 33 of the 76 (43.4%) were located at the proximal myotendinous junction. The mean return to play for grades 2, 3, and 3^r injuries were 14.3, 12.4, and 37 days, respectively. Injuries affecting the proximal myotendinous junction had a mean return to play of 31.7 days while those affecting the distal part of the myotendinous junction had a mean return to play of 23.9 days. The analysis of the grade 3^r biceps femoris long head injuries located at the free tendon showed a median return to play time of 56 days while the injuries located at the central tendon had a shorter return to play of 24 days (p = 0.038). The statistical analysis showed an excellent predictive power of the MLG-R classification system with a mean absolute error of 9.8 days and an R-squared of 0.48. The most important

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factors to determine the return to play were if the injury was at the free tendon of the biceps femoris long head or if it was a grade 3^r injury. For all the items of the MLG-R classification, the intra-observer and inter-observer reliability was excellent (k > 0.93) except for fibres blurring (κ = 0.68).

Conclusions The main determinant for a long return to play after a hamstring injury is the injury affecting the connective tissue structures of the hamstring. We developed a reliable hamstring muscle injury classification system based on magnetic resonance imaging that showed excellent results in terms of reliability, prognosis capability and objectivity. It is easy to use in clinical daily practice, and can be further adapted to future knowledge. The adoption of this system by the medical community would allow a uniform diagnosis leading to better injury management.

Extended author information available on the last page of the article

Key Points

The main determinant for a longer return to play after a hamstring injury is the injury affecting the connective tissue structures of the hamstring.

Injuries affecting the biceps femoris long head/semitendinosus free tendon have a longer return to play than those located at the central tendon.

Extracellular matrix structure and its role in force generation and transmission is a likely key factor in the prognosis of muscle injuries.

1 Introduction

Muscle injuries are very common in sports that require explosive movements such as football [1], rugby [2], American Football [3], or track and field [4]. In professional football, between 92 and 97% of all muscle injuries are located in the lower extremity: hamstrings (28–37%), quadriceps (19–32%), adductors (19–23%), and calf muscles (12–13%) [1]. Deciding when a player is ready to return to play (RTP) following a muscle injury is challenging because of the high variability in recovery and types of injuries [5, 6]. A premature RTP can be one of the reasons for the high re-injury rates (12–43%) and prolonged time loss [1, 5, 7, 8].

Top-level professional sports place such a high demand on an athlete's body that despite all preventive strategies, the incidence of muscle injuries seems to keep growing [9]. The problem is even worse, as many athletes recovering from the muscle injury succumb to re-injury during rehabilitation. Several reasons could explain this situation: the lack of a clear consensus regarding RTP criteria for hamstring muscle injuries (HMIs) [10], large variability in recovery times and types of injuries [5], the higher physical demands during games [11], different criteria to design rehabilitation protocols [12], or the influence of a congested period of games on players' health [13].

Furthermore, even sophisticated imaging modalities such as magnetic resonance imaging (MRI) have not yielded an accurate predictive tool. Current evidence on the predictive value indicates that even a complete resolution of the injured tissue on MRI is not a predictive indicator of a safe RTP [14].

One of the fundamental problems using MRI as a predictive tool is that the skeletal muscle injury induces a large number of imaging signs such as oedema, haematoma, variable rupture of the myotendinous unit, and varying retraction length of the ruptured muscle stumps; and sometimes these acute/subacute signs are also associated with scars or fat infiltration due to previous injuries [15]. Thus, there is a demand to develop a classification system for the evaluation of the magnetic resonance images that would assist in providing an accurate prognosis.

A classification system should avoid ambiguous terms to reduce subjectivity, be easy to apply, facilitate communication with the staff and other colleagues, and describe clearly demonstrable objective findings [16]. It should also have prognostic validity to help healthcare professionals with rehabilitation protocols and RTP decisions.

For years, multiple muscle injury grading and classification systems have being published, based on clinical parameters first, then ultrasound and lately on MRI [17]. Recently, several classification systems based on MRI are being tested with good intra-observer and inter-observer reliability [18, 19]. Unfortunately, they have failed to provide accurate RTP prognosis [20].

The MLG-R is a MRI-based, four-letter initialism classification system (MLG-R), referring to the mechanism of skeletal muscle injury (M), its location (L), grading of severity (G), and number of muscle re-injuries (R). The complete description of the proposal and the scientific background has been previously published [16], along with a second article about how to apply this classification system [21].

The connective tissue surrounding each individual muscle fibre as well as forming myotendinous junctions (MTJs) at both ends of the muscle plays a key role in muscle injuries, clinical symptoms, and severity [22]. The connective tissue structures of the injured skeletal muscle have not received as much clinical attention as they warrant until recently [23]. It has become evident that the extent of the damage to the connective tissue structure could be the main determinant of the severity of the injury and could provide the most accurate predictive value for clinicians. Hence, the main aim of our new classification proposal is to evaluate by MRI how much connective tissue structure is being affected by the injury [16]. The MRI-based evaluation of connective tissue structures is not limited to the main connective tissue structures at the end of the muscle–tendon unit, i.e. tendons, but to evaluate its complete structure, endomysium, perimysium, and epimysium, independently of its density or anatomy [24]. Therefore, to correctly use the MLG-R proposal, a deep knowledge about the anatomy of muscles and their MTJs is needed.

