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Special Issue

# "Challenges and Solutions for Musculoskeletal Disorders in Athletes"

**Guest Editors**

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# Challenges and Solutions for Musculoskeletal Disorders in Athletes

***Dear Colleagues,***

Musculoskeletal disorders are very common health problems in athletes. These conditions affect sport performance and result in withdrawal from training and competitions, with huge costs. Several types and locations of musculoskeletal disorders might occur in athletes according to different sport modality, particularly affecting joints, skeletal muscles, and tendons in most cases. Considering the high frequency of these conditions and their significant impact on sport performance, several studies are focused on investigating their pathogenic mechanisms as well as potential therapeutic approaches.

This Special Issue aims to investigate the biological mechanisms, diagnostic challenges, and rationale of available therapeutic strategies in the field of sport-related musculoskeletal disorders. In particular, the pathways regulating the muscle–bone crosstalk that guides healing processes in skeletal muscle injuries will be investigated. A dedicated paper will provide an evidence-based update on the main instrumental approach, ultrasound imaging, for the diagnosis of soft-tissue injuries in sport practice. Two papers will deal with two emerging painful conditions that require an early diagnosis and appropriate management to avoid disabling consequences: early osteoarthritis and complex regional pain syndrome type I (CRPS I). Finally, six articles will be dedicated to clarifying critical issues of commonly used pharmacological and non-pharmacological interventions to treat sport-related musculoskeletal disorders.

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# Challenges and Solutions for Musculoskeletal Disorders in Athletes

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The etymology of the word "athlete" derives from the ancient Greek ἀθλητής (athletés, from âthlos that is, fight, competition). The athlete, therefore, is the one who is striving in the effort to overcome a sport challenge, but, even more, in the effort to overcome himself. Sport-related musculoskeletal (MSK) disorders very commonly lead to poor performance and/or loss of competitions [1]. Several types and locations of MSK disorders might occur in athletes according to different sports, particularly affecting joints, skeletal muscles, and tendons. Considering the high frequency of these conditions and their significant impact on sport performance, several studies are focused on investigating their pathogenic mechanisms, as well as potential therapeutic approaches.

Although primary prevention mainly involves coaches and trainers, secondary and tertiary prevention of sport-related injuries, that are the reduction of reinjury, as well as their consequences to allow an effective sport participation, are the main challenges for healthcare professionals that treat athletes [2]. In this context, several unmet needs are required to be addressed, such as heterogeneous epidemiological data reporting of sport related MSK injury, natural history of the healing process of injured tissues, and safe return to play timing. Other topics of huge interest for physicians could be how different athletes respond to a specific injury and its complications, which outcomes are to be collected and monitored (e.g., return to play, physical function, pain, psychological, and/or socioeconomic measures) for assessing efficacy and/or effectiveness of different interventions, which management strategy or combination of treatments can modulate pathogenic mechanisms or address specific risk factors to reduce recurrence and/or to prevent disabling consequences of sport-related injury [2]. These conceptual and practical considerations should be investigated at both research (basic science and randomized controlled trials) and clinical levels (real-life practice), along with the athlete's compliance, as well as the professional club agreement with proposed therapeutic strategies, and how medical specialists can implement these strategies. In this complex scenario, the Special Issue "Challenges and solutions for musculoskeletal disorders in athletes" aims to provide reliable and evidence-based answers to these challenging unmet needs.

In our opinion, the above mentioned issues can be addressed through a comprehensive and interdisciplinary teamwork that includes specialists with specific expertise in the management of MSK disorders, such as orthopedists, rheumatologists, and physiatrists, as well as by applying knowledge translation to stakeholders (e.g., clinicians) regarding debated sport-injury issues, such as diagnostic imaging pitfalls in muscle injury classification or the controversial role of exercise and other conservative measures in the occurrence and management of early osteoarthritis (EOA). This approach might overcome conceptual and language barriers among different stakeholders, and it can be better than simply adding each individual contribution in terms of decision-making and evidence-based interventions, finally contributing to the general wellbeing and safe and effective participation of athletes to sport practice.

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In particular, the Special Issue consists of ten articles of wide interest for clinicians that manage MSK injuries in athletes, starting from the definition and epidemiology of these lesions [3] and an update about the role of ultrasound (US) imaging in muscle injuries [4]. These lesions frequently affect lower limb muscles, particularly in football players and track and field athletes, leading to long recovery times and risk of re-injury. Diagnostic US has several practical advantages in this context, such as fast evaluation, portability, good spatial resolution, and the ability to perform dynamic tests.

The Special Issue also includes two papers addressing challenging conditions in sport practitioners, such as the bone marrow edema (BME) [5] and the Complex Regional Pain Syndrome (CRPS) type I [6] that call the clinician to face several pitfalls thus requiring early diagnosis and appropriate management to avoid disabling consequences. Bone marrow edema is an umbrella term used to define the instrumental findings of low signal intensity on T1-weighted (T1W) magnetic resonance imaging (MRI) and intermediate or high signal intensity findings on T2-weighted (T2W) MRI [7]. This condition is often reported in stress-related bone injuries of both professional and amatorial athletes, although its clinical significance remains unclear. Complex regional pain syndrome type I is a rare, chronic condition characterized by disproportionate pain, usually affecting distal limbs, that may develop in athletes following traumatic or overuse injuries that require a troublesome approach in term of diagnostic issues and therapeutic decisions [8–13].

Furthermore, the Special Issue includes six articles addressing pharmacological and non-pharmacological approaches to treat sport related MSK disorders. These papers provide an overview of the drug therapy for acute pain following sport-related trauma [14], a key issue for training and competition participation; a review about conservative treatment of sport-related tendinopathies with local injections of hyaluronic acid [15], a biologically active molecule secreted by synovial cells of the tendon sheath that contribute to shock absorbing and regenerative properties of tendons [16]; a focus on the biological role of vitamin D and clinical implications of its administration in skeletal muscle regeneration and function in athletes [17]. This latter is a topic of growing interest, considering that vitamin D modulates several functions of skeletal muscles, including tissue repair after injury, through vitamin D receptor expressed in satellite cells, and that vitamin D deficiency, reported also in athletes, results in fast-twitch fiber atrophy, fatty infiltration, and fibrosis. Finally, the Special Issue addresses commonly used non-pharmacological interventions for sport related MSK injuries, including therapeutic exercise and physical agent modalities for the management of EOA [18–20]. The development of EOA is a cause of concern for all people involved in sport practice, even if many open questions remain about its definition, natural history, and diagnostic criteria with relevant issues also in term of treatment strategies and timing of interventions [21]. Although highly demanding sports are considered risk factors for joint degeneration because of overload, repetitive microtrauma or other direct and indirect joint injuries, regular and progressive loading seems to positively affect articular cartilage. Indeed, exercise is a core treatment for EOA by increasing muscle strength, reducing fat mass, and enhancing viscoelastic properties of joint tissues thus preventing joint degeneration. Moreover, several physical modalities are commonly used as complementary treatment for patients with EOA, considering that physical agents trigger biological responses by regulating different intracellular pathways, thus acting as a drug.

In conclusion, the papers included in the Special Issue provide a comprehensive update of much debated topics in the field of MSK pathology focusing on the health issues

that can affect and torment the athlete, putting at risk not only the early return to play, but also the professional career itself. The topics addressed from the point of view of MSK disorders specialists provide useful and practical information for both clinicians and researchers, also considering the unmet needs in the field of sport related MSK injuries.

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# Epidemiology of Musculoskeletal Injuries in Adult Athletes: A Scoping Review

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**Abstract:** *Background and Objectives*: Sport-related musculoskeletal injuries (MSK-Is) are a common health issue in athletes that can lead to reduced performance. The aim of this scoping review was to synthetize available evidence on injury incidence rates (IIRs), types, and sites that affect the musculoskeletal (MSK) system of adult athletes. *Materials and Methods*: We performed a scoping review on the Pubmed database limiting our search to 33 Olympic sports. *Results*: We identified a total of 1022 papers, and of these 162 were examined in full for the purpose of this review. Archery was the sport with the highest risk of injuries to the upper extremities, marathons for the lower extremities, and triathlon and weightlifting for the body bust. In the majority of the sports examined, muscle/tendon strain and ligament sprain were the most common MSK-Is diagnoses, while athletics, karate, and football were the sports with the highest IIRs, depending on the methods used for their calculations. *Conclusions*: Our scoping review highlighted the general lack and dishomogeneity in the collection of data on MSK-Is in athletes.

**Keywords:** musculoskeletal injuries; sport; Olympic Games; athletes; incidence; sprain; strain



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## 1. Introduction

Musculoskeletal injury (MSK-I) is a general term that includes any trauma that causes damage to muscles, bones, tendons, joints, ligaments, and other soft tissues. MSK-Is represents one of the most common health conditions in athletes, with consequences not only in terms of the lowering of performance, or withdrawal from competitions, but also of economic costs [1].

The International Olympic Committee (IOC) in its manual on sports injuries defined MSK-Is as "new or recurring musculoskeletal complaints incurred during competition or training that require medical attention, regardless of the potential absence from competition or training" [2].

The origin of the term athlete is from the Greek "athlos" that means achievement and serves to indicate an extraordinary physical performance [3]. In 2016, C.G.S. Araujo and J. Scharhag identified four criteria that should be simultaneously fulfilled to define an athlete for health and research purposes: "(a) to be training in sports aiming to improve his/her performance or results; (b) to be actively participating in sport competitions; (c) to be formally registered in a local, regional, or national sport federation as a competitor; and (d) to have sport training and competition as his/her major activity or focus of interest, almost always devoting several hours in all or most of the days to these sport activities, exceeding

the time allocated to other professional or leisure activities" [3]. Athletes competing in Olympic Games are called Olympic Athletes.

Olympic Games, or the Olympics, are a set of international sporting competitions taking place every four years, each time in a different country. They represent the most important sporting competition in the world, with more than 200 nations involved. The Olympics are divided into summer and winter games which alternate every two years. Due to the COVID-19 health emergency, the 2020 summer Olympics, were rescheduled and took place from 23 July to 8 August 2021 in Tokyo, Japan. The official program for Tokyo 2020, approved by the IOC on 9 June 2017, included 339 events in 33 different sports, for a total of 50 disciplines [4].

During the previous summer Olympic Games (Rio de Janeiro, 2016), the medical staff reported 1101 injuries over the 17-day period for an overall proportion of 8% of the athletes that incurred at least one injury, which was slightly lower than in prior Olympic Games [5]. The sport with the highest proportion of athletes injured was BMX cycling (38%), while the ones with the lowest were canoe slalom, rowing, shooting, archery, swimming, golf, and table tennis (0–3%) [5].

Injury incidence data on MSK-Is in adult athletes are limited. In the majority of cases injury data are reported all together and it is difficult to extrapolate information related only to the MSK system. Moreover, there are several ways to calculate injury incidence rates (IIRs), therefore it is not possible to generalize the results of available epidemiological studies [6]. Among the other methods, three of the most popular ones are:

- injuries/1000 h exposures (/1000 h) which represents the number of injuries per 1000 h of exposures;
- injuries/1000 athlete-exposures (/1000 AEs), which is based on the total number of athletes exposed during a competition or training irrespective of their actual time of exposure [7]. An athlete-exposure is defined as "one athlete's participation in one practice or game in which there is a possibility of sustaining an athletic injury" [6];
- injuries/1000 player-hours, represents the actual time of player-exposure that is the probability of injury for 1 player over 1000 h of total exposure" [7].

The aim of this paper was to synthetize available evidence on the IIRs, types, and sites of MSK-Is in adult athletes of Olympic Games sports.

## 2. Materials and Methods

In performing this scoping review, the PRISMA-ScR model was followed [8].

Sports and disciplines in the Olympic Games can vary from one edition to another, therefore, for the purpose of this scoping review we decided to limit our search to the 33 Olympic sports that would have taken place in the Tokyo 2020 edition.

We ran a search on the PubMed database on 25 June 2021, using the following search strategy: ("Epidemiology"[Mesh] OR "Incidence"[Mesh]) AND ("Musculoskeletal System/injuries"[Mesh] OR "Athletic Injuries"[Mesh]) AND ("Water Sports/epidemiology" [Mesh] OR "Water Sports/injuries"[Mesh] OR "Swimming/epidemiology"[Mesh] OR "Swimming/injuries"[Mesh] OR "Diving/epidemiology"[Mesh] OR "Diving/injuries" [Mesh] OR archer* OR "athletics injuries" OR "Track and Field/injuries"[Mesh] OR "Sports/epidemiology" [Mesh] OR "Sports/injuries"[Mesh] OR "Racquet Sports/injuries" [Mesh] OR "badminton injuries" OR "Baseball/injuries"[Mesh] OR "Basketball/injuries" [Mesh] OR "Boxing/ epidemiology"[Mesh] OR "Boxing/injuries"[Mesh] OR "Bicycling/ injuries"[Mesh] OR "equestrian injuries" OR "fencing injuries" OR "Hockey/injuries" [Mesh] OR "Football/ injuries"[Mesh] OR "Golf/injuries"[Mesh] OR "Gymnastics/injuries" [Mesh] OR "handball injuries" OR "Martial Arts/injuries"[Mesh] OR "modern pentathlon" OR sailing OR "shooting injuries" OR "Skating/injuries"[Mesh] OR "sport climbing" OR "table tennis" OR "Tennis/injuries"[Mesh] OR "triathlon injuries" OR "Volleyball/injuries" [Mesh] OR "Weight Lifting/injuries"[Mesh] OR "Wrestling/injuries"[Mesh]).

We limited the search to studies published from 1 January 2001 to 31 May 2021. We included papers with: (1) a population of adult (older than 18 y.o.) professional, non-

Paralympic, athletes playing any of the 33 sports selected; (2) reporting information about the IIRs of MSK-Is was in one of the following formats: injuries/1000 h, injuries/1000 AEs, or injuries/1000 player-hours; (3) any study design; and (4) written in English.

The study selection and data extraction were done by two authors independently (MA, and FiG), and in case of any controversies, a third author (FG) was consulted.

## 3. Results

We identified a total of 1022 papers with our search string (see the flow diagram, Figure 1).

