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Annals of Sports Medicine and Research

Mini Review

Effects of SARS-COV-2 Infection on Muscle Injury Healing in Professional Football Athletes, Preliminary Results

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Submitted: 08 February 2023

Accepted: 28 March 2023

Published: 29 March 2023

ISSN: 2379-0571

Keywords

- Football athletes; SARS-CoV-2; Prognosis; Return to sport; Lower extremity

Abstract

Objectives: Muscle injuries are a serious problem for professional athletes, hampered by long recovery periods and absence from competition. The purpose of this study is to evaluate if there is any difference in recovery time between SARS-CoV-2 positive and negative professional football players.

Methods: This is a retrospective case-control study. 109 high-level professional athletes with lower limb muscles injuries were studied with MRI. Two groups were formed and who tested positive was followed until exhibit negative test. Positive athletes were divided into sub-groups according to the duration of the disease. Linear regression test was performed to assess the correlation degree between the variable "disease grade (0-3)" and injury duration and between the variable "injury length (mm)" and injury duration. Analysis of variance with ANOVA study was then performed assessing the individual influence of "disease grade" and "injury length" on injury time.

Results: 26 lesions fulfilled the inclusion criteria. "Injury length" and "injury duration" showed correlation (p = 0, 2026); "disease grade" and "injury duration" showed mild correlation (y = 25, 5789 + 7, 1026 x; p = 0, 1). An increasing trend was noted in the correlation between the duration of swab positivity and the injury time.

Conclusions: It is plausible that the generalised inflammatory state may disturb the healing processes by interfering with the cytokine environment; further studies may find important information which will have a direct impact on athletes' systemic therapies aimed at rebalancing body homeostasis.

ABBREVIATIONS

ACE2: Angiotensin Converting Enzyme 2; DP: Proton Density; RTS: Return to sport; SARS-CoV-2: Severe acute respiratory syndrome Coronavirus 2; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TMPRSS2: Transmembrane serine protease

INTRODUCTION

Muscle injuries are a serious problem for professional athletes, hampered by long recovery periods and absence from competition.

The main issue regarding muscle injuries is their accurate identification and classification, in order to accurately predict the return to the field time for each player [1,2].

An inaccurate estimate of the degree of injury and, consequently, an incorrect prognosis, can lead to a premature return to the field with an increased risk of re-injury [3,4].

Over time, numerous classifications have been proposed with the goal of providing a prognostic tool in the management of muscle injuries. However, these classification systems tend to group even very different injuries into broad categories, often providing little correlation between the actual severity of the injury, its aetiology, treatment and prognostic significance [2,4-6].

In 2012, Mueller-Wolfarth et al., proposed a classification to facilitate diagnostic and therapeutic pathways and scientific communication [7]; this comprehensive and practical classification system has been widely used and integrated into other studies, such as that of Calvi M et al. [8], who, based on the latter, attempted to discriminate stable from unstable muscle injuries by following them over time using contrast medium MRI. A number of studies exist in the literature evaluating the involvement of muscle tissue in patients with Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection, however there is little information about how this pathology may affect the recovery time of professional athletes following injury [9-15].

The purpose of this study is to evaluate the differences in recovery time between professional football players who tested positive for the infection and simultaneously developed a muscle injury, compared to athletes who tested negative for the molecular test. The results of this study refer to a period prior to the introduction of the vaccine.

MATERIALS AND METHODS

This is a retrospective study based on existing clinical data. Patients were not directly involved, provided that written informed consent for contrast-enhanced MRI was obtained from each of them. Patients also signed a comprehensive consent form which satisfied all the requirements of the Declaration of Helsinki and the Italian national law for the protection of personal data.

Between November 2020 and March 2021, 109 MRI studies of high-level professional athletes with clinically suspected lower limb muscles injuries were evaluated. Each athlete complained of acute pain in the lower limb with indirect trauma during physical activity; the clinical suspicion of a muscle lesion was confirmed by the club physician. MRIs specific protocols will be discussed in the following sections.