The principal aim of the present study was to evaluate the capability of the MLG-R classification system to grade injuries by severity, offer a prognosis for RTP, and identify injuries with a higher risk of re-injury in a sample of hamstring injuries from top-level professional athletes (FC Barcelona [FCB] football teams). The secondary goal of this study was to assess the consistency of our proposed system by investigating its intra-observer and inter-observer reliability.

2 Methods

2.1 Study Population and Ethics

The FCB medical department offers medical care for the FCB athletes, and registers all medical assistances in a private electronic medical record named COR ("Conocimiento, Organización y Rendimiento"). All medical episodes are coded using the Orchard Sports Injury Classification System, Version 10 [25, 26]. The COR contains all data from FCB athletes' injuries and illnesses from every episode (diagnosis, physical exploration, complementary studies, injury date, time off, treatment performed, and reinjures) in a prospectively collected database.

All male professional football players from FCB (senior A and B and the two U-19 teams) with injuries that occurred between February 2010 and February 2020 were approached for eligibility. Only players with HMIs were included in the present study. The project has been assessed and approved by the Ethics Committee of the "Consell Català de l'Esport" with the number 10/CEICGC/2020. The present study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki.

2.2 Data Collection and Extraction

We reviewed episodes coded under the Orchard Sports Injury Classification System section "Thigh Muscle strain/ Spasm/ Trigger Points" to filter HMIs. All episodes with symptoms compatible with a HMI were included and evaluated.

Each injury was assessed individually and only injuries with a clinical presentation matching a HMI, and confirmed by MRI (within 72 h after the injury) were included in the final analysis. If diagnosis was confirmed only by ultrasound or the MRI from the acute phase of the injury was not available, the injury was excluded from the final sample. In each case, a rehabilitation programme aiming at the RTP was carried out by team physicians in accordance with the club's clinical practice guidelines for HMIs [27]. The RTP was defined as the moment when the player returned to full unrestricted practice with the team, or game participation and was always recorded in electronic medical records.

Re-injuries were recorded in medical records according to our previous definition. A re-injury is the occurrence of a muscle injury affecting the same muscle and/or MTJ as the initial injury during the rehabilitation process or within the next 2 months after the RTP [16].

2.3 MRI Protocol

The MRIs were performed with two different MRI devices. The great majority of them (54 cases) were performed in the FCB's medical center using a 3.0 T MRI system (Vantage Titan; Canon Medical Systems, Sant Joan Despí, Spain). The rest of the cases (22 players) were evaluated in an external medical center by a 3.0 T system (Magnetom VERIO; Siemens Medical Solutions, Barcelona, Spain). In all cases, the magnetic resonance images were evaluated by the same researchers (see Sect. 2.4). The patients were positioned in supine decubitus, the examination was performed focused on the injured limb and the symptomatic area marked on the patient with a cutaneous vitamin marker. A multi-purpose coil was used, with speeder technology. This allowed the acquisition of five sequences according to the standardised protocol for evaluating muscle injuries in the lower extremities. Axial, Sagittal and Coronal T2 Fat Sat, TR 5200, 5000 and 3700 ms, TE 44–60 ms, Eco train 7.5, SL 2.5–3.5 mm, in-plane resolution 0.9–1.4 × 0.88–0.97 m m^2, FOV 256 × 256, 192 × 272, 288 × 320 mm, and Axial and Coronal TSE T1, TR 900–980 ms, TE 11 ms, Eco train 7.5, SL 2.5–3.5 mm, in-plane resolution 0.71–0.9 × 0.71–0.9 9 mm^2, and FOV 352 × 352, 288 × 320 mm were acquired and evaluated.

2.4 Image Review

A cross-sectional review of each injury's MRI was performed independently by one musculoskeletal radiologist (SM), and one sports medicine physician (XV). All injuries were classified using the MLG-R classification system [16]. Both researchers were familiar with this classification, have years of experience working with muscle injuries, and evaluating magnetic resonance images from soft-tissue injuries [15].

To summarise the MLG-R proposal, the category M stands for mechanism, i.e. direct (T), and indirect (I) muscle injuries. Subcategories of the mechanism category were created to define stretching type (subindex s) and sprintingtype (subindex p) indirect HMIs, as they can influence the outcome. The category L (location) informs of the anatomical location of the injury at the proximal (P), middle (M), or distal (D) third of the muscle belly and a subindex describes the relationship of the injury either with the proximal (p) or distal (d) MTJ. The MLG-R classification system does not quantify oedema; the oedema characteristics will be relevant to differentiate between grade 1 and 2. Grade 3 is defined as quantifiable gap between fibres in craniocaudal or axial planes. Grade 3 implies that there are torn fibres located affecting the muscle, the connective tissue or both. If the fibre ruptures affects the connective tissue, the superscript “r” is added to the grade. For injuries affecting the MTJ at two different locations, we use the one located proximally to define the grade (i.e. code). Finally, a grade 0 injury is an indirect injury with clinical suspicion but negative MRI. In these cases, the second letter describes the pain locations in the muscle belly. The category R informs of the injury chronology, the index injury will be R0, and the first reinjury classified as R1. Examples of grades, loss of tension, and cross-sectional area measurement are available in the Electronic Supplementary Material (ESM).