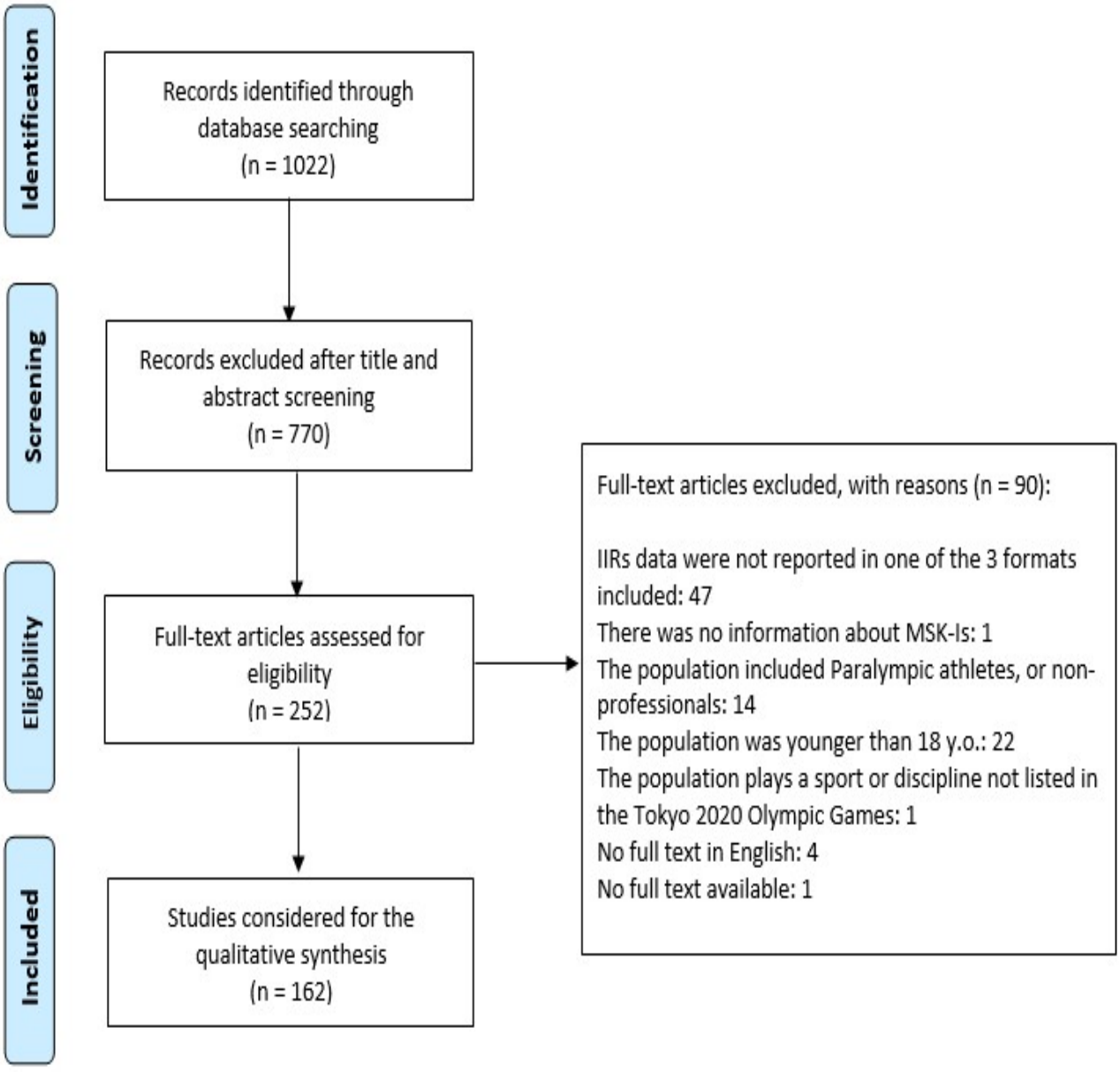


**Figure 1.** PRISMA-ScR flow chart of the study selection process.

Of these papers, 613 were about one of the 33 sports (50 disciplines) included and 67 dealt with more than one of these sports. As shown in Figure 1 the number of papers that met the inclusion criteria and were analysed for the purpose of this scoping review was 162. Table 1 reports the most recent and generalizable data on injuries per type of sport, including the most common MSK-Is sites (excluding the head and sometimes the neck if the data were given together with the head), types, and their IIRs. With the exception

of marathons where specific MSK IIRs were available, in all other cases, data that are reported in Table 1 referred to any kind of injury. Of the 33 sports included, no data were available for badminton, canoeing, cycling, equestrian, modern pentathlon, rowing, shooting, skateboarding, surfing, and table tennis. When examining data related to injury sites, we can see that archery was the sport with the highest risk of injuries to the upper extremity, mainly to the shoulder of the dominant side. Marathon was the highest risk sport for the lower extremity, while triathlon and weightlifting were the highest risk for the body trunk. In the majority of the sports examined, muscle/tendon strains and ligament sprains were the most common MSK-Is. When considering the different IIRs reporting methods, for 12 disciplines data available on IIRs were expressed as injuries/1000 h exposures and archery (0.00536/1000 h) was the sport with the lowest IIR, while athletics (overall IIR for marathon—65.0/1000 h, 95% CI 61.4, 68.7) was the highest; the injuries/1000 AEs method was used in 13 disciplines and women's gymnastics (1.40/1000 AEs, 95% CI 1.09, 1.71) had the lowest IIR vs. karate (88.3/1000 AEs, 95% CI 66.6, 117.2) which had the highest; in only four cases were IIRs reported as injuries/1000 player-hours and the lowest IIR was reported for handball (4.3/1000 player-hours) while the highest was for football (50.8/1000 player-hours, 95% CI 41.0, 60.6).

**Table 1.** MSK-Is in Olympic Games.

| Sport (Disciplines) | Injury Sites [2] | Types of Injury | IIRs [1,2] |
|---|---|---|---|
| Aquatic (Swimming [9], Marathon swimming, Diving, Artistic swimming, Water polo [10]) | Swimming: upper extremity (38.7%), lower extremity (42.0%), body trunk (19.3%)<br>Water polo: upper extremity (38.7%), lower extremity (18.8%), body trunk (16.9%) | Swimming: tendonitis (58%), strain (35.5%), and sprain (6.5%)<br>Water polo: (sub)luxation/sprain (22.7%), strain (9.9%), tendinosis/arthritis/bursitis/ impingement or similar (9.1%), fracture (5.1%), muscle spasm (4.0%), tendon/ligament rupture (1.1%) | Swimming: 3.04/1000 h (95% CI 2.04, 4.49) or 5.55/1000 AEs (95% CI 3.73, 8.18)<br>Water polo: 56.2/1000 h (95% CI ± 6.74) competition |
| Archery [11] | Overuse: upper extremity (86.2%), body trunk (11.8%).<br>Acute: upper extremity (83.4%). | Overuse: tendons, ligaments, and articulation injuries (67.9%)<br>Acute: fractures (83.3%) | 0.00536/1000 h (overuse and acute) |
| Athletics [12,13] | Marathon: lower extremity (92.6%)<br>Pole vault: upper extremity (20.8%), lower extremity (59.8%), body trunk (18.1%) | Marathon: tendonitis (10.3%), strain (2.4%), sprain (2.3%), bursitis (1.0%) (major and minor injuries)<br>Pole vault: strain (37.5%), sprain (18.1%), stress reaction (13.9%), tendinitis (11.1%), fracture (11.1%) | Marathon: 65.0/1000 h (95% CI 61.4, 68.7); major MSK-Is 0.8/1000 h (95% CI 0.4, 1.3), minor MSK-Is 11.2/1000 h (95% CI 9.8, 12.9)<br>Pole vault: 7.9/1000 AEs (95% CI, 6.2, 10.0) |
| Badminton | Data not available | Data not available | Data not available |
| Baseball [14]/Softball [15] | Baseball: upper extremity (51.4%), lower extremity (30.6%), body trunk (11.7%)<br>Softball: upper extremity (33.1%), lower extremity (42.1%), body trunk (9.8%) | Baseball: data not available<br>Softball: ligament sprain, muscle-tendon strain (data not available) | Baseball: 3.61/1000 AEs (95% CI = 3.49, 3.74)<br>Softball: 4.30/1000 AEs (95% CI = 4.13, 4.47) competition; 2.67/1000 AEs (95% CI = 2.57, 2.77) training |
| Basketball (3 × 3, basketball [16]) | Men: upper extremity (18.5%), lower extremity (58.7%), body trunk (8.4%)<br>Women: upper extremity (14.5%), lower extremity (63.1%), body trunk (6.4%) | Men: sprain (30.1%), strain (14.3%), tendonitis (3.8%), fracture (3.2%), dislocation (3.0%), spasm (2.6%), inflammation (1.8%)<br>Women: sprain (29.0%), strain (16.7%), tendonitis (5.2%), inflammation (4.6%), dislocation (3.2%), fracture (3.0%), spasm (2.6%) | Men: 7.97/1000 AEs (95% CI 7.65, 8.30)<br>Women: 6.54/1000 AEs (95% CI 6.22, 6.85) |
| Boxing [17] | Upper extremity (24.5%), lower extremity (15.6%), body trunk (14.1%) | Tear (12.0%), pain (7.8%), strain (4.2%), rupture (2.0%), fracture (1.0%) | 12.8/1000 h (training) |

**Table 1.** *Cont.*

| Sport (Disciplines) | Injury Sites [2] | Types of Injury | IIRs [1,2] |
|---|---|---|---|
| Canoeing (slalom, sprint) | Data not available | Data not available | Data not available |
| Cycling (BMX freestyle, BMX racing, mountain bike, road, track) | Data not available | Data not available | Data not available |
| Equestrian (eventing, dressage, jumping) | Data not available | Data not available | Data not available |
| Fencing [18] | Upper extremity (42.9%), lower extremity (35.7%), body trunk (21.4) | Sprain (25.0%), Pain (25.0%) | 2.43/1000 AEs |
| Hockey (field hockey [19]) | Men: upper extremity (19.0%), lower extremity (41.0%), body trunk (4.0%) Women: upper extremity (14.0%), lower extremity (28.0%), body trunk (0.0%) | Data not available | 36.2/1000 player-hours (95% CI 31.6, 40.8) Men: 48.3/1000 player-hours (95% CI 30.9, 65.8) Women: 29.1/1000 player-hours (95% CI 18.6,39.7) |
| Football (soccer [20]) | Upper extremity (10%), lower extremity (65%), body trunk (7%) | Strain/muscle fibre rupture (24%), sprain/dislocation (8%), fracture (6%), tendon or ligament rupture/meniscus lesion (4%) | 29.3/1000 h (95% CI 21.9, 36.7); 50.8/1000 player-hours (95% CI 41.0, 60.6) |
| Golf [21] | Upper extremity (40.7%), lower extremity (26.1%), body trunk (29.0%) | Tendinosis/tendinopathy (21.2%), ligament sprain (13.6%), meniscus lesions (11.2%), muscle strain, rupture, or tear (9.1%), and inflammation of unknown cause (7.0%) | 8.5/1000 AEs (competition), and 3.3/1000 AEs (training) |
| Gymnastics [22] (artistic, rhythmic, trampoline) | Severe injuries: upper extremity (16.5%), lower extremity (64.5%), body trunk (8.9%) | Severe injuries: sprain (31.6%), strain (13.9%), fracture (13.9%), dislocation (8.9%), sub-luxation (3.8%), inflammation (2.5%) | Women: 1.40/1000 AEs (95% CI 1.09, 1.71) |
| Handball [23] | Upper extremity (28.7%), lower extremity (52.0%), body trunk (17.2%) | Sprain (26.5%), rupture (12.2%), strain (4.9%), fracture (4.4%), subluxation/dislocation (2.3%) | 4.3/1000 player-hours |
| Judo [24] | Upper extremity (10.2%), lower extremity (9.7%), body trunk (10.9%) | Data not available | 4.2/1000 h (training) |
| Karate [25] (kata, kumite) | Lower extremity (12.0%) | Data not available | 88.3/1000 AEs (95% CI 66.6, 117.2) |
| Modern pentathlon | Data not available | Data not available | Data not available |
| Rowing | Data not available | Data not available | Data not available |
| Rugby (rugby sevens [26]) | Upper extremity (21.4%), lower extremity (58.3%), body trunk (5.5%) | Joint sprains (25.2%), muscle injury (16.7%), tendon injury (12.1%), cartilage injury/impingement (9.3%), joint dislocation/instability (5.5%), bone injury (5.5%) | 43.2/1000 player-hours (95% CI, 43.0–43.3) |
| Sailing [27] | Upper extremity (12%), lower extremity (23%), body trunk (29%) | Muscle cramp/spasm (20%), muscle strain (13%), sprain (13%), tendinopathy (13%) | 0.59/1000 h |
| Shooting | Data not available | Data not available | Data not available |
| Skateboarding | Data not available | Data not available | Data not available |
| Sport climbing [28] | Lower extremity (11.1%), body trunk (5.6%) | Sprain (11.1%), fractures (5.6%) | 3.1/1000 h |
| Surfing | Data not available | Data not available | Data not available |
| Table tennis | Data not available | Data not available | Data not available |
| Taekwondo [24] | Upper extremity (22.8%), lower extremity (9.1%) | Data not available | 19.09/1000 AEs (competition) |

**Table 1.** *Cont.*

| Sport (Disciplines) | Injury Sites [2] | Types of Injury | IIRs [1,2] |
|---|---|---|---|
| Tennis [29] | Upper extremity (23.2%), lower extremity (51.4), body trunk (18.5%) | Muscle rupture/tear/spasm/cramp (32.9%), synovitis (20.4%), tendon tear/tendinopathy/bursitis (17.6%), ligament injury (8.3%), dislocation/subluxation/instability (6.0%), lesion of meniscus/articular cartilage (3.2%), fasciitis (2.3%), fracture (0.9%) | 56.6/1000 h (95% CI: 49.5, 64.6) competition; 62.7/1000 h (95% CI: 54.8, 71.6) training |
| Triathlon [30] | Upper extremity/shoulder (up to 19%), lower extremity (36–85%), body trunk (up to 72%) | Muscle/tendon lesions (30–55%), tendinitis (13–25%), and ligament/joint injuries (6–29%) | 17.4/1000 h (competition), 0.7–5.4/1000 h (training) |
| Volleyball (beach volleyball, volleyball [31]) | Men: upper extremity (30.5%), lower extremity (46.3%), body trunk (12.2%) Women: upper extremity (19.2%), lower extremity (58.0%), body trunk (11.7%) | Men: sprains (22.0%), and strain (19.5%), inflammatory conditions (19.5%), fracture (6.1%), dislocation/subluxation (2.4%), entrapment/impingement (2.4%), sacroiliac dysfunction (1.2%), spasm (1.2%) Women: sprains (23.8%), strain (21.4%), inflammatory conditions (14.7%), fracture (2.8%), spasm (2.4%), entrapment/impingement (2.0%), patella femoral pain syndrome (1.8%), sacroiliac dysfunction (1.4%), dislocation/subluxation (1.0%) | Men: 4.69/1000 AEs (95% CI, 3.68–5.70) Women: 7.07/1000 AEs (95% CI, 6.45–7.68) |
| Weightlifting [32,33] | Upper extremity (39%), lower extremity (23%), body trunk (37%) | Data not available | 2.4–3.3/1000 h (training) |
| Wrestling (Greco-Roman, freestyle) [34] | Upper extremity (23.1%), lower extremity (35.8%), body trunk (10.5%) | Knee internal derangements (18.9%), ankle ligament sprains (7.4%), shoulder strains (4.6%) | 5.7/1000 AEs (95% CI 5.5–5.8) training; 26.4/1000 AEs (95% CI 25.4–27.3) competition |

Notes: [1] IIRs are expressed in one of these 3 formats: (1) injuries/1000 h, (2) /1000 AEs, (3) 1000 player-hours. [2] Data are referred to as any kind of injury and not only to MSK-Is if not otherwise specified.