From the initial sample, we selected all athletes who had tested positive for SARS-CoV-2 infection by molecular testing during the time period between November 2020 and March 2021. All athletes underwent regular swab monitoring during training period and before each official match. All athletes in the study were tested with the same molecular test using FLOQ® Swabs (COPAN, Brescia, I) in UTM® Universal Transport Medium (COPAN, Brescia, I). The research of SARS-CoV-2 RNA was carried out by reverse transcription polymerase chain reaction (RT-PCR) amplification profile with Cobas® SARS-CoV-2 Test on the automated Cobas® 6800 Systems (both from Roche Diagnostics). The test detects conserved regions for ORF-1a/b and E-gene regions on SARS-CoV-2 after RNA automatic extraction. Non-infectious plasmid DNA containing a specific SARS-CoV-2 sequence and a pan-Sarbecovirus sequence are used in the test as positive control. A non-Sarbecovirus related RNA construct is used as internal control. Cut-off of <40 Cycle Threshold (CT) was applied for the positivity ot the test, i.e. the presence of SARS-CoV-2 RNA [16,17].

Each athlete who tested positive on the swab was then followed up clinically until exhibit negative test and total disease duration (defined as molecular test positivity) was calculated. No player ever developed symptoms except for mild flu-like syndromes or cold symptoms. The positive athletes were then divided into groups according to the duration of the disease (grade 1/2/3) considering as grade '0' the athletes who always tested negative added to some (n=6) ''historical'' cases with injuries dating back to the years 2017/2018/2019 when SARS -CoV-2 infection would have been statistically unlikely. These latter cases were not tested with the molecular swab. The 'historical' cases were randomly selected among the injuries which occurred between 2017 and 2019 to equalise the numerosity between the study group and the control group; they are not consecutive data. On the other hand, the athletes subjected to molecular testing were selected consecutively. No athletes in the study were given any vaccine before, during the period of positivity nor during the 3 months after testing negative.

The data concerning the injury duration and the actual return to the field were provided by the sports club doctor. In this study, only injuries with complete data were included, leaving out those occurring at season's end. Examinations of athletes with chronic or recurrent pain or with contraindications to MRI were excluded. Urgent need for surgery, complete avulsion injuries, presence of concomitant fracture or presence of double lesions were considered exclusion criteria. Type 4 injury classification [12] were not included in the study.

A radiologist (EAG), with more than 20 years of experience in musculoskeletal radiology, retrospectively evaluated all the studies. Each lesion was examined in both axial and coronal planes using protonal-density (DP)/T2 weighted images with and without fat saturation, supported by DWI sequences [3]; the grade according to the Mueller-Wohlfarth classification [7] and the longitudinal extent of each lesion were assessed, lesion length was measured in the coronal plane (Figure 1). Follow-up of muscle tears included contrast medium FSE T1 sequences [8].

All images were obtained using a 1.5-Tesla magnet system (Philips Ingenia Ambition/Elition, Philips Medical System) with a phased array 16 channels body matrix coil. The MRI after the injury was performed according to the protocol illustrated in Table 1.

Athletes included in the prospective case series received either a similar rehabilitation program, or individualized rehabilitation at the club or federation. Time to RTS was defined as the number of days from injury until the athlete was cleared to resume unrestricted training by the treating physician or

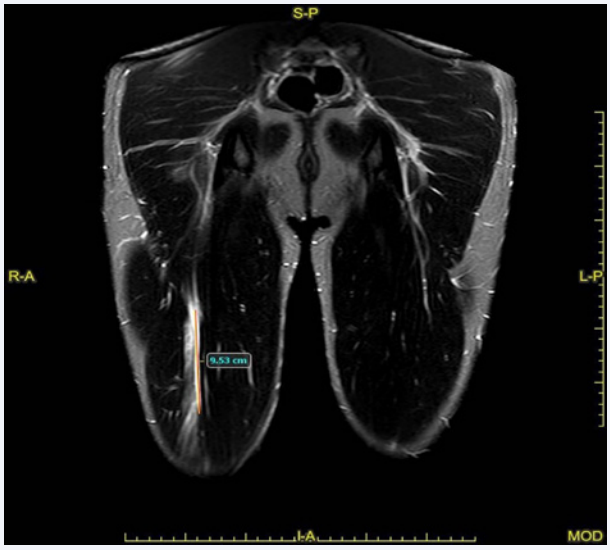

Figure 1 MRI. Coronal STIR TSE weighted image at the level of femurs showing a longitudinal tear of right biceps femori having longitudinal extension about 9,5 cm.

Table 1: MRI protocol. Sequences used in the study of muscle injuries.