Magnetic resonance images from each injury were reviewed three times in a patient-blinded manner by the two researchers. The first review was not performed independently so as to review the classification system before MRI readings and unify criteria on how to apply it. A second MRI review was performed independently by the radiologist (SM) and the sport medicine physician (XV) after 3–8 months from the first evaluation. Finally, all injuries were evaluated for the third time by both evaluators and discrepancies discussed altogether in order to reach a consensus regarding the injuries classification.

2.5 Outcome

The primary outcome variable was RTP, measured in days. The independent variables, or covariates, included in the models derived from magnetic resonance images were: injury location at the tendon (free tendon, central tendon, or other location), location at the muscle belly (proximal, medial, or distal third), MTJ injury location (proximal or distal), grade of injury (0, 1, 2, 3, or 3^r), re-injury (0, 1, or 2) and the muscle injured (biceps femoris long head [BFlh], biceps femoris short head, semimembranosus, or semitendinosus [SMT]). We entered the variables in the models in a binary format.

2.6 Statistical Analysis

In order to validate the classification and understand the factors that determine the RTP, we used three different statistical models. First, multiple linear regression as a baseline model; second, random forest; and third, eXtreme Gradient Boosting (XGBoost). This approach was used to check if different models lead to the same conclusions.

We chose linear regression as it is the gold-standard model for analysing RTP data and it has been used in previous studies of hamstring injuries [28, 29]. Random forest, which is based on bagging and uses ensemble learning, was used as a second model as it can efficiently handle non-linearities in the data, it does not tend to overfit, and it reduces the variance, leading in turn, to an improvement in accuracy with respect to multiple linear regression (30). Finally, XGBoost offers increased accuracy and predictive power by using an ensemble of weak learners [31]. We optimised the hyperparameters by conducting a grid search. We performed leave-one-out cross-validation as a model validation technique to assess the generalisability of the results in order to leverage as much as possible the information provided by each observation.

We computed mean absolute error (MAE), root mean squared error (RMSE), and the coefficient of determination (R^2) as measures of the quality of the predictors. Moreover, we computed the accumulated local effects (ALEs) to understand the relative importance and contribution of each feature on average in predicting the RTP [32, 33]. Positive ALEs contributed to a longer average RTP while negative ALEs decreased the average RTP. The alpha level was set at 0.05. All analyses were conducted in R 3.6.3 [34].

In addition, weighted and unweighted Cohen's kappa as well as the intra-class correlation coefficient were used to assess the MLG-R classification reliability. First, we quantified the diagnostic reliability between the two physicians (inter-observer reliability). Second, we measured the reliability of the diagnosis within each independent physician at two different timepoints (intra-observer reliability).

3 Results

From a sample of 3875 injuries during the period of study, all episodes with symptoms compatible with an HMI were included and evaluated (Fig. 1). The patients and injury characteristics are shown in Table 1. Of note, most of the hamstring injuries affected the BFlh (N = 54; 71.1%), were grade 3^r (N = 50; 65.8%), and were located at the proximal third [proximal MTJ] (N = 33; 43.4%). Among all BFlh and SMT injuries located at the proximal third (N = 41), seven were located at the FT, 19 at the central tendon, and 15 at other locations of the MTJ.

When assessing the difference in the RTP by the severity of injury (grade), the interquartile range (25.2) of the RTP was the longest for grade 3^r injuries. Grade 3^r injuries exhibited the longer RTP than the other grades when all muscle injuries were assessed and also when the BFlh injuries were analysed independently (Fig. 2). In contrast, there were no statistically significant differences among any other grades (Fig. 2). The mean RTP of the BFlh injuries between grades 1, 2, and 3, were 11, 15, and 18 days, respectively.

In grade 3^r BFlh injuries, there were no statistically significant differences in the RTP among the several locations (Fig. 3). Injuries located at the proximal third and affecting the proximal MTJ (P_p) had a larger variance in the RTP compared with the other locations. The RTP for injuries located