## 4. Discussion

To the best of our knowledge, this is the first review summarizing data that are related to the epidemiology, sites, and types of MSK-Is that are related to the sports included in the last Olympic Games. Sport is not only an activity that benefits participants' physical and mental health, but it is first and foremost valuable in the context of social inclusion and integration.

Epidemiological data on MSK-I in athletes are limited. With the exception of marathons, all injury data reported in Table 1 are general and do not specifically refer to the MSK system. Moreover, the available data are difficult to generalize as there are several reporting methods for IIRs. Our study shows that depending on the reporting method the sports associated with the highest IIRs were athletics, karate, and football. We cannot say that these are the three sports with the absolute highest IIRs as we can see, for example, that for football this is only true when we refer to the data reported as injuries/1000 player-hours and not when they were expressed as injury/1000 h. The same is true for archery, gymnastics, and handball which were the sports with the lowest IIRs as measured with the three different methods, respectively. It would have been interesting to have more homogeneous data also in terms of the timing of the injuries (i.e., during training or competition), and the severity of the injuries, including if they resulted in time loss from sport or not.

Based on our findings, evidence suggests that archery and baseball were the sports with the highest risk of injuries to the upper extremity. Upper extremities seem to be more compromised in sports with a greater overhead involvement and in which the throwing

mechanism can lead to overuse or acute microtraumas affecting, above all, the dominant shoulder and elbow [35]. On the contrary sports such as athletics (marathon), triathlon, football, gymnastics (women), basketball, pole vault, rugby sevens, volleyball (women), handball, and tennis have a risk of injuries affecting the lower extremities that is higher than 50%. These are all sports in which the lower limbs are more stressed. The knee was the most injured joint above all in competitive sports involving stop-start movements, direction changes, jumps, and landings, with or without passing and/or shooting a ball [36]. It has been shown that repetitive landing, dynamic knee abduction, and shallow knee flexion angles can cause medial collateral ligament, medial patellofemoral ligament, and anterior cruciate ligament injuries [37]. The body trunk had more homogeneous injury proportions across all examined sports. This might be due to the fact that it is not an anatomical site directly involved in any of these sports. As demonstrated in Table 1, the sports with the highest proportions of injuries affecting the body trunk were triathlon and weightlifting.

In terms of the most common types of MSK-Is among professional athletes of Olympic sports and disciplines, muscle/tendon strains and ligament sprains were the most common MSK-Is. Sprains may be acute or chronic; an acute sprain is caused by a sudden injury that forces the joint beyond its functional range of motion, while a chronic sprain is due to repetitive movements that lead to an overuse injury [38]. Field hockey is one of the sports that is most commonly associated with sprains, especially at the ankle [39]. Balance training and foot dorsiflexor strengthening exercises and wearing ankle bracing might reduce the risk of ankle sprains [40,41]. Strain is the other most frequent injury in sports that require a major muscular effort. Up to 50% of injuries in field hockey are classified as strains. This is probably due to the fundamental requisite of dribbling the ball and moving rapidly in a semi-crouched posture [42]. As reported in Table 1 strains were very common injuries also in pole vault and swimming. In pole vault, muscular strain represents one of the most common causes of lower back injuries [13]. The injury mechanism might be related to the plant/takeoff movement that forces the spine into hyperextension as the athlete drives forward off the ground [13]. Swimmers, especially those who practice the breaststroke style, have an increased risk for strain injuries localized to the knee medial collateral ligament and hip flexors and adductor muscles [43]. Sport-related MSK-Is includes bone fractures which even though are less frequent they are considered as a major injury as they are associated with a greater rate of time loss from sport [44].

The main limitation of our scoping review is that we ran the literature search only on PubMed. Another important limit of the review, as well as of the existing literature on sport injuries, is that there are too many and not comparable ways to report IIRs. Moreover, even though MSK-Is represents one of the major health issues in professional athletes, there are only very limited data reporting selectively on MSK IIRs.

The strength of the paper is that it gives an overview of sports injury risk rates and types. This could represent valuable information for athletes, coaches, and trainers that might adapt their training programs and competition strategies to reduce the risk of the most common and specific sport related injuries.

## 5. Conclusions

In recent years there is a greater awareness on the importance of the prevention of injuries in sport. If we compare the IIRs during football World Cups from the 1998 to the 2014 editions, we can see how the number of injuries has been constantly decreasing thanks to the improvement of preventive measures [20]. Sporting injuries should be systematically recorded in databases in a standardised way, thus allowing for data comparison. It is necessary to enforce interdisciplinary cooperation among all involved parties, including coaches, trainers, physiotherapists, physicians, clubs, and federations. Moreover, we believe that future literature should be focused not only on the structural components of the injuries but on the whole functioning profile of the athlete, and that the use of the bio-psycho-social framework proposed by the International Classification of Functioning, Disability, and Health might enrich our knowledge on this topic [45].

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*medicina*

MDPI

*Review*

# Ultrasound Imaging in Sport-Related Muscle Injuries: Pitfalls and Opportunities

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**Abstract:** Muscle injuries occur frequently in athletes, accounting for more than one-third of sport-related trauma. Athletes most affected by these injuries are those practicing football and track and field, with hamstrings and gastrocnemius-soleus as the mainly involved sites. Muscle injuries lead to loss of competitions, long recovery times and risk of re-injury with a consequent increase of the management costs. It is therefore advisable to make an accurate and timely diagnosis to establish appropriate interventions for proper healing in the shortest time. In this context, ultrasound imaging is widely used for diagnosis of musculoskeletal disorders because of several advantages including absence of radiation, portability, good spatial resolution, and the ability to perform dynamic tests. The aim of this review is to address the role of US in the evaluation of athletes with muscle injuries. US may play a pivotal role for the management of sport-related muscle injuries because it is fast and relatively cheap, allowing dynamic muscle assessment and time series evaluation of the healing process.

**Keywords:** ultrasound; muscle injuries; sports; athletes; skeletal muscle; return to sport; imaging; rehabilitation



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## 1. Introduction

Sport-related muscle injury has been defined as "a traumatic distraction or overuse injury of the muscle leading to a player being unable to fully participate in training or match play" [1] (p. 3). Muscle injury represents more than one-third of sport-related trauma and its incidence increases with the age [1–3]. The risk of occurrence of this lesion is mostly observed in sports requiring maximal contractions, such as soccer and track and field. In these sports, muscle injury mainly affects biarticular muscles, in particular those with high percentage of fast-twitch fibers [2,4]. Soleus-gastrocnemius lesions are the most common muscle injuries in high-speed running, although in other sports (i.e., soccer) hamstrings and the rectus femoris are most involved [4].

Muscle lesions might cause loss of competitions and long functional recovery times [5]. Moreover, a premature return to play (RTP) may be related to high risk of recurrent injury and prolonged healing time [6]. Therefore, a timely and accurate diagnosis is required to identify the type and severity of injury to propose an appropriate management plan for complete muscle healing, reducing the risk of re-injury [7]. Magnetic Resonance Imaging (MRI) is the most sensitive technique for the detection of muscle injuries, also for minimal lesions, representing a reference standard to complete the workup of muscle injuries following physical examination. However, ultrasound (US) imaging is most used in clinical practice [8]. This cheap and non-invasive method provides an adequate characterization of

muscle lesions thanks to an optimal spatial resolution. Moreover, US allows to perform dynamic assessment before and after contraction [9]. The aim of this paper is to carry out an extensive review about US imaging in sport-related muscle injuries.

## 2. Technical Aspects of Ultrasound Imaging in Skeletal Muscle Examination

Skeletal muscle is a classical target for US imaging considering it is a relatively superficial tissue. The choice of an appropriate probe for US imaging to investigate skeletal muscle depends on different factors [10]. Usually, muscle injury can be adequately visualized using high frequency linear probes (>10 MHz). In certain cases, in patients with conspicuous adipose tissue or thick muscle mass, low frequency convex probes can be used [2,11].

As the frequency of the waves increases, the spatial resolution (the ability to distinguish two separate objects) also improves. Therefore, the smaller lesions will be easier to visualize as the frequency increases but at the same time there will be a greater absorption of the waves. In this condition it will be more difficult to visualize the deep tissues. [2,12,13]. Considering advances in hardware technology and software systems, such as the use of tissue harmonic imaging, postprocessing algorithms of the returned signal or ultra-high frequency probes (up to 17 MHz), it is possible to improve the signal-to-noise ratio and tissue contrast to better visualize muscle architecture. Under optimal conditions, such as the use of high frequency probes and observation of superficial structures, it is possible to reach a spatial resolution of less than 200 microns with tissue sections of 1–0.5 mm thickness, that results even higher than the resolution of MRI [9]. In case of large lesions, extended field of view imaging (FOV) may be useful to define the real extent of the damage [9]. In a routine US exam, it has been suggested to start visualizing long and short axis on the hypothetical site of the lesion (suggested by physical examination) and then continue with slow and accurate movement of the probe on muscle belly from its origin to distal insertion. It is appropriate to evaluate enthesis, myotendinous junction, as well as epimysium and intermuscular septa that may be also affected depending on the mechanism of muscle injury. The lesion area can be dynamically detected during muscle contraction or passive mobilization to define the extent of the injury, particularly related to functional impairment [9,11].

The appearance of the myotendinous junction (MTJ) will vary depending on the type of muscle, but generally it has a progressively hyperechoic appearance with respect to the muscle tissue. Tendons and the epimysium have a hyperechoic appearance, but the former can give artifacts of anisotropy due to their fibrillar structure [2,9,11].

## 3. Ultrasound Anatomy of Skeletal Muscle

In the context of US imaging, myofibers appear hypoechoic compared to adjacent connective and nervous structures, while fibroadipose tissues (perimysium and epimysium) are hyperechogenic. Different orientation of muscle fibers with respect to the US beam might cause artifacts of anisotropy, especially in long axis evaluation. Longitudinal axis images of muscle tissue show an alternation of parallel hypo/hyperechoic bands *("veins on a leaf")* with a variable orientation depending on pennation angle (Figure 1).

In the transverse axis, the tissue appears to be formed by a background hypoechoic compound with hyperechoic dots inside *("starry night")* (Figure 2).

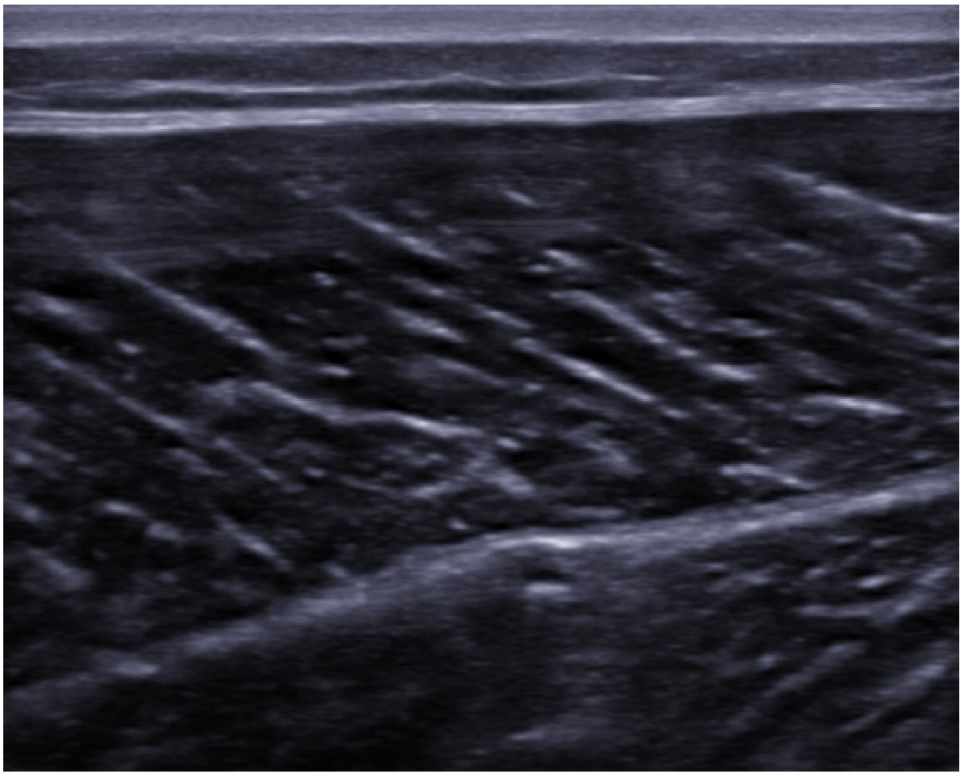

**Figure 1.** Long-axis view of the medial head of the gastrocnemius muscle in healthy individual showing normal skeletal muscle architecture.