- Coronal STIR TSE (TR 2700-6000, TE 90, TI 140ms, FOV 400-450x400, Slice thickness 4 mm, Matrix 328x310, ETL 6, TURBO FACTOR 20, NSA 2, SENSE reduction factor 2)
- Axial TSE dual proton density-weighted SPAIR and without fat suppression (TR 3000-4000, TE-1 5.7 ms, TE-2 80ms, FOV 400X300, Slice thickness 4 mm, Matrix 400x250, TURBO FACTOR 18, NSA 2, SENSE reduction factor 2)
- Axial T1 TSE (TR 520, TE 18, FOV 400X300, Slice thickness 4 mm, Matrix 400x250, TURBO FACTOR 5, NSA 2, SENSE reduction factor 2); Axial DWI (b=0-450-900) (TR 1759, TE 80-90, FOV 450X400, Slice thickness 4 mm, Matrix 152x133, NSA 4, SENSE reduction factor 2).
- Axial DWI (b=0 - 450 - 900) (TR 1759, TE 80-90, FOV 450X400, Slice thickness 4 mm, Matrix 152 ×133, NSA 4, SENSE reduction factor 2).
Sequences used in the study of muscle injuries.

physiotherapist at the club or federation. The treating physician or physiotherapist making the RTS decision was not blinded to the MRI findings.

The sample in study was tested for normality regarding injury duration using Pearson's test. Thereafter, the linear regression test was performed to assess the correlation degree between the variable "disease grade (0-3)" and injury duration and between the variable "injury length (mm)" and injury duration. Analysis of variance with ANOVA study was then performed assessing the individual influence of "disease grade" and "injury length" on injury time.

This paper is consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) cohort reporting guidelines [18].

RESULTS

Of the initial 109 MRI studies, 26 fulfilled the inclusion criteria (Figure 2). We examined 26 high level professional football players MRIs. The average age of the selected sample was 25 years (SD±6 years; range 19-39). The involved muscles are summarized in Table 2, 35% of the lesions were located at the myotendinous junction while 65% were at the myofascial junction. Molecular test-positive athletes with a positivity lasting between 1 and 20 days were a total of five (grade 1); those with

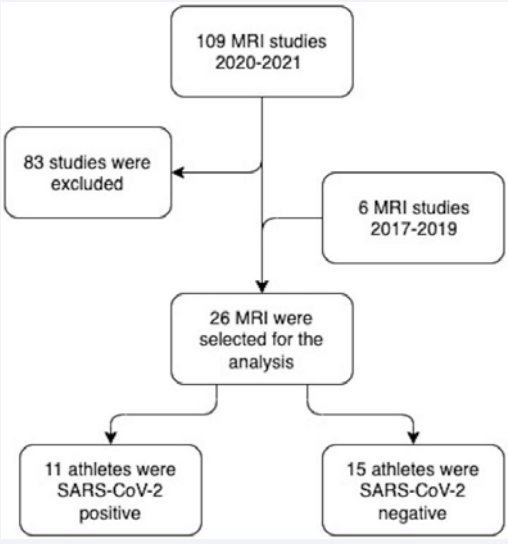

Figure 2 Flowchart showing athletes selection applying inclusion and exclusion criteria.

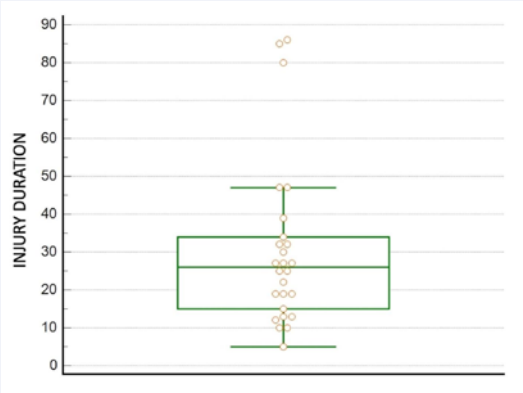

Figure 3 Normal distribution of injury duration among athletes.

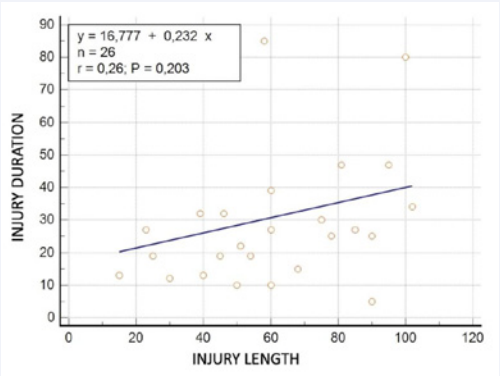

Figure 4 Graphics showing poor correlation between "injury length" of and "injury duration" (p = 0,2026).