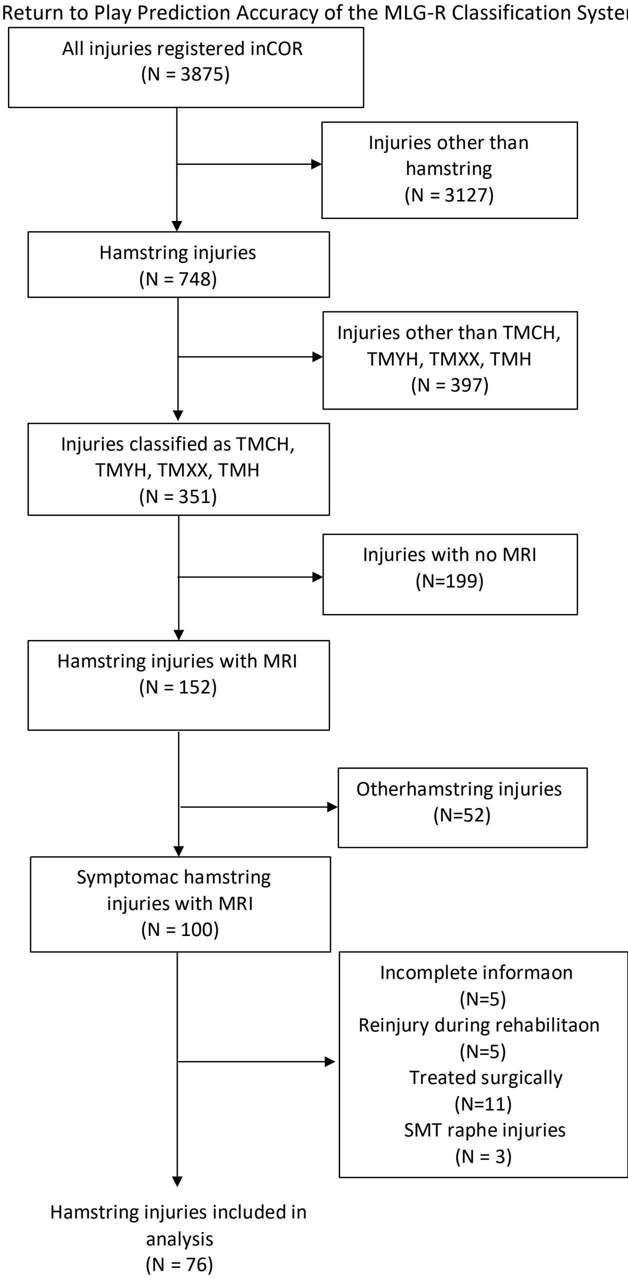

Fig. 1 Flowchart of included injuries in the analysis. *COR* Conocimiento, Organización y Rendimiento, *MRI* magnetic resonance imaging, *SMT* semitendinosus, *TMCH* hamstring cramping suring exercise, *TMH* hamstring strain, *TMXX* thigh muscle strain/ spasm/ trigger points, *TMYH* hamstring trigger points

at the medial third affecting the proximal MTJ (M_p) and the distal MTJ (M_d) was very similar. Likewise, injuries closer to the insertion, Dd and Pp, had a similar RTP as no statistically significant differences (p = 0.91) were found (Fig. 3).

The analysis of the grade 3^r BFlh injuries located at the FT showed a median RTP time of 56 days while the injuries located at the central tendon had a shorter RTP of 24 days (p = 0.038) (Fig. 4). For the SMT, injuries located at the FT

Table 1 Sample description

	Overall
N	76
RTP days, mean (SD)	29.1 (16.9)
Age, years, mean (SD)	24.2 (5.0)
Team senior, *n* (%)	62 (81.6)
Muscle injured, *n* (%)	
BFlh	54 (71.1)
BFsh	1 (1.3)
SMB	12 (15.8)
SMT	9 (11.8)
Grade, *n* (%)	
0	1 (1.3)
1	3 (3.9)
2	17 (22.4)
3	5 (6.6)
3^r	50 (65.8)
Reinjury = 1 (%)	9 (11.8)
Injury location, *n* (%)	
D_d	20 (26.3)
D_p	3 (3.9)
M_d	7 (9.2)
M_p	13 (17.1)
P_p	33 (43.4)
Stretching injury mechanism, *n* (%)	13 (17.1)
Tendon location, *n* (%)	
Other	50 (65.8)
Central	19 (25.0)
Free	7 (9.2)

BFlh biceps femoris long head *BFsh* biceps femoris short head, Injury located at the distal third affecting the distal myotendinous junction (MTJ) (D_d), injury located at the distal third affecting the proximal MTJ (D_p), injury located at the middel third affecting the distal MTJ (M_d), injury located at the middel third affecting the proximal MTJ (M_p), injury located at the proximal third affecting the proximal MTJ (P_p), *RTP* return to play, *SD* standard deviation, *SMB* semimembranosus, *SMT* semitendinosus

still had a worse prognosis (median RTP of 54.5 days) than those located at the central tendon (median RTP of 34 days), but the differences were not statistically significant (p = 0.43) (Fig. 4). For the BFlh, the RTP after sustaining a complete MTJ gap was significantly