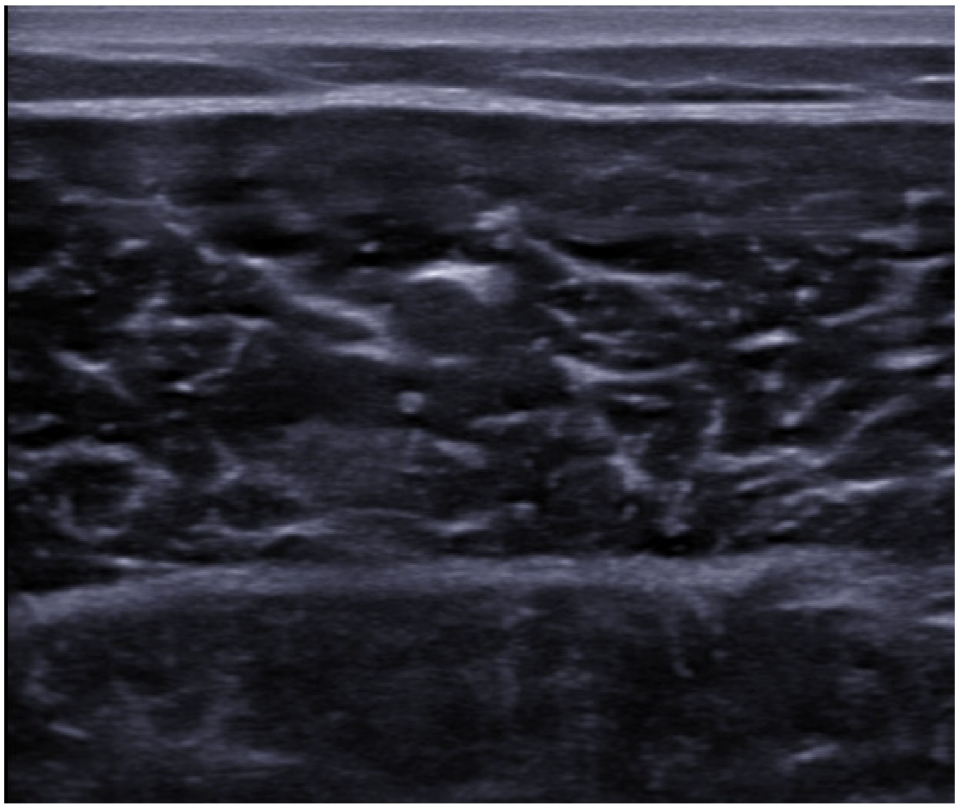

**Figure 2.** Short-axis view of the medial head of the gastrocnemius muscle in healthy individual.

## 4. Muscle Injuries: Types and Mechanisms

Acute muscle injuries are classified as direct if the muscle damage occurs at the site of application of external injury force or indirect if due to an internal force (e.g., mechanical stress generated by muscle contraction or stretching) [7,14,15].

Direct injuries include contusions and lacerations, in case of penetrating trauma, and are typical of contact sports such as soccer or rugby [2,16,17]. The extent of tissue damage depends on the amount of force applied. However, a muscle contraction during the impact could better absorb the force, resulting in lower damage [7,18,19]. Moreover, the size of direct muscle injuries might not correlate with clinical signs and functional impairment [5].

Direct lesions have been classified according to the extent of the clinical signs in [5,9]:

- mild form (loss of range of movement (ROM) less than one-third with short recovery time);
- moderate form (loss of ROM between one- and two-thirds with moderate recovery time);
- severe form (with loss of ROM larger than two-thirds with long recovery time).

Indirect injuries include muscle strain. The mechanism underlying this type of damage is a forced elongation of the muscle fibers, usually occurred during an eccentric contraction that exceeds viscoelastic limits of the tissue. Myotendinous junction is most involved probably due to a different tissue elasticity, which is significantly lower in the tendon component than in the muscular one [8,15]. Factors favoring the onset of indirect muscle injuries are eccentric contraction, muscles crossing two joints (e.g., hamstring, rectus femoris), high percentage of fast-twitch fibers within muscle, and muscle imbalance between agonist and antagonists resulting in failure in absorbing or dissipating applied forces [9,20,21]. In rare cases, during a strong contraction, an avulsion injury may occur with detachment of the bony surface of tendon insertion [22]. Indirect muscle injuries can be classified according to clinical criteria in:

- grade 1: no significant loss of function and strength, and minimal tissue tearing (less than 5%);
- grade 2: myotendinous junction injury with evident reduction in strength and function;
- grade 3: complete injury to the myotendinous unit and total loss of strength and function [9].

A further type of indirect muscle injury is the "delayed onset muscle soreness" (DOMS). This is typically caused by an excessive physical activity requiring eccentric contractions. In DOMS, a reduction in strength and muscle function associated with pain develops in the 24–72 h following the muscle effort, with a progressive and spontaneous slow recovery [9,23].

## 5. Ultrasound Findings of the Muscle Lesions

Muscle lesions show different US appearance depending on the type, extent and anatomical site involved. Following a blunt trauma of mild intensity, the capillaries and muscle fibers break causing interstitial hemorrhage that appears as a region of hyperechogenicity with poorly defined margins. In case of high intensity blunt trauma, an intramuscular hematoma will develop appearing to the US as a variable echogenicity zone (Figure 3) [11,24], depending on the time of the lesion. In the acute phase (24–48 h) the hematoma undergoes solidification appearing hyperechoic, due to its corpuscular component, compared to the surrounding tissue. In the next phase (48–72 h) it will undergo colliquation and progressive resorption, appearing as an iso-hypoechoic fluid zone. In the later stages, internal levels and debrides may be found in the hematoma fluid, and a focal scar may form as it undergoes resorption [25]. At the power/color Doppler it will be possible to observe a zone of hyperemia around the lesion due to the formation of granulation tissue representing the beginning of the reparative mechanisms [24]. In some cases, the rupture of the muscle fascia can occur with consequent herniation of the

muscle in the interfascial space or in the subcutaneous tissue. This lesion can be seen, especially with dynamic US, as a muscle mass that emerges from the fascial defect during contraction [26]. A potential consequence of high-energy trauma is a Morel–Lavallée lesion. This condition is caused by the detachment of the fascia from the overlying subcutaneous tissue with a consequent accumulation of hemolymphatic fluid that can be easily identified through US [27].

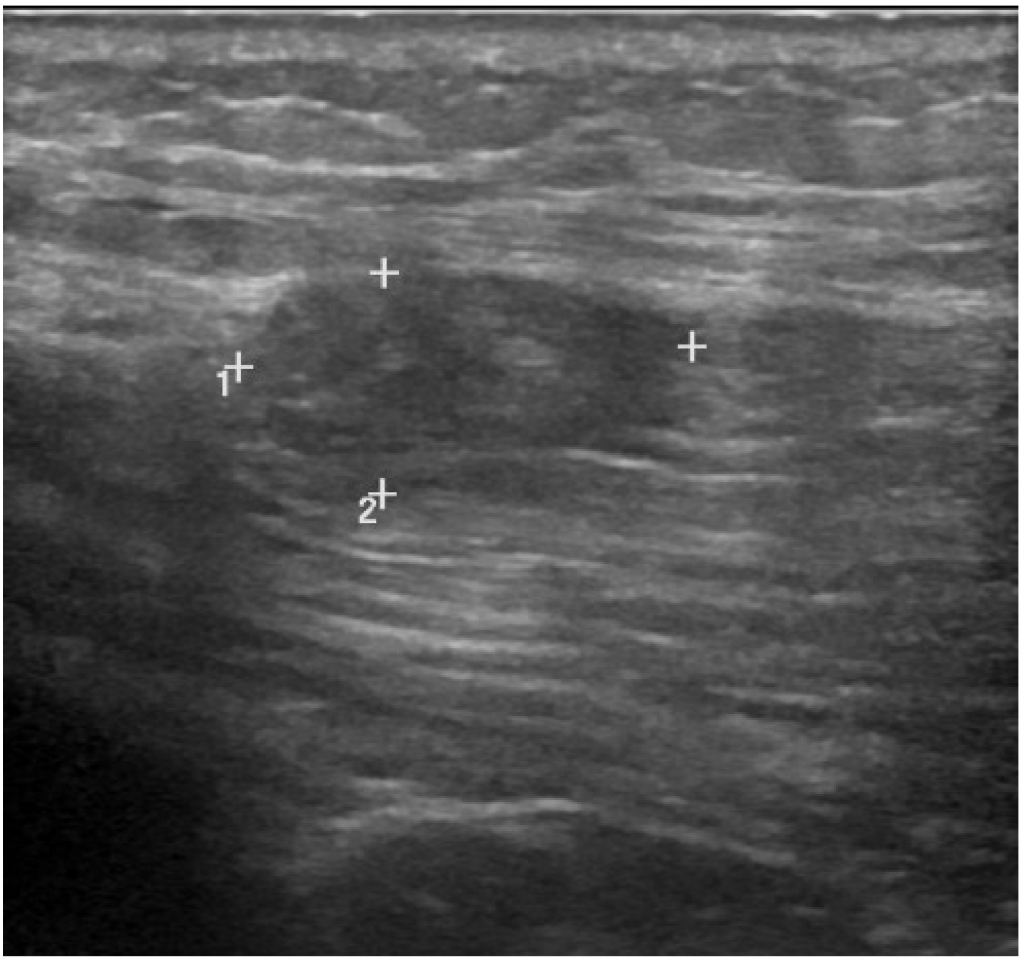


**Figure 3.** Grade 2 injury of the gluteus medius with interruption of muscle fibers and formation of hypoechoic local hematoma.

Peetrons et al. graded US features of indirect muscle injury [28]. In grade 1, US images may be negative or show minimal signs of lesion. A poorly defined area of hypercogenicity can be found at the site of the lesion, commonly involving MTJ. Furthermore, a focal interruption in the muscle fibers can be found, affecting less than 5% of the cross-sectional area of the muscle belly, represented by a well-defined anechoic or hypoechoic zone. In this area, a small hematoma might be observed. Grade 2 injuries include partial lacerations and are identified by the presence of an area of interruption of the muscle fibers larger than 5% but lower than 100% of the cross-sectional area of the affected muscle. This condition is characterized by the presence of a large hematoma of variable echogenicity depending on the time of the lesion. Grade 3 injuries identify a total muscle tear characterized by complete interruption of the muscle fibers with different degrees of retraction of the lesion stumps and the formation of a large hematoma.

In all degrees of injury, we can observe perifascial fluid [9,24].

## 6. Classification and Grading of Muscle Injury

Despite the fact that muscle injuries are the most common sport-related trauma, there is a lack of consensus about their classification [29]. From the 1960s these lesions were classified according to clinical signs and pathophysiologic mechanisms. In 1966 Rachun proposed a three-grade classification based on clinical signs and symptoms, such as pain, swelling, loss of function, grade of disability [30]. Later, Wise focused on differences between normal and injured muscle circumferences, pain severity and loss of strength following contraction, and muscle spasm [31]. From the 1980s, with the development of US and MRI, classifications were modified taking into account imaging findings [32]. Lee et al. graded muscle injuries based on the tear extension and the percentage of function loss [33]. Schneider-Kolsky et al. emphasized functional aspects of muscle tears, considering ROM limitations to distinguish the various grades of lesions [34].

A new classification of muscle injuries, which derives from the previous grading systems, has recently been introduced (Table 1):

- Grade I: muscle injury with low disability, localized pain, small hemorrhage and swelling with mild ROM limitation (<10°);
- Grade II: moderate disability, pain and swelling, loss of function between 5% and 50% and moderate ROM limitation (10–25°);
- Grade III: muscle rupture with severe disability and pain, loss of function more than 50% and severe ROM limitation (up to 25°) [29].

**Table 1.** Grading systems for muscle injuries.

| | **Rachun 1966 [30]** | **Wise 1977 [31]** | **Lee et al. 2004 [33]** | **Schneider-Kolsky et al. 2006 [34]** | **Grassi et al. 2016 [29]** |
|---|---|---|---|---|---|
| **Grade I** | Localized pain, aggravated by movement, minor disability, mild swelling, ecchymosis, local tenderness, minimal haemorrhage. | Minimal pain to palpation, well localized. | Small tear, <5% loss of function | <10° ROM loss. | Minimal and localized pain, minimal hemorrage and swelling, mild ROM loss (<10°). |
| **Grade II** | Localized pain, aggravated by movement, moderate disability, moderate swelling, ecchymosis, local tenderness, stretching and tearing of fibers, without complete disruption. | Substantial pain to palpation, poorly localized; 6–12 mmdifference in circumference, develops within 12–24 h; <50% loss of ROM; pain on contraction with loss of power and disturbed gait. | Larger tear, 5–50% loss of function. | 10–25° ROM loss. | Moderate pain, moderate swelling and disability, loss of function between 5% and 50% and moderate ROM loss (10–25°). |
| **Grade III** | Severe pain, and disability, severe swelling, ecchymosis, hematoma, palpable defect and loss of muscle function; muscle or tendon rupture. | Intractable pain to palpation, diffuse; >12 mm difference in circumference, develops rapidly within one hour; >50% loss of ROM; severe pain on contraction with almost total loss of power with flicker contractions and unable to bear weight. | Complete tear >50% loss of function. | >25° ROM loss. | Severe pain and disability, more of 50% of loss of function and severe ROM loss (up to 25°). |

Based on US appearance of muscle lesions, several authors have proposed different grading systems (Table 2). Takebayashi et al. and Peetrons classified muscle lesions according to the percentage of cross-sectional area of muscle involved [28,35]. In 2004 Lee et al. introduced other US findings, such as hypervascularity around damaged fibers and possible detachment of adjacent fascia, describing several types of muscle injuries [33]. In 2012, Chan et al. took into consideration the same US findings but introduced other additional features, i.e., the site of lesion, such as the proximal MTJ, muscle belly or distal MTJ and the specific part of muscle involved, such as intramuscular, myofascial, myotendinous [36].