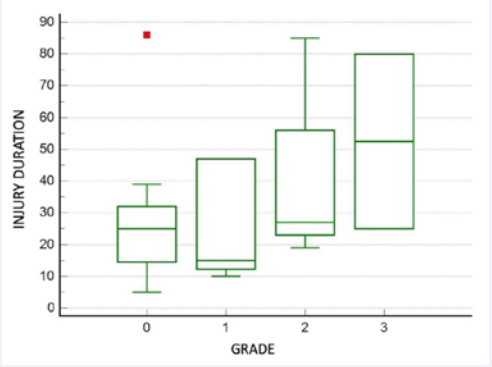

Figure 5 Graphics showing mild correlation between "disease grade" and "injury duration" in linear regression test (y = 25,5789 + 7,1026 x; p = 0,1)

Table 2: Table summarizing involved muscles, location and length extension of the lesion, duration of injury, and molecular test results

List and characteristics of lesions included in the study.

N°	Age	Involved muscle	Lesion site	MUNICH	Injury duration (RTS - days)	SARS-CoV-2 infection (Y/N)	Lesion length (coronal plane – mm)
1	23	Biceps Femoris	Myo-aponeurotic	3A	47	Y	95
2	25	Biceps Femoris	Myotendinous	3A	10	Y	60
3	27	Semitendinosus	Myofascial	3A	13	Y	15
4	23	Soleus	Myotendinous	3A	10	Y	50
5	39	Biceps Femoris	Myo-aponeurotic	3A	47	Y	81
6	39	Long abductor	Myofascial	3A	15	Y	68
7	38	Soleus	Myotendinous	3A	12	Y	30
8	38	Soleus	Myo-aponeurotic	3B	34	Y	102
9	25	Medial Gastrocnemius	Myo-aponeurotic	3A	86	N	45
10	22	Semimembranosus	Myofascial	3A	19	N	54
11	23	Biceps Femoris	Myotendinous	3A	22	N	51
12	23	Medial Gastrocnemius	Myotendinous	3A	27	N	85
13	21	Long abductor	Myofascial	3A	27	Y	23
14	21	Biceps Femoris	Myo-aponeurotic	3A	19	Y	45
15	21	Semimembranosus	Myotendinous	3A	32	N	46
16	31	Rectus Femoris	Myofascial	3A	30	N	75
17	30	Biceps Femoris	Myotendinous	3A	19	N	25
18	19	Biceps Femoris	Myotendinous	3A	80	Y	100
19	26	Long abductor	Myofascial	3A	32	Y	39
20	21	Medial Gastrocnemius	Myo-aponeurotic	3A	27	Y	60
21	21	Rectus Femoris	Myofascial	3A	25	Y	90
22	20	Rectus Femoris	Myofascial	2B	5	N	90
23	20	Biceps Femoris	Myo-aponeurotic	3A	13	N	40
24	20	Biceps Femoris	Myo-aponeurotic	3A	39	N	60
25	23	Biceps Femoris	Myotendinous	3A	85	Y	58
26	23	Semitendinosus	Myofascial	2B	25	Y	78

RTS: return to sport

a positivity between 20 and 40 days were four (grade 2); and those with a positivity greater than 40 days were as many as two. Athletes who never tested positive including cases from the years 2017/2018/2019 (grade 0) were a total of fifteen. Injuries lasted an average of 30 days (SD±22 days; range 5-86) (Figure 3). Lesions measured in the coronal plane measured on average about 60 mm (SD±25mm; range 15-102) and were mostly classified as 3a (88%). The sample in study followed a normal distribution regarding the injury duration. The linear regression test evaluating the correlation between "injury length" and "injury duration" showed correlation (p = 0, 2026) (Figure 4). The linear regression test evaluating the correlation between "disease grade" and "injury duration" showed mild correlation (y = 25, 5789 + 7, 1026 x; p = 0,1). An increasing trend was noted in the correlation between the duration of swab positivity and the injury time (Figure 5).

DISCUSSION

Muscle injuries are one of the most common traumas occurring in sports [8,19], represent one of the most frequent and most relevant injuries in professional football which is one of the major causes of absence from competition [4,8].