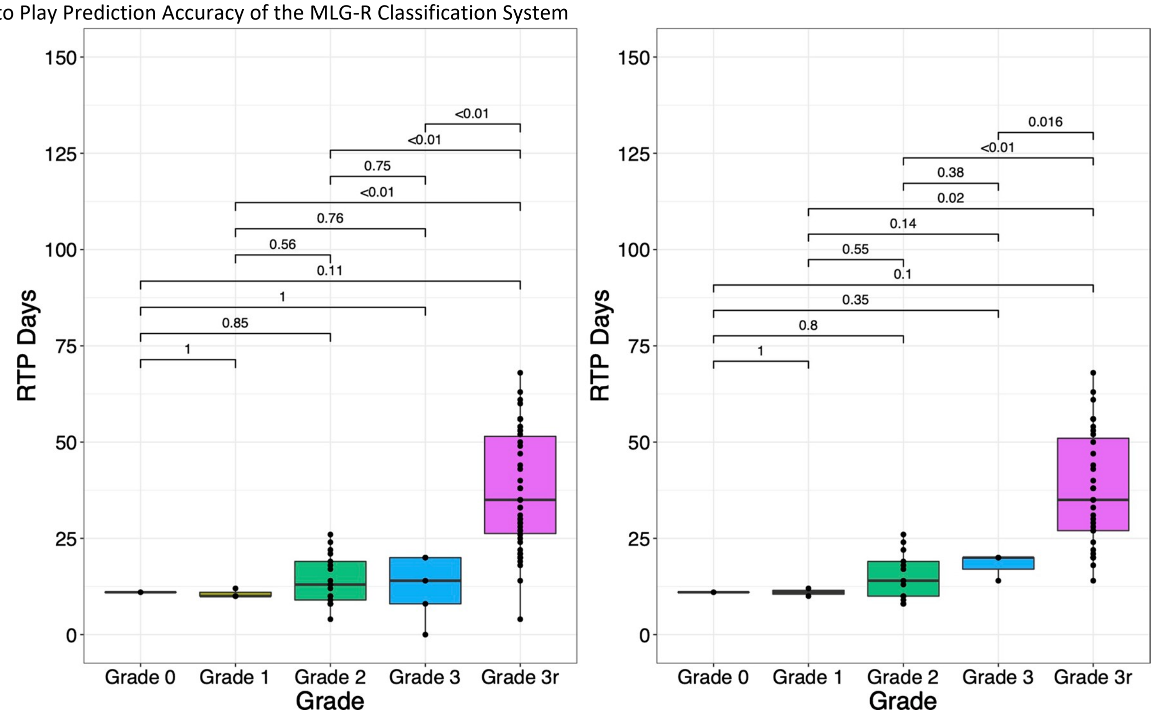

Fig. 2 Return to play (RTP) by grade: all muscles (left), and for biceps femoris long head (right)

longer (p = 0.0087) compared with partial injuries (Fig. 4). Imaging of partial and complete tendon injuries is provided in Fig. 4 of the ESM.

The three models (linear regression, random forest, and XGBoost) converged with respect to variable importance and accumulated local effects (Table 1 and Figs. 1–6 of the ESM). However, it was the XGBoost model that yielded the best performance according to all the metrics as shown in Table 2. The MAE, the RMSE and the R-squared were 9.7884, 12.145, and 0.4847, respectively. In addition, when

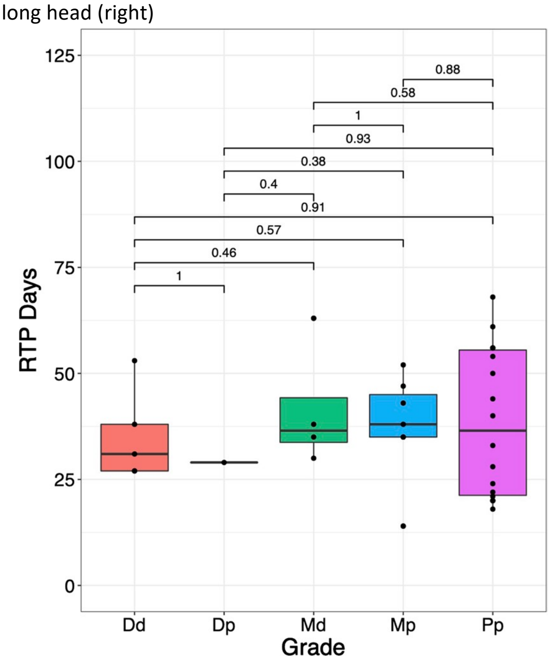

Fig. 3 Return to play (RTP) biceps femoris long head grade 3^r by location, and related to the myotendinous junction. Injury located at the distal third affecting the distal myotendinous junction (MTJ) (D_d), injury located at the distal third affecting the proximal MTJ (D_p), injury located at the middel third affecting the distal MTJ (M_d), injury located at the middel third affecting the proximal MTJ (M_p), injury located at the proximal third affecting the proximal MTJ (P_p)

looking at the performance measures stratified by grade, we observed that the predictive power was higher in injuries of lower grade compared with those of grade 3 (Table 3). These results could not be compared with other classification systems as these performance measures were not reported [35, 36].

We observed that the grade of the injury was the most important variable to determine the RTP followed by the MTJ location (free, central, other) or muscle injury. Furthermore, when looking at the ALE, we identified FT injuries as the most relevant factor driving the long RTP (Fig. 6 of the ESM). Moreover, grade 3 ʳ was identified as the second most relevant factor for long RTP followed by re-injuries (Fig. 6 of the ESM). In terms of inter-rater and intra-rater reliability, the Cohen's kappa and the intra-class correlation coefficient showed an excellent level of agreement between the different measurements (Table 2 of the ESM).