**Table 2.** US-based grading systems for muscle injuries.

| | Takebayashi et al. 1995 | Peetrons 2002 | Lee et al. 2004 | Chan et al. 2012 |
|---|---|---|---|---|
| **Grade I** | "<20% cross-sectional area." | "Minimal elongations with less than 5% of muscle involved." | "Normal, or focal/general areas of increased echogenicity +/− peri-fascial fluid." | "Normal appearance; focal or general increased echogenicity with no architectural distortion." |
| **Grade II** | "20–50% cross-sectional area." | "5–50% muscle involvement, partial muscle rupture, demonstrable hypo or an echoic gap, with "bell clapper" sign." | "Discontinuity of muscle fibers in echogenic perimyseal striae; hypervascularity around disrupted muscle fibers; intramuscular fluid collection; partial detachment of adjacent fascia or aponeurosis." | "Discontinuous muscle fibers; disruption site is hypervascularized and altered in echogenicity; no perimyseal striation adjacent to the MTJ." |
| **Grade III** | ">50% cross-sectional area." | "Complete tear of muscle or fascia, with extravasation of collection away from injured part of muscle." | "Complete myotendinous or osteotendinous avulsion; complete discontinuity of muscle fibers and associated hematoma; "bell clapper" sign." | "Complete discontinuity of muscle fibers; hematoma and retraction of the muscle ends." |

In 2012, a consensus meeting endorsed by International Olympic Committee (IOC) and Union of European Football Associations (UEFA), proposed a comprehensive classification system, the "Munich Muscle Injury Classification" considering the mechanism of trauma [37]. According to this classification, direct injuries are divided into lacerations and contusions, both caused by blunt external force, with lacerations characterized by muscle rupture. Indirect injuries are divided into structural injuries and functional disorders. Structural injuries, unlike functional, show an anatomically evident lesion and need longer lay-off times [37,38].

Functional disorders are divided in overexertion-related muscle disorder (Type 1) and Neuromuscular disorder (Type 2). These lesions do not present any findings on US and MRI, although sometimes oedema could be observed.

Type 1 functional disorders include:

- Type 1A—*Fatigue-induced muscle disorder*, mostly caused by change in playing surface, is characterized by focal increased "muscle tightness" and dull pain;
- Type 1B—*Delayed Onset Muscle Soreness (DOMS)*, that is a more generalized dull pain caused by decelerations during eccentric contractions. It peaks within 24–72 h after activity.

Type 2 functional disorders include:

- Type 2A—*Spine-related neuromuscular muscle disorder*, that is a focal increase of muscle tone caused by structural or functional spinal disorder;

- Type 2B—*Muscle-related neuromuscular muscle disorder*, characterized by increased muscle firmness and cramp-like sensation, due to neuromuscular disorder.

Structural injuries are divided in Partial muscle tear (Type 3) and Complete muscle tear (Type 4) and are characterized by the following findings on US and MRI:

- Type 3A—*Minor partial muscle tear* involves less than a muscle fascicle and is characterized by localized pain and absence of visible hematoma;
- Type 3B—*Moderate partial muscle tear* involves more than a muscle fascicle but not all muscle belly, with palpable defect painful to touch, and visible hematoma;
- Type 3C—*Subtotal/Total muscle tear or tendinous avulsion* involves up to 90% of muscle belly, is characterized by severe pain, immediate functional impairment, and muscle retraction in case of avulsion [37,38].

In 2013 the "Italian Society of Muscles, Ligaments and Tendons" (ISMuLT) proposed guidelines about the management of athletes after muscle injury and added some items to the Munich Classification. Authors divided indirect injuries into structural and not structural, replacing the taxonomy "structural injuries" and "functional disorders". Moreover, they added the prognosis of all types of muscle injury in terms of lay-off time before RTP and added the anatomical site of structural injuries, differentiating proximal (P), middle (M) and distal (D) muscle injuries. For example, considering the same severity of the lesion, a distal triceps surae injury is worse than proximal or middle ones, as well as a proximal lesion of hamstrings and rectus femoris is worse than middle or distal ones. Finally, authors divided contusions, considered as direct injuries, in three grades according to the ROM limitation [39].

It should be underlined that in some grading systems the disability and the loss of function are not objectively defined through validated rating scales.

## 7. Healing Process and Prognosis of Muscle Injury

After injury, muscle tissue undergoes a repair process which schematically includes three phases:

- Destructive phase: it occurs immediately after the trauma and is characterized by the necrosis of the muscle fibers, the development of an inflammatory process and the formation of a local hematoma;
- Reparative phase: usually starts from the second day, it is characterized by the removal of cellular debris and necrotic tissue by macrophage cells; the local production of growth factors will promote the formation of a fibrous scar and the revascularization of the area. During this phase, the satellite cells may differentiate into myoblasts and can partly drive the regeneration of muscle tissue;
- Remodeling phase: with the reorganization of the fibrous scar and the maturation of regenerated myofibrils, a progressive recovery of the functional capacity of the muscle can be observed [15].

Depending on the type and extent of the lesion, US imaging can provide useful information about muscle healing. In low grade muscle injury (grade 1) the reparative process appears as an increase in the echogenicity of the lesion area, with a progressive reduction of its extension. Higher grade lesions are characterized by the formation of a hematoma. During the reparative process, hematoma undergoes liquefaction resulting hypoechoic, with progressive resorption and reduction of its extension. Lesion margins will be hyperechoic and echogenic material inside the lesion, representing the deposition of scar tissue, will be observed [28] (Figure 4).

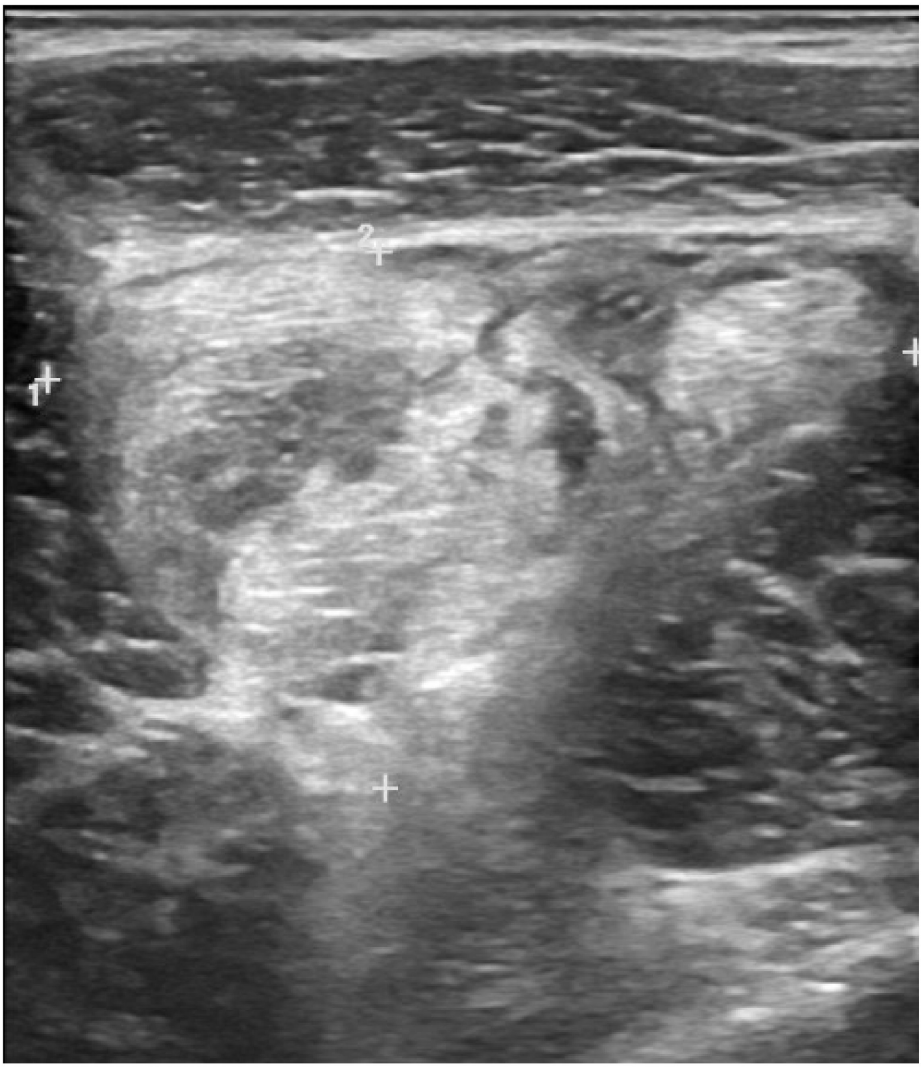

**Figure 4.** Grade 2 injury of the vastus medialis with hyperechoic healing fibrotic tissue.

The site of scar formation should be properly evaluated, especially in case of abnormal symptoms persistence. This area has a greater collagen component and lower elasticity than normal muscle tissue, representing a site at higher risk for recurrent injuries [40]. Moreover, a dynamic US assessment during concentric contraction of the affected muscle is useful for proper identification of the lesion margins and the persistence of fiber disruption over the healing time [9].

An additional tool for healing evaluation of muscle injuries is the elastosonography. This technique allows real-time imaging of the tissue's elasticity and is based on the principle that the compression of a tissue produces a strain or a displacement, which will be higher in soft tissue [41]. Normal muscle tissue shows a characteristic pattern on elastosonography, described as a heterogeneous mosaic of red, blue, and green colors [42]. The elastosonography findings following muscle injury will show increased elasticity (i.e., increased red color) in the site of the lesion attributable to the formation of the hematoma [43]. Later with the progressive resorption of the hematoma and the development of the scar, a blue area indicating the loss of elasticity will appear. Lesions with worse prognosis tend to show an area of reduced elasticity that extends beyond the US zone of the scar [44–46].

Few studies evaluated the prognostic value of US imaging in sport-related muscle injury. A longitudinal study of acute hamstring lesions assessed by MRI and US, examined the correlation between diagnostic findings and recovery time of the players (i.e., RTP). The authors found that the extent of the lesion, defined as cross-sectional area, and the

presence of intramuscular hematoma, evaluated by US, are significantly correlated with prolonged RTP time [47]. Conversely, another study investigating the prognostic value of US in hamstrings injury in soccer players did not find any association between US findings, including the size of the lesion area and the RTP time [48]. Renoux et al. examining the role of connective tissue in muscle injuries, reported longer RTP times in elite athletes with connective tissue involvement at US imaging [49].

## 8. Complications of Muscle Injuries and Atypical Lesions

### *8.1. Myositis Ossificans*

Myositis ossificans is a heterotopic ossification of muscle tissue usually secondary to trauma, which is found in up to 50% of cases [24] with higher prevalence in young adults practicing contact sports [50]. It appears as a new space-occupying mass in the muscle tissue that may be painful. It seems to be due to metaplasia of intramuscular connective tissue which result in local ossification [51]. This process takes 2 to 6 weeks before being visible to X-ray, therefore US is useful in the early evaluation of myositis ossificans. Different US findings can be found depending on the stages of the lesion. In the initial stages, myositis ossificans appears hyperechoic in the center of the muscle lesion with a hypoechoic periphery. Then an external hypoechoic zone with an increased Doppler activity develops, along with a hyperechoic intermediate zone and a hypoechoic central zone. In the later phase, calcification will begin from the periphery of the muscle lesion with the typical egg-shell aspect that will appear progressively more hyperechoic and reflective, with a posterior acoustic shadow, as the process progresses [52]. In case of doubt, it is advisable to carry out second level examinations such as computed tomography (CT) to better identify the calcified component of the lesion and differentiate it from other conditions like sarcomas or abscess [24].

### *8.2. Muscle Hernia*

Muscle hernia is a rare condition characterized by the herniation of healthy tissue through an area of disruption of the lining muscle fascia (epimysium) following direct trauma [11], particularly in the lower limbs (i.e., the anterior tibialis is the most affected muscle) [53]. It presents as a chronic mass that can be painful and most evident during contraction. Ultrasound shows healthy muscle tissue protruding from a fascial gap more visible with dynamic evaluation. Moreover, a slight pressure of the probe on the lesion reduces it through the hernial path [54].

### *8.3. Compartment Syndrome*

Compartment syndrome is a painful condition due to the increased pressure in a narrow fascial space that leads to compression and collapse of the capillary network in the affected compartment, with consequent ischemic tissue injury. Tissue damage is attributable to the formation of abundant intramuscular oedema or a large hematoma which increase the pressure in the closed compartment [24]. This syndrome affects the anterior, deep posterior, lateral, and superficial posterior muscle compartments of the lower limbs more often [55]. It presents as chronic and recurrent well localized pain, induced by physical activity [56]. Ultrasound can be useful to highlight lesions that can increase local pressure such as hematomas. Therefore, it can help in the differential diagnosis with other painful lesions such as venous thrombosis or arterial occlusion [57]. Ultrasound findings specific to compartment syndrome are often difficult to visualize and include increased muscle reflectivity, fascial bowing, loss of the fascicular aspect of the muscle, complete loss of central aponeurosis of the muscle in advanced stages associated with signs of diffuse muscle damage and rhabdomyolysis [58].

### *8.4. Muscle Atrophy*

Muscle atrophy is the progressive degeneration of muscle tissue with loss of its function. It is generally consequent to complete rupture of muscle belly not adequately treated

or following peripheral nerve injury, and it is an infrequent complication of sport-related injury [2]. Upon US examination, atrophy will appear as a progressive fat replacement of the muscle tissue (i.e., more echogenic than normal) starting from the central tendon of the muscle affected or from the MTJ. Later there will be a progressive thinning of the muscle with poor vascularization assessed by the Doppler [28].

## 9. Rehabilitation and Interventional Therapy

Appropriate management of sport-related muscle injury is based on a comprehensive personalized treatment, that include therapeutic exercise, physical therapies, and interventional approaches. Therapeutic exercise, starting from the 2nd day, consists of stretching techniques of the muscle group involved followed by isometric muscle strengthening according to the clinical and US findings. From the 4th to the 8th week, it will be possible to start functional training with muscle strengthening aimed to achieving pre-injury strength level [59]. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is not recommended because they can alter the healing process by interfering with the synthesis of prostaglandins that are involved in early phases of tissue healing [60].

One of the most used interventional procedures is hematoma aspiration. It is particularly indicated in chronic hematomas that do not resolve after about 2 weeks, or in case of intense painful lesions or to accelerate the recovery, especially of elite athletes [61]. Aspiration of chronic hematomas might avoid complications such as calcifications, cyst formation, compression of nerve structures, compartment syndrome [28,62]. To successfully perform this procedure, it is mandatory to evaluate that the hematoma is in the liquid phase. An US-guided in-plane or out-of-plane aspiration can be performed once the precise location and extent of the hematoma have been identified. A standard 10 mL syringe with an 18–20 G needle can be used, taking care to maintain sterility during the procedure to avoid infections (Figure 5) [61].