In the literature, relationships between SARS-CoV-2 infection and various muscle diseases have been described. Many studies have recently described persistent symptoms in subjects infected with SARS-CoV-2 and hospitalized beyond 3 months [20–23]. Although these studies have generically described fatigue, myalgias, and persistent joint pain, the severity, type, and location of persistent rheumatic and musculoskeletal symptoms have not been documented in detail [24].

Some studies suggest skeletal muscle, synovia, and cortical bone as potential sites of direct infection by SARS-CoV-2 [15]. It has been described that myalgias and generalized weakness occur in about 1/2 of symptomatic patients with SARS-CoV-2 infection.

Specifically, as described by Omar et al. [25], four main categories of muscle injury SARS-CoV-2 infection related were detected: myalgias, myositis, myonecrosis, and rhabdomyolysis.

However, some authors have concluded that the pattern of muscle pain is not related to the severity of SARS-CoV-2 infection. On the contrary in patients with abnormal computed tomography (CT) lungs, myalgia have been an important predictor of overall disease severity [15].

Several authors have analysed the relationship between SARS-CoV-2 infection and musculoskeletal disorders, predominantly considering patients with moderate to severe disease or requiring critical care [11-15,20-24].

Few studies have analysed the impact of mild-to-moderate

disease on the skeletal system, and to our knowledge there is no available evidence that correlates imaging data with disease course [9].

Some studies have evaluated the loss of muscle strength in patients with SARS-CoV-2 infection [26,27], but again these were patients with severe disease.

Other studies have assessed the impact of the disease from a neuromuscular perspective [28], again showing signs of myopathy with reduced strength in 55% of individuals.

The theories that could explain the interaction between the viral particles and the striated muscle are essentially two, as described by Dos Santos et al. [9], and include either direct damage by the virus to the muscle fibres or the so-called cytokine storm. However, Disser et al. [15], describe how muscle cells only express Transmembrane serine protease 2 (TMPRSS2) while lacking the expression of Angiotensin converting enzyme 2 (ACE2). Both proteins are in fact only expressed by smooth muscle and this would supports the cytokine storm theory [29-32].

A further theory, not directly related to the effects of viral infection, claims that muscle damage could also be traced back to muscle relaxation due to rest period imposed by quarantine, which in professional athletes used to rhythms of constant high intensity training leads to muscle detraining. Such loss of trophism determines a greater possibility of damage when the athletes return to training, particularly when the pressure of a rapid return leads to excessive training, not weighted on gradual recovery [33]. Though this theory is not significant to our study, as even during the isolation period due to the positivity, when asymptomatic, the athletes underwent regular training.

In our study, we evaluated how the disease impacts the healing time of muscle injuries in professional athletes. Based on what was described by Järvinen et al. [19] about the muscle tissue healing phases, the fibroblast proliferation phase with subsequent production of extracellular matrix is crucial in the formation of scar tissue. The Granulation tissue that forms in this phase is, in fact, an unstable tissue before there is deposition of collagen fibres, and premature return to the field would predispose to an increased risk of re-injury.

Scar maturation also depends on a delicate balance between matrix production and degradation, with the aim of achieving migration of the myofibrils until they rejoin, restoring the functional unity of the injured muscle [19,32,34-35].

CONCLUSION

The results obtained with our study are in line with what is described in the literature regarding the size of the lesion, which in fact proved to be of little influence on recovery time regardless of the presence or absence of the disease [1-3,8,36].

On the other hand, a positive correlation was observed between the persistence of the viral load and the period of scar instability assessed by gadolinium enhanced MRI.

According to what was previously stated, it is plausible that the generalised inflammatory state due to the infection, although being subclinical or with little symptomatology, may have been sufficient to disturb the healing processes by interfering with the cytokine environment [19, 27-32]

Our study certainly has limitations due to the small sample, but it remains unique and opens up a never-before attempted perspective in the study of variables that may influence healing time after muscle injury. Further studies with a larger sample size are desirable in analysing the possible interaction between an altered cytokine environment and the slowdown in the healing time of a muscle injury. The results would in fact have a direct impact on the therapy of athletes, who would then not only benefit from locoregional therapy, but also from systemic therapies aimed at rebalancing body homeostasis.

ACKNOWLEDGEMENTS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Marco Calvi and Eugenio Annibale Genovese. The first draft of the manuscript was written by Marco Calvi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. No funds, grants, or other support was received. The authors have no financial or proprietary interests in any material discussed in this article.

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