Table 2 Performance measures of validation models

	Linear regression	Random forest	XGBoost
MAE	10.3609	10.1037	9.7884
RMSE	12.8070	12.5296	12.1450
R-squared	0.4345	0.4195	0.4847

MAE mean absolute error, *RMSE* root mean squared error, *XGBoost* eXtreme Gradient Boosting

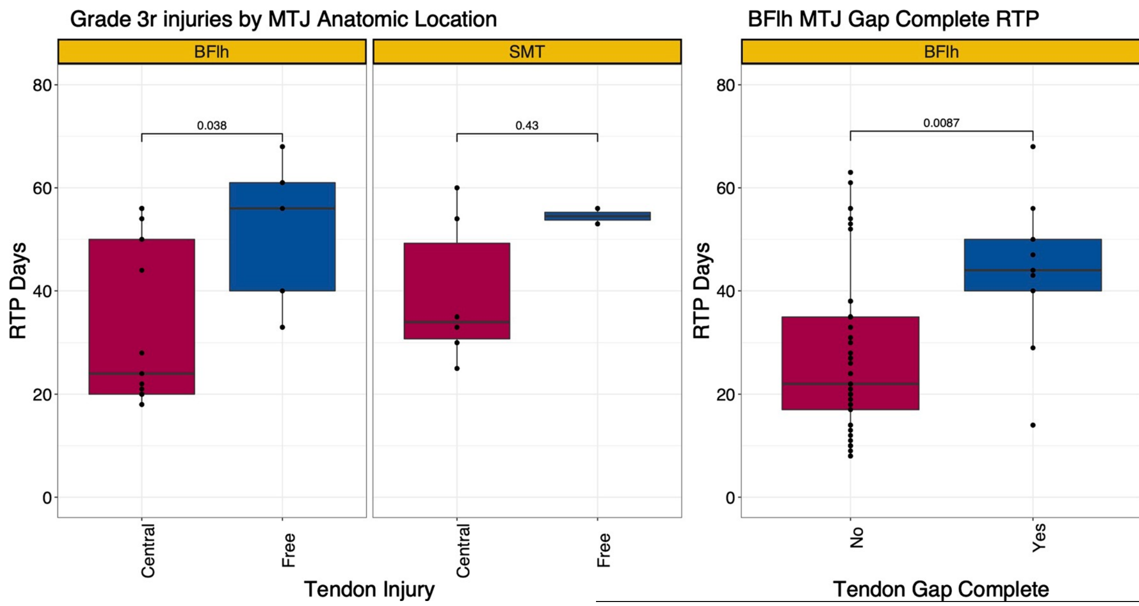

Fig. 4 Return to play (RTP) of grade 3 ʳ biceps femoris long head (BFlh) and semitendinosus injuries (left). Return to play of grade 3ʳ BFlh in partial vs complete tendon injury (right). *MTJ* myotendinous junction

Table 3 XGBoost performance by grade

Grade	*N*	Re-injuries	IQR	MAE	RMSE
0	1	0	0.0	4.0	4.0
1	3	0	1.0	5.0	5.1
2	17	2	10.0	5.9	7.4
3	5	0	12.0	6.2	7.6
3ʳ	50	7	25.2	11.8	14.0

IQR interquartile range of observed values, *MAE* mean absolute error, *N* number of observations, *RMSE* root mean squared error, *XGBoost* eXtreme Gradient Boosting

4 Discussion

We demonstrate in this study that the MRI-based MLG-R classification system provides an accurate prognosis on hamstring injuries sustained by professional athletes. Our study shows that the main determinant for long RTP after hamstring injury is the injury affecting the connective tissue structures of the hamstring. The strength of our study is that our results came from a very homogeneous sample of professional football players, with the same resources and philosophy for diagnostic, rehabilitation, and RTP criteria. All the players were followed up for at least one season after the injury, which also allowed us to monitor re-injuries or new injuries in the same region. The distribution of injuries within different hamstring muscles in our patient samples is similar to previous studies [5], as is also the number of re-injuries [2].

When we explored for the predictive MRI findings, the difference in RTP between 3r and all other grades was statistically significant for all injuries, and individually for BFlh injuries. The small number of injuries with a grade other than 3 is a limitation of our study. Although the mean RTP time increased from grades 1 to 3 in the BFlh sample, the differences are not statistically significant because of the low number of injuries.

The longer RTP time for 3r injuries in the BFlh or the SMT FT compared with those injuries located at the central tendon supports the concept that injuries affecting the proximal part of the MTJ are worse than the more distal injuries [37]. We could not find a similar outcome in the RTP between BFlh 3r injuries involving the middle and distal part of the proximal MTJ. However, we were again hampered by the low number of these injuries.

The role of central tendon injuries on the RTP has been evaluated in thigh muscles, where it was reported that a significant injury to the intramuscular tendon is associated with a prolonged RTP and an increased re-injury risk [38]. In line with the literature, we found a statistically significant difference between BFlh proximal MTJ with partial vs complete tendon gap injuries. In general, any injury involvement of the proximal MTJ will have a great impact in the RTP. This may be due to the fact that the time needed for the connective tissue to heal is longer than for the muscle fibres [39]. Based on the data from our sample, we should state that the injury in any grade of the principal connective tissue structure, which is the MTJ, will be the main factor that needs to be considered to estimate the RTP.