Following the procedure, a tight elastic bandage should be kept in place to prevent the recurrence of the hematoma [63]. In this latter case, it may be useful to inject low doses of corticosteroids following drainage [64]. Another potentially useful interventional method in muscle injuries is the in-situ injection of Platelet-Rich Plasma (PRP) [24]. The rationale for the use of this tool lies in the ability of platelets to release growth factors that can promote tissue regeneration, myogenesis and angiogenesis. In this way, faster healing of the injured tissue may be achieved [65]. There are different formulations of PRP, depending on their production process: leukocyte-poor PRP (pure PRP, P-PRP) and leukocyte PRP (L-PRP) [66]. Both formulations are used in sports medicine in the form of a liquid or gel solution, with the latter having higher concentration of platelets. The dosage and timing of administration are variable. According to Orlandi et al., from 2 to 10 mL of PRP, and from one to three total injections, might be effective depending on the degree and extent of the lesion [61]. Several in vitro studies support the potential benefits of PRP in the treatment of muscle injuries [67,68], even if clinical studies reported conflicting results about the effectiveness of this procedure [69–73]. Setayesh et al. in a recent review suggest that these uncertainties are probably attributable to the great heterogeneity in PRP formulations and treatment protocols [74].

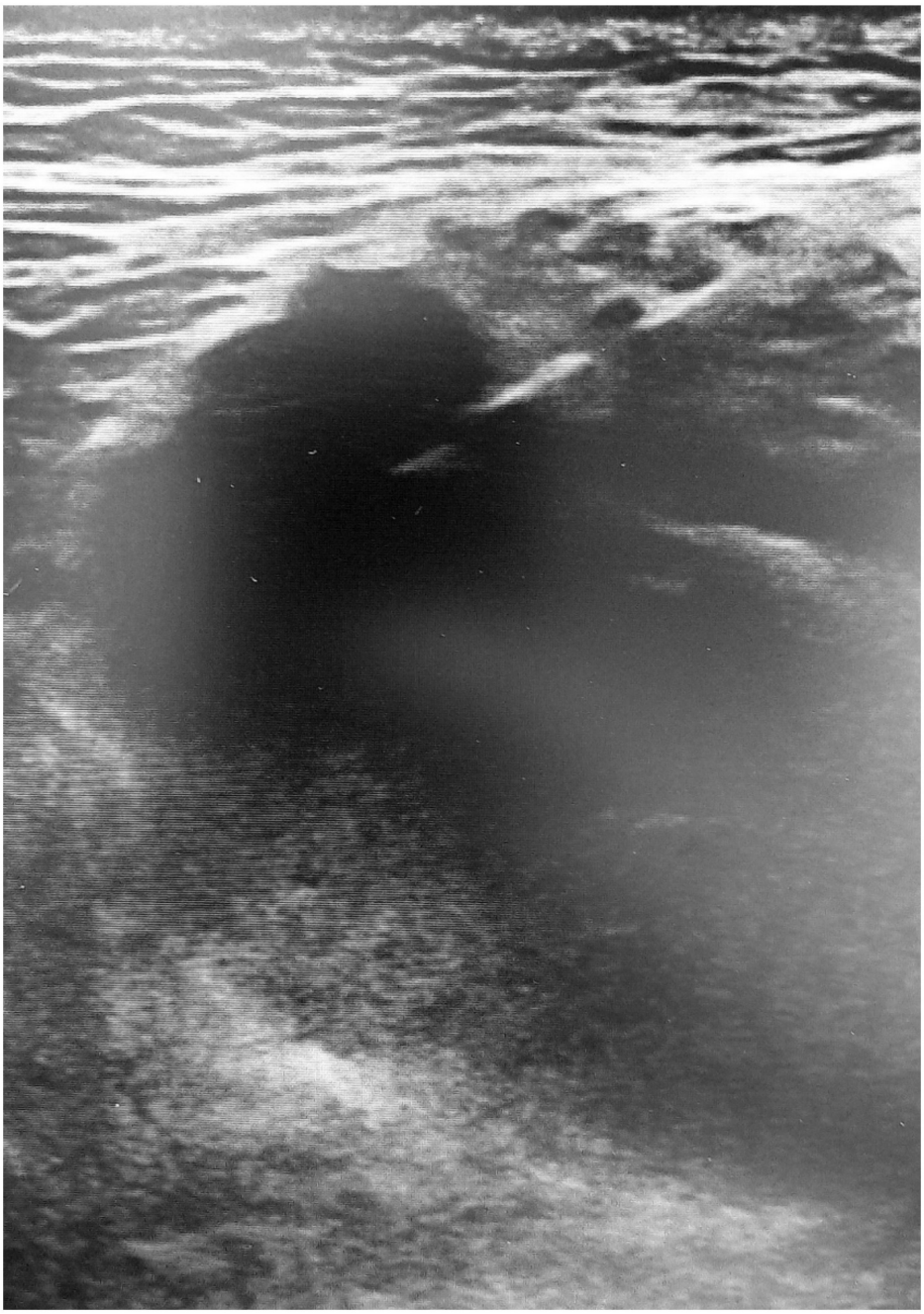

**Figure 5.** Anechoic fluid collection (large hematoma) drainage by hyperechoic needle (direct in-plane technique).

## 10. Strengths and Limitations of US Imaging in Sport-Related Muscle Injury

US imaging is frequently used in the evaluation of musculoskeletal pathologies as a first-line approach. Indeed, it is widely available, well tolerated, easy to use, fast, and cost-saving compared to MRI. Moreover, US imaging offers dynamic evaluations in real-time, being able to take advantage of the patient's collaboration to better characterize the lesions. In particular, it allows the practitioner to visualize how and if the imaging findings change before and after an isometric contraction [9]. Therefore, US is useful in the clinical exam in identifying injured muscle and in differentiating between lesions with similar clinical features [2].

Despite the utility of US in the diagnosis and clinical management of muscle injury, it has some limitations. This technique is less sensitive than MRI in depiction of minor

lesions, such as mild contusion and DOMS, because it is not able to visualize minimal oedema and lesions lacking fiber disruption. Regarding major trauma, the US and MRI demonstrate almost comparable sensitivity. In particular, there is complete agreement in the visualization of severe contusions [8]. On the other hand, both US and MRI prognostic values are uncertain.

## 11. Conclusions

Muscle injuries are responsible for loss of competition, long recovery times and risk of recurrent injury, both in professional and amateur athletes. An appropriate management is necessary for adequate healing to minimize RTP time, complications, and risk of recurrent injury. In this context, US may play a main role because it is fast and relatively cheap, allows serial evaluation of the healing process and dynamic muscle assessment. Dynamic evaluation of the anatomical and functional damage and the monitoring of healing progression of muscle injury represent key elements to better define the recovery in terms of both RTP time and sports performance, also driving the rehabilitation course of affected athletes.

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*Review*

# Reviewing Bone Marrow Edema in Athletes: A Difficult Diagnostic and Clinical Approach

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**Abstract:** Bone marrow edema (BME) is defined as an area of low signal intensity on T1-weighted (T1W) MRI images and associated with intermediate or high signal intensity findings on T2-weighted (T2W) MRI images. BME represents a typical imaging finding that characterizes common stress-related bone injuries of professional and amateur athletes. The etiology of stress-related injuries is influenced by numerous factors, including the initiation of a new sports activity or changes in an existing training protocol. The clinical significance of BME remains unclear. However, a correlation between the imaging pattern of BME, the clinical history of the patient and the type of sports activity practiced is essential for correct diagnosis and adequate therapeutic treatment. It is also important to clarify whether there is a specific threshold beyond which exercise can adversely affect the bone remodeling process, as the clinical picture may degenerate into the presence of BME, pain and, in the most severe cases, bone loss. In our review, we summarize the current knowledge on the etiopathogenesis and treatment options for BME and highlight the main aspects that make it difficult to formulate a correct diagnosis and establish an adequate therapeutic treatment.

**Keywords:** bone marrow edema; magnetic resonance imaging; athletes; joint overuse; pain



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## 1. Introduction

Bone marrow edema (BME) is a nonspecific finding with multiple etiologies, defined as an area of low signal intensity on Tl-weighted (T1W) and high signal intensity findings on T2-weighted (T2W) on magnetic resonance imaging (MRI) [1]. Although on MRI what is detected is true local edema, histological evaluations have shown that lymphocyte infiltrates, fibrous tissue, increased vascularization, and decreased bone mineralization are also present. For this reason, BME has only recently been placed in the more generic and inclusive context of bone marrow lesions (BML), a heterogeneous clinical picture including lesions of the osteochondral unit [2]. The increase of water content in the bone marrow stroma, in association with a high density of blood vessels, seems to be the cause of the appearance of the signal detected on MRI [2,3]. Among imaging techniques, dual-energy CT is commonly used to map BME [4,5]. However, MRI is considered to be the gold standard for detecting bone marrow changes, guiding the decision-making process [6,7].

From a clinical point of view, MRI underlines the presence of BME in both symptomatic and asymptomatic subjects, particularly in high-level athletes and military recruits [8]. However, considering the significant importance of physical exercise in ensuring a healthy lifestyle, this condition extends to the population of nonprofessional athletes as well (Figure 1). Indeed, changes in an existing training protocol, equipment used, or the start of

a new sport, especially in nonprofessional athletes, are frequent causes of stress injuries [9]. In Figure 2, we show the clinical case of a 38-year-old woman runner suffering from inguinal pain. Transient BME is suspected on MRI in STIR sequence, but T1 images show a small irregularity of the cortical bone profile. Dual-energy CT confirmed the edematous pattern of the right femoral head. However, the edema appears more conspicuous in the subchondral area.

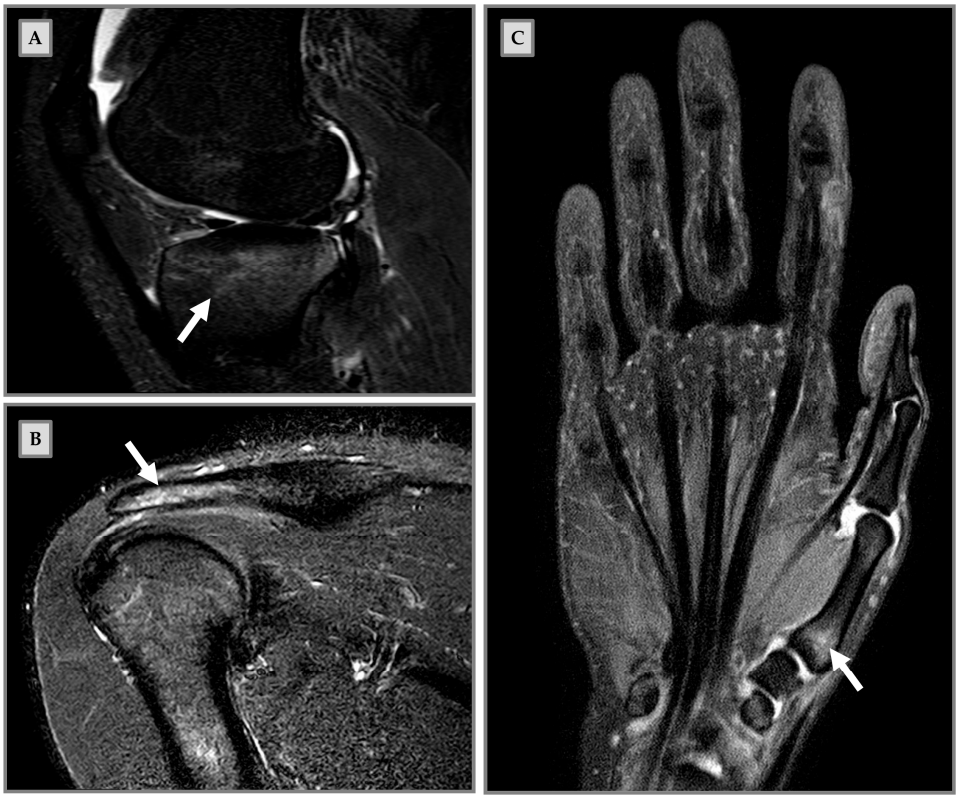


**Figure 1.** Bone marrow edema (BME) on magnetic resonance imaging (MRI) in clinical cases of nonprofessional athletes. (**A**) Male patient, 18-years old, art martial player. The patient had been in pain for three weeks during sports activities, elicited by kicking in the air. MRI sagittal short-tau inversion-recovery (STIR) shows BME (arrow) at the tibial plate. (**B**) Male patient, 20 years old, padel player. One-month pain and hypersensitivity during sports activity; he continued to train until functional impairment development. MRI coronal STIR shows BME (arrow) at the humerus diaphysis and the distal acromion end. (**C**) Female patient, 29 years old, volleyball player. The patient resumed intense physical activity after a period of no training. She presented pain onset during sports activity and functional impairment. MRI coronal STIR shows BME (arrow) at the first metacarpal bone.

In addition, the etiology of the injury may depend on a combination of the type of training, the playing load and intrinsic/extrinsic risk factors [10].

Biomechanical overload of joints and joint overuse can be caused by physical activity and intensive training, even in the absence of trauma, which also leads to the occurrence of BME in athletes. However, it has been suggested by some authors that the appearance of BME on MRI may also occur during the physiological process of bone remodeling as a consequence of regular overloading of the joint [11,12]. In particular, it has been hypothesized that in athletes, repetitive mechanical loading and an insufficient period of functional recovery may lead to joint overload and thus determine the nontraumatic onset of BME. In addition, this phenomenon may induce a reaction from the bone, known as a stress reaction, usually interpreted by the clinician as a prefracture [10]. In turn, the prefracture may evolve into a stress fracture in both normal and damaged bone [13]. Finally, there are contradictory studies in the literature regarding the hypothesis that the pattern of

BME detected by MRI may be due to biomechanical aspects of the specific sports activity practiced [8,9].

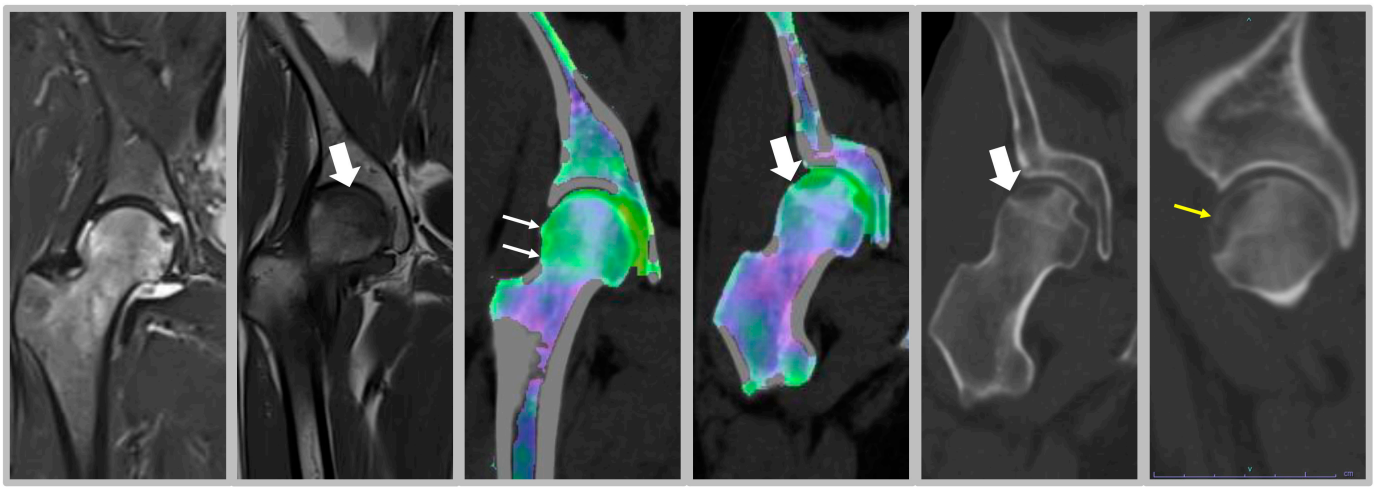

**Figure 2.** Clinical cases of nonprofessional runner. Female nonprofessional runner, 38 years old. MRI images in STIR show transient edema; T1 images (thick arrow) show small irregularity of cortical bone profile. Dual energy CT confirms the edematous pattern of the right femoral head, with BME appearing green against a purple background of normal bone (thin arrow). However, the edema appears more conspicuous in the subchondral area, where a large hypodense area appears on the partition images, with a small subchondral fracture well confirmed on the coronal (thick arrow) and sagittal (yellow arrow) reconstructions.

Based on this evidence, the aim of our review was to (i) summarize the current knowledge on the etiopathogenesis of BME and (ii) highlight the main aspects that make it difficult to formulate a correct diagnosis and establish an adequate therapeutic treatment.

## 2. Literature Search Strategy

For this narrative review, 38 articles were selected from an initial number of 100 articles. The search was performed using the bibliographic databases Medline (1945, start date; 2021) and Pubmed (1916, start date; 2021). The search strategy was based on the use and/or combination of the following keywords: "bone marrow edema", "athletes", "sport", "physical activity", "joint", "magnetic resonance imaging", "bone marrow injury", "diagnosis", and "treatment".

This narrative review included articles on the etiology, diagnosis, and treatment of BME in professional and amateur athletes. We considered studies that met the following inclusion criteria: (1) English language; (2) diagnosis established through clinical and MRI findings indicative of BME; (3) studies that included outcomes such as pain resolution, functional recovery, and time to return to sporting activity.

Studies were excluded if the patients considered had BME secondary to trauma, tumor, avascular necrosis, osteoarthritis, or infection.

The search process was performed on a worldwide basis, without excluding specific geographical areas or different ethnic groups. Language and species filters were applied to the results list to eliminate non-English articles.

## 3. BME Etiopathogenesis and Altered Bone Remodeling

Conflicting data are currently present in the literature about the causes of BME detection on MRI. Usually, a pure acute traumatic etiology is the main cause of BME in athletes, although in some cases this condition may also result from repetitive or chronic trauma [12]. As mentioned above, repeated stress triggers a stress reaction in the bone, which may result in hypertrophy and trabecular remodeling. Indeed, trabeculae subjected to this forced process exhibit microfractures, accompanied by the presence of BME on MRI. Mild trauma causes the appearance of BME without detectable damage to the cellular elements, whereas more severe trauma causes the appearance of microfractures and hemorrhage in the trabecular bone [10,12,14].

Biologically, bone responds to repetitive stress with an imbalance between the activity of osteoclasts and osteoblasts, which causes an alteration in bone turnover and therefore a weakening of the bone itself. Initially, the bone adapts by forming new periosteal bone to provide structural support. If the source of stress persists, there is a significant increase in osteoclastic activity to the detriment of osteoblastic activity, resulting in microfractures [10].

An interesting study by Matheny and colleagues demonstrated that joint overload leads to increased bone remodeling in regions affected by BME. Using a rabbit model, it was shown that microdamage induced by mechanical overload in epiphyseal bone results in enhanced bone remodeling and the appearance of BME within 1–2 weeks. In cortical bone, the generation of tissue microdamage appears to cause apoptosis of osteocytes in the immediate vicinity of the injury. This event, in turn, leads to increased receptor activator of nuclear factor kappa-B ligand (RANKL) expression in osteocytes surrounding the region of injury, with consequent increase of bone resorption and remodeling [15]. The authors concluded that BME occurrence can be preceded by bone physiology changes, thus representing a potential target for preventive treatment strategies.

## 4. BME in Symptomatic and Asymptomatic Athletes

Numerous scientific studies have revealed that BME can be found in symptomatic athletes (Table 1). Symptoms are nonspecific but include the onset of pain, which is initially tolerable and not affecting the performance of physical activity, and tenderness during exercise. In this phase, the athlete continues to train, applying more stress to the joint, causing a stress reaction that can degenerate into a stress fracture [9].

To date, it remains unclear whether there is a significant correlation between BME and clinical symptoms, as the present studies are conflicting.

To validate the most reliable method for early detection of lumbar bone stress injury, Sims et al. analyzed the lumbar vertebral bodies of 65 healthy cricket players who reported lumbar symptoms and lumbar stress injuries. Their results showed that symptomatic relevant BME in the vertebral body was associated with a signal intensity $\geq$2. This suggests the existence of a potential correlation between symptomatic lumbar stress fractures and BME signal intensity [7].

In contrast, Paajanen and colleagues, through a 2-year follow-up study of 102 elite players (football, ice hockey, and bandy), found no significant correlation between the occurrence of BME and groin pain, as pubic joint BME was detected by MRI in 50% of both symptomatic and asymptomatic players [16]. Similarly, Varkas et al. analyzed the occurrence of BME of the sacroiliac joint in 22 military recruits before and after 6 weeks of intense standardized physical training. The evaluation after this time showed no statistically significant relationship between back pain and the occurrence of BME and no increase in its size [17].

According to some authors, the occurrence of BME can also occur in asymptomatic athletes (Table 1) [8]. For example, Major and Helms evaluated MRI changes in the knee joint of high-level collegiate basketball players before the start of the season that could have been misinterpreted as abnormal during the season [18]. The authors showed that 14 of the 34 players included in the study had BME in at least one location, concluding that the changes observed on MRI were asymptomatic abnormalities. Furthermore, it was hypothesized that microtrauma transmitted through the meniscus, dissipated by the cartilage, and absorbed by the bone, may be at the origin of these lesions. Finally, the continuous repetition of jumps and runs may have led to the appearance of BME [18].

The BME can be associated with any type of sports activity, which influences the localization of BME. In fact, Grampp and colleagues reported on a 29-year-old golfer with mild pain and swelling of the proximal phalanx II of her left hand. MRI revealed an involvement of the metacarpal joint and the proximal second phalanx of the left hand [19]. In agreement, Yochum and Barry reported the clinical case of a 42-year-old female jogger, who had persistent painful symptoms on the back of her foot, aggravated by the physical activity itself. Again, MRI showed involvement of the third tarsometatarsal joint characterized by the presence of stress-induced BME [20]. Moreover, rugby players show BME tending to the tibiofemoral joint (e.g., medial condyle), whereas runners show more involvement of the patellofemoral joint, due to more linear movement [21,22]. The different distribution of applied stress could also explain the different localization of BME and its lack of manifestation in some sites, such as the carpal bones [23]. Mandalia and colleagues, in a study of 25 asymptomatic university athletes, demonstrated a correlation between total training time, training intensity, and the occurrence of BME ($p < 0.05$) [22]. Based on their results, the authors suggest that the onset of BME might be particularly influenced by the intensity and duration of repeated impacts. Finally, that study confirms how the type of sport practiced is related to the incidence of BME, as 5 of the 13 rugby players showed a high incidence of BME, not detected in contrast while none of the swimmers, showing how the type of sporting activity dictates the incidence of BME [22].

Finally, some studies also suggest how BME size and its disappearance may be influenced by sports activity. In this regard, the study by Horga et al., in which the knees of 71 asymptomatic middle-aged athletes 6 months before and half a month after a marathon were evaluated, showed a reduction in the size of subchondral BME after the marathon for 19 of 58 subjects in whom the onset of BME had previously been detected [23]. Appearing and disappearing patterns were observed in a study by Kornaat and colleagues, in which 16 asymptomatic professional runners were followed for 7 months to study the clinical and radiological progression of BME [21]. At the beginning of the study, BME was purely localized in the foot and ankle joint in only 14 runners, whereas at the end of the evaluation period, 20% of BME appeared and 22% disappeared, showing a fluctuation pattern not associated with any clinical symptoms. The authors therefore concluded that BME may participate in the physiological process of bone remodeling, by not causing symptoms for at least the first 7 months after its onset [21].

**Table 1.** Studies carried out on the athletic population: main aspects of BME clinical picture in symptomatic and asymptomatic athletes.

| | Reference | Participants | Age (Years) | Physical Activity/ Sport | Investigated Skeletal Segment/Joint | Follow-Up | Imaging Method | Results | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Symptomatic BME | [7] | 65 men | <17<br><19 | Bowling (cricket) | Posterior vertebral arch | 8 months | MRI | BME signal intensity (2 or more) was positively associated with lumbar bone stress injury | BME MRI pattern is significantly correlated to symptomatology at the spine level |
| | [16] | 102 men | >18 | Soccer, ice-hockey, and bandy | Pelvis | 2 years | MRI | No significant difference was found in the percentage of pubic BME between symptomatic players (8/15) and controls (20/43) | No direct correlation between the detection of BME on MRI and the perception of symptoms |
| | [17] | 22 men | 18–45 | Standardized military recruits physical training | Sacroiliac joints | 6 weeks | MRI | 9/22 recruits (40.9%) already presented BME at MRI; these lesions did not increase significantly after 6 weeks of intensive physical training | BME size was not influenced by the performance of intense physical activity |
| Asymptomatic BME | [18] | 12 men<br>5 women | 18–22 | Basketball | Knee | Preseason | MRI | 14 (41%) of 34 knees showed BME in at least one location | BME on MRI may represent an asymptomatic abnormality; long-term evaluation is necessary to clarify the significance of these findings |
| | [22] | 12 men<br>13 women | 19–23 | Football<br>Rugby<br>Running<br>Netball<br>Swimming<br>Hockey<br>Lacrosse | Knee | Postseason | MRI | 7 participants (28%) were found to have BME (six in one knee and one bilaterally)<br>5 of 13 rugby players had BME, while none of the swimmers | The type of sport performed influenced BME incidence; the amount of training time, during the season, was significantly associated with BME appearance |
| | [23] | 51 men<br>64 women | 25–73 | Marathon running | Knee | 6 months before and half month the marathon | MRI | After the marathon, MRI showed a reduction in BME size in 19 of 58 previously detected BMEs | Physical training can influence BME size and disappearance |
| | [21] | 13 men and 3 women | Mean age: 22.9 ± 2.7 | Running | Pubic bones<br>Hips<br>Knee<br>Ankle | Preseason and postseason | MRI | 14 of the 16 athletes had BME lesions before the start of the season: 31/45 were in the ankle joint and foot; 26/45 fluctuated during the season, with new lesions occurring (9/45) and old lesions disappearing (10/45), without causing any symptoms | The observed fluctuation pattern could indicate that BME participate in the normal bone remodeling process and, within 7 months, does not cause symptoms |

BME: bone marrow edema; MRI: magnetic resonance imaging.

## 5. BME Treatment Options

If left untreated, BME usually resolves spontaneously within 3–9 months. However, there are several treatment strategies, conservative or surgical, that aim to bring about a reduction in pain symptoms, when present, and accelerate the normal course of the condition [24]. Non-operative treatments of symptomatic BME include partial/non-weight-bearing, or the administration of pharmacological treatment, based on nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates and monoclonal antibody [25,26]. Müller et al. demonstrated that zoledronic acid can be recommended for relieving joint pain in athletes, and reduced recovery time by 50%, so that high-performance players can resume training [27,28]. Confirming the findings of Müller et al., Vasiliadis and colleagues demonstrated that the combination of a single dose of zoledronic acid with partial weight bearing for one month improves mobility and reduces BME [29]. In this study, 54 patients with bone marrow edema syndrome, who complained of prolonged pain and presented BME on MRI, were enrolled. At the 6-month follow-up visit, improved mobility was observed in 29 patients and resolution of BME was detected in 20 out of 54 patients [29].

On the other hand, ibandronate's effectiveness has been shown in controlling pain symptoms in patients with knee BME. Küchler and colleagues report that a single intravenous administration of ibandronate leads to a reduction in pain in subjects with knee BME, regardless of the severity of the condition detected on MRI [30]. Among monoclonal antibodies, denosumab has proven to be the most efficient in the treatment of BME. Usually used for the treatment of osteoporosis, denosumab has also been shown to be effective in the treatment of bone marrow edema syndrome, as reported by Rolvien and colleagues [31]. In this study, 14 patients with idiopathic BME of the lower extremity were treated with a single dose of denosumab. After 6–12 weeks, MRI showed almost complete disappearance of BME in 93% of patients, while a complete recovery was observed in 50% of the individuals. Furthermore, visual analogue scale (VAS) evaluations revealed a clear decrease in pain perception. Finally, the serum dosage of some markers of bone metabolism showed a significant reduction in bone turnover after treatment [31].