The fact that the grade, followed by the involvement of tendon injury (free, central or other), are the most important variables to determine the RTP in hamstring injuries, support our concept that the extent of the damage to the connective tissue structures is key for the RTP. The small difference in the mean RTP of the BFlh injuries between grades 1, 2, and 3, without connective tissue structure damage (11, 15, and 18 days) strengthens the idea that the main driver for longer RTP is to have an injury affecting the MTJ.

Indirect/strain muscle injuries are typically located close to a MTJ [40, 41]. A recent publication highlights the notion that damage in muscle injuries is located in places where muscle fibres attach to connective tissue structures. This shows evidence that damage to the connective tissue plays a more important role than for the muscular component in terms of recovery [23]. The data from our sample show that 50 (65.8%) injuries are grade 3r, which means that the MTJ is injured at some point on its length. From the 55 (72.4%) injuries of grade 3 and grade 3r, 24 (43.6%) have no muscle fibre injury other than oedema described in grades 1 or 2. We refer to all of these injuries as muscle injuries when we are really describing injuries of the MTJ in most of the cases.

We present a novel approach to validate and understand the clinical prognosis of hamstring injuries by using three advanced statistical models. The approach we used is clearly superior to previous studies [28, 29] as we compared the performance of three different statistical and machine learning models. These models allow the capture of nonlinearities in the data, they are more prone not to overfit and they have reduced variance. The best model in all the performance measures, the XGBoost, managed to obtain a MAE of 9.8, implying that on average, for any given injury, the RTP time prediction will only fail by 9.8 days. Nonetheless, better results in terms of the RMSE and MAE were observed for less severe injuries as shown in Table 3. Therefore, one has to bear in mind the nature and complexity of the injury when using the MLG-R to predict the RTP. Moreover, the R^2 presented was more than double that of previous studies with similar characteristics [28]. Thus, the approach presented is robust as all models converged to similar results, had a high predictive power, the MAE and RMSE were very good, and we managed to explain a large proportion of the variance in the RTP time with very few variables. In addition, we provided a clear interpretation to the contribution of each factor to the RTP by means of the variable importance and the ALEs, something that has never been applied in the sports medicine field to the best of our knowledge.

This comprehensive approach showed evidence that the grade of the injury was the most important variable to determine the RTP followed by the MTJ injury location (free, central, other) and the muscle injured as shown (Fig. 5 of the ESM). When looking at the accumulated local effects, we identified FT injuries as the most relevant factors driving the RTP. Moreover, grade 3^r was identified as the second most relevant factor for RTP followed by re-injuries. Because of the anatomy of the distal BFlh MTJ, the location of the injuries is in a smaller area than in the proximal MTJ, which has a higher length, this could be one of the reasons why the dispersion is higher in the injuries affecting the proximal MTJ.

4.1 Injuries Affecting the Free Tendon

Although the injured patients were obtained from four professional teams with a substantial number of experienced players in them, all 11 free tendon ruptures that required surgery, and were not included in the statistical analysis, took place exclusively in players between 17 and 21 years of age. The finding is striking and novel, but there could be several plausible explanations for it. The injuries were located at the ischial tuberosity avulsion in younger athletes [42], but we do not have a clear explanation why we only saw injuries affecting the central tendon in older/more experienced football players. However, our results suggest that there might be remodelling/maturation in the hamstring bone-tendon–muscle unit well into the mid-20 s in professional athletes and should warrant further investigation. If this is indeed the case, then we see avulsion fractures during puberty, injuries affecting the central tendon in fully mature players, and in this window of 4 years, the most severe injuries take place at the FT. We cannot emphasise the importance of this type of injury enough owing to its high re-injury tendency, the heavy burden of time loss related to it, and because we eventually treat these injuries surgically to restore the structure function of the hamstrings and the player performance [39, 43].

4.2 Extracellular Matrix

A.R. Gillies already quoted: “skeletal muscle are primarily contractile material. However, because muscle is a composite tissue of connective tissue, blood vessels, and nerves, as well as contractile material, these “minor tissues” (in terms of relative mass) may strongly influence muscle function” [22]. In the context of the major findings of this study, we believe that focus should be shifted to the connective tissue structures of the muscle–tendon unit in the evaluation of its injuries.

The skeletal muscles and their tendons are not the only structures transmitting and bearing tensile loads. In some muscles, less than 20% of the muscle fibres span the entire distance between the origin and the insertion, while the remaining fibres end in the muscle belly, being connected only via their endomysium or by adhering to the myofascial junction, which is the extension of the MTJ [44].

Muscle contraction has been analysed for years as linear and unidimensional, in a simplistic model, as the extracellular matrix (ECM), organised in three independent passive layers. Muscle contraction happens in three dimensions, and it is necessary to evaluate the muscle as a whole to understand its structure, function, mechanics and pathology [45]. This three-dimensional transmission of force generated at the sarcomere level is of importance also when evaluating the superior organisation beyond the sarcomere, and draws attention to the role of the structural components of the muscle in muscle function [45].

Despite the important role of the ECM in muscle function and pathology, the amount of research on it is very limited; knowledge on the muscular functional properties of the ECM [22] and its geometry [46, 47] is very limited. It is clear now that the three layers of the ECM, classically described as endomysium, epimysium and perimysium, are not individual layers covering the muscle structure from small to bigger levels; instead, it has being described as a three dimensions network, with a complex geometry and multiple connexions between layers [47]. The ECM is a three-dimensional structure going from a higher to a lesser density structure with an asymmetric distribution [24], because of that, complete knowledge of the anatomy of the MTJ muscles is key to correctly understanding muscle injuries.

4.3 Confusing Terminology

Despite the high prevalence and the challenging nature of hamstring injuries, some anatomical regions in the hamstrings need to be clarified more thoroughly especially in light of describing magnetic resonance images. Namely, the "SMT raphe" or the "semimembranosus membrane" are two classic examples of terms used to describe hamstring anatomy. The "raphe" is not yet fully understood, and we do not know if it is part of the proximal or distal MTJ, or if it should be considered an independent element. The injuries affecting the semimembranosus membrane should be classified as affecting the proximal MTJ. However, unlike injuries affecting the MTJ, they do have a good prognosis.

In addition to the certain anatomic regions not defined universally, we also describe injury "patterns" with descriptive, but not universally accepted terms such as myotendinous [48], musculotendinous [49], myoaponeurotic [50], myofascial [48], epimysial [51], peripheral [52], superficial involvement [53] or distal aponeurosis [54], and it still happens, despite recent efforts to reach agreement in terminology [55]. The only aim of all these names is to describe the topographical location of the injury related to the length of the affected MTJ and to provide an idea whether the connective tissue structures were torn.

Another example of the subjectivity in this field is the medical meaning of the term fascia, it has evolved during history [56], with several attempts to reach an agreement about the nomenclature of the fascial system and its elements [57]; and despite its extensive use in the literature, the variable application of the name still creates confusion [57].

4.4 Limitations

As described in the methods sections, our sample came from football, one club, and one medical team with the same philosophy and own experience in the use of this classification and in the field of football. Further studies should be conducted to test this classification system in different sports, and by different people with different degrees of experience, perhaps through a multicentre study. This will help to evaluate the external validity of this classification system and the possibilities of generalisation to other sports and application conditions. The normal learning curve implied in any new medical procedure (i.e. classifying a muscle injury) should be seen as a universal limitation in medical research, but we believe that this is a very important first step with promising possibilities for the complex topic of classification of muscle injuries.

5 Conclusions

With the introduction of our classification system, we strongly believe that there is no need to use any of these subjective terms to describe a muscle injury. With our four letters initialism, we report the muscle belly and mechanism of injury, and offer an objective topographic (where), chronologic (how many times), and structural (grade of injury) description of the injury, minimising the subjectivity of the description.

Our study shows that the main determinant for long RTP after hamstring injury is the injury affecting the connective tissue structures of the hamstring. Therefore, the ECM structure and its role in force generation and transmission is the key factor in the signs, symptoms and prognosis of muscle injuries

[58], and because of that, we designed our proposal of classification with the main aim to evaluate the amount and severity of the ECM damage [16]. The concept of evaluating and quantifying ECM damage as a key point in a muscle injury classification was first described in our previous paper [16].

With this work, we tested the theoretical model published before [16]. The proposal proved to have a good inter-observer and intra-observer reliability, being capable of grading injuries based on their severity, and offering a good prognosis. Our model can predict RTP with greater accuracy than previous proposals; and with a further adoption of our proposal, thus a larger sample size, the model will be able to generate more knowledge helping us to better manage HMIs.

In light of the results showed in this work, we strongly believe that the use of our proposal will represent a scientific advance, a more objective approach to muscle injury management, and with the capability to adapt and incorporate future knowledge into our classification system. We welcome future replication studies in other football teams and indeed other sports.

Supplementary Information The online version contains supplementary material available at https://d oi.org/1 0 .1007 /s 40279-022-0 1672- 5.

Declarations

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Conflict of interest None of the authors has a conflict of interest related to the present investigation.

Ethics Approval This study was assessed and approved by the Ethics

Committee of the “Consell Català de l’Esport” with the number 10/ CEICGC/2020. The present study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki.

Consent to Participate Appropriate written informed consent to participate in research projects was obtained from all FC Barcelona football players.

Consent for Publication Appropriate written informed consent for publication was obtained from all participants in the present study.

Availability of Data and Material The datasets generated during and/ or analysed during the current study are not publicly available because of the fact that many of the players had their injury status publicly informed in the mass media and, therefore, some personal information from the players regarding their injuries could be deduced. This could imply a violation of the patients’ privacy and confidentiality noted in statement number 24 of the Declaration of Helsinki. We could make it available from the corresponding author on reasonable request, from a medical institution.

Code Availability Not applicable.

Author Contributions XV and XY collected all the data. XV and SM analysed the magnetic resonance images. AM conducted all the statistical analyses. XV, SM, EAG, TJ and AM prepared the manuscript. RP, LL, GR, JCM, JI, MG and RB were the major contributors to the preparation of the manuscript. All authors contributed to the last editing and approval of the final manuscript.

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