According to the literature, teriparatide is used for the treatment of both fractures showing complications in the repair process and pathological conditions characterized by the presence of BME on MRI, such as complex regional pain syndrome I (CRPS I). Galluccio and colleagues, based on their clinical experience, argue that teriparatide is effective in the treatment of BME secondary to CRPS I, exerting a lasting effect in reducing pain symptoms and in the functional recovery of the joint. According to the authors, these effects may be due to the anabolic capacity of the drug, which is able to affect the cellular pathways of bone metabolism. They suggest a short-term period administration [32].

Since BME occurs because of altered bone turnover, vitamin D administration has also been identified as an effective strategy for treating this condition, as it is a key element in maintaining the homeostasis of the bone microenvironment. In the study by Horas and colleagues, 31 subjects with BME of the foot and ankle were enrolled [33]. Among patients, a high rate of hypovitaminosis D was detected (mean value of 19.03 ng/mL). Consequently, the authors considered that an inadequate vitamin D level may be a cofactor in the onset of BME [33]. Capacitively coupled electrical field (CCEF) is one of the conservative treatments for BME. To investigate the role of CCEF stimulation, Piazzolla and colleagues enrolled 24 patients with acute vertebral compression fractures [34]. At 90-day follow-up, the group of patients treated with CCEF showed a reduction in vertebral edema and a significant improvement in VAS, compared to the untreated group [34]. In this regard, we propose in Figure 3 the clinical case of a professional rugby player, who came to our attention after a CT scan and MRI, which showed a stress fracture at the base of the II metatarsal of the right foot ( Figure 3A–C); an altered signal intensity, hyperintense in short-tau inversion recovery (STIR) images, related to BME can be observed ( Figure 3B,C,E). Initially, a pharmacological treatment based on the administration of calcium (1200 mg/day), vitamin D3 (800 I.U./day) and teriparatide (20 µg/day) was recommended, associated with CCEF. Control CT and MRI after three months of therapy showed an advanced healing process of the fracture; the

patient also showed regression of painful symptoms ( Figure 3D–F). CT scan after 6 months of therapy showed complete healing of the fracture with subsequent disappearance of symptoms and resumption of competitive sports activity (G and I). Plain radiography after 9 months of therapy showed complete recovery of the patient (H and J).

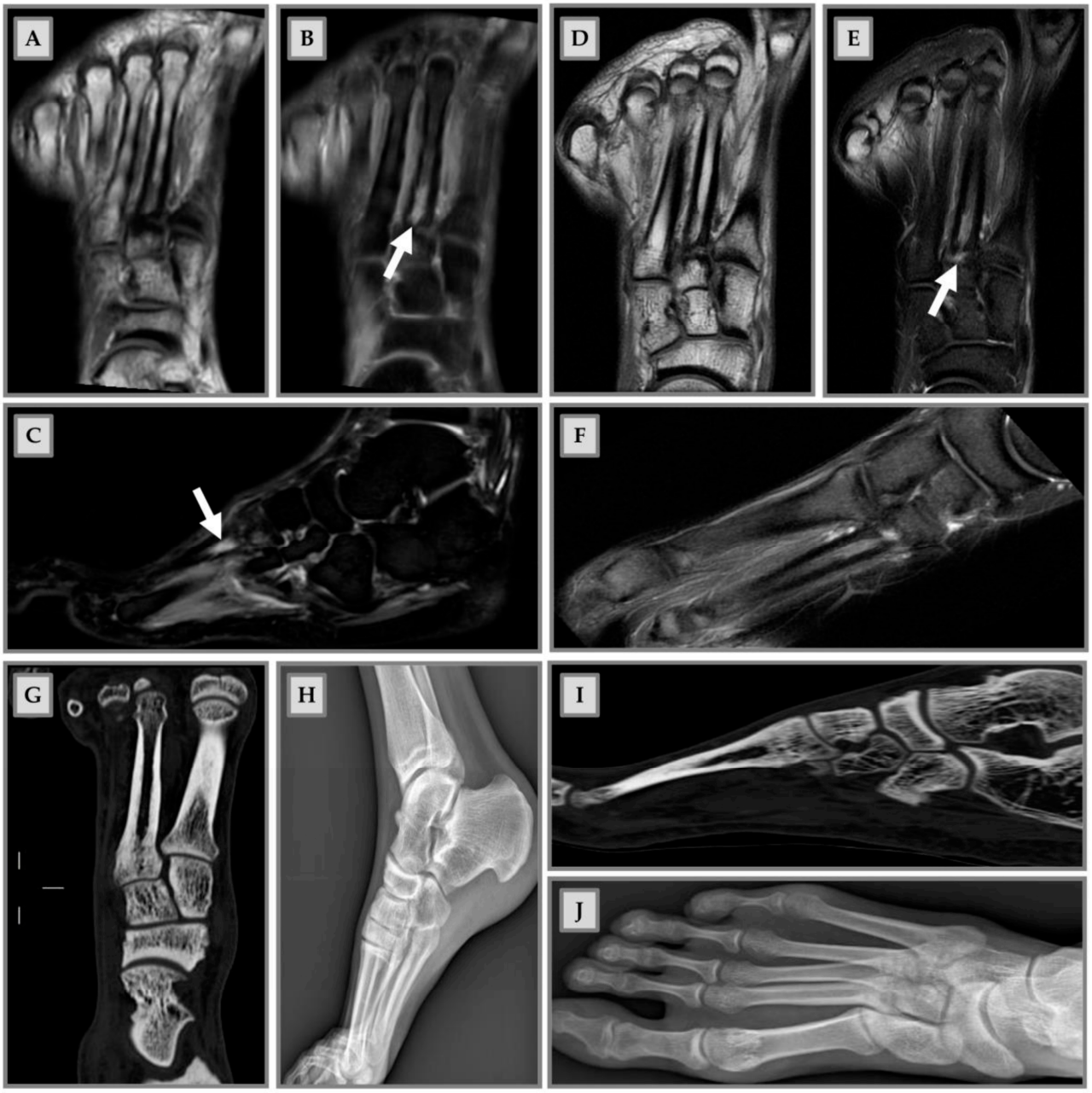


**Figure 3.** Male patient, 22 years old, professional rugby player. (**A**–**C**): Stress fracture of II metatarsal base; (**B**,**C**,**E**): altered signal intensity, hyperintense in short-tau inversion recovery (STIR), related to BME (arrows); (**D**–**F**): MRI check after 3 months: advanced fracture healing process and pain release; (**G**,**H**): CT check at 6 months after therapy. Fracture healing, pain release and sport restart; (**H**–**J**): radiography check at 9 months after therapy and 1 month of sports activity. Patient recovery.

Operative treatments are considered if conservative treatment fails. Among them, core decompression and calcium phosphate bone substitute are included [25]. According to the literature, core decompression results in faster functional recovery, less chance of recurrence and better control of pain symptoms than patients treated with NSAIDs or paracetamol [35]. Calcium phosphate injection is a valuable technique by which fluid synthetic calcium phosphate is injected to fill the space between the trabeculae of spongy

bone in the subchondral region, which is also referred to as subchondroplasty. Calcium phosphate mimics the strength and porosity of normal spongy bone, which will be used by osteoclasts and osteoblasts in the following months as a scaffold to remodel the local bone [24,36].

## 6. Discussion

BME can be considered a clinical picture with an unclear etiology, characterized by specific concerns. In the context of the athletic population, it appears that the primary cause of the occurrence of BME is not actual trauma, but repeated mechanical overload over time, which triggers a stress reaction from the bone. Under physiological conditions, the bone remodeling process is triggered by high intensity exercise [10]. Beyond a certain threshold, the remodeling process is not completed, resulting in an imbalance between bone apposition and resorption and alteration of the normal architecture of trabecular bone. In our opinion, this is when the stress reaction progresses to a stress fracture (depending on location), which on MRI appears to be characterized by BME [13]. The resulting imbalanced bone turnover may also trigger an inflammatory cascade, which only creates the necessary conditions for BME to begin.

Another issue associated with BME is its appearance on MRI in both symptomatic and asymptomatic subjects, suggesting that there are no warning signs that can predict the onset of this condition. Therefore, for the purpose of understanding the etiopathogenesis of BME, it is essential for the clinician to trace the patient's medical history. When present, symptoms include the onset of pain and tenderness during sports activity. The characterization of the pain must be carefully controlled: its intensity, acute onset or chronicity, and its correlation with physical therapy must be recorded [8,37].

Because the symptoms are not specific, the athlete usually tends to underestimate them and continue training, causing repeated mechanical overload, which in turn leads to stress fracture and the appearance of BME on MRI. Therefore, it is essential to identify early signs of this type of condition to avoid incurring the fracture [9]. Based on our clinical experience, we can say with certainty that patients who regularly perform physical activity, at a competitive level or not, are characterized by a different ability to adapt to stress. The performance of an intense physical activity can have pathological outcomes or not, depending on the different adaptive response of the organism.

It is our opinion that this aspect could make it difficult to establish a standard protocol for the elaboration of a diagnosis of BME and, consequently, an adequate therapeutic treatment. There is currently no specific treatment for BME in athletes. Therefore, we strongly recommend that BME be treated in the context of everyone's characteristics, with reference to mechanics, injury history, force load, and musculoskeletal maturation.

If joint mechanical overload due to physical activity is the primary cause of the occurrence of BME, the clinician should consider the intensity and mode of training, as well as periods of rest from exercise. In the absence of acute trauma but painful symptoms, the first approach is conservative treatment: immobilization for short periods, rest from training, and pharmacological treatments (such as NAIDs, bisphosphonates and monoclonal antibody) [25]. However, disrupting the injury dynamic with simple rest appears to be insufficient for optimal regression of the injury. In cases where conservative treatment fails, invasive strategies such as core decompression and subchondroplasty are used.

It is noteworthy that BME turns out to be accompanied by very small and difficult-to-detect lesions in the osteochondral unit. In this regard, MRI is confirmed as the most valid assessment tool for this type of phenomenon. In addition, the use of magnetic resonance spectroscopy (MRS) in the clinical workflow should be of interest in the field. As shown in Figure 4, MRS provides more accurate information about bone edema, and the subsequent presence of water immediately after trauma, and three months later. In agreement with reports in the literature, MRS has provided crucial information on bone composition based on the ratio of fat to water in osteoporosis [38]. Unfortunately, in our experience, MRS is not useful for the diagnosis of BME, but is important in the follow-up of patient recovery.

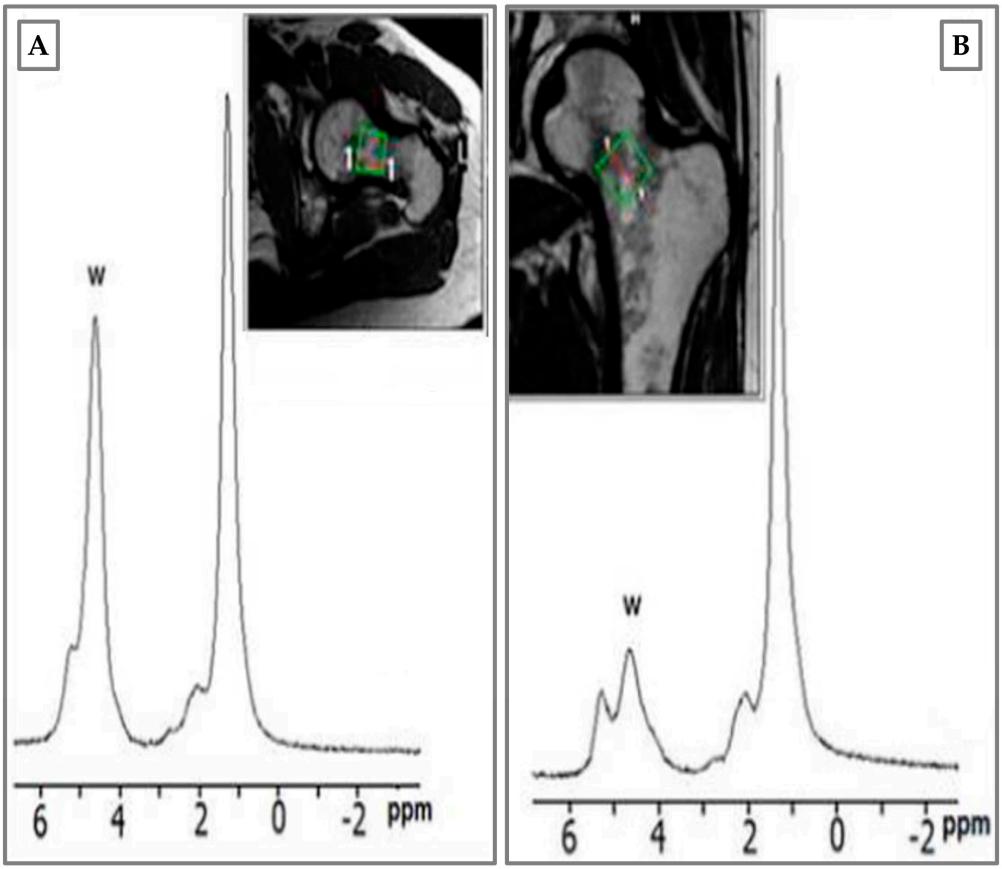


**Figure 4.** Magnetic resonance spectroscopy (MRS) of male patient, 34 years old, hockey player. BME of femur neck after tackling. (**A**) Water peak rising immediately after trauma; (**B**) BME disappearance at 3 months with water peak re-allineation to baseline. Green square: femoral neck area where the spectroscopic analysis was performed.

## 7. Conclusions

BME represents an aspecific clinical pattern with an unclear etiology that occurs in both symptomatic and asymptomatic subjects. In fact, studies in the literature show that the MRI-detectable pattern is not always accompanied by a well-defined symptomatology. Moreover, while some authors consider BME as part of the normal remodeling process, others consider it as bone abnormalities that should be treated.

Based on our experience, the clinician may therefore be faced with two types of situations: a BME found occasionally on MRI, unaccompanied by painful symptoms, and a BME detected following pain referral by the patient. In the first case, pain may or may not present over time; therefore, it is our opinion that the clinician should perform MRI to monitor the status of the BME and possibly reevaluate the patient's clinical condition. In the second case, however, the clinical picture requires pharmacological treatment and surgical treatment in case of nonoperative treatments fail. Furthermore, since BME manifests with specific histologic features, such as inflammatory infiltrate, fibrous tissue, increased vascularity, and reduced bone mineralization, a histologic evaluation of BME could represent a predictive investigation of the patient outcome. This could represent a potential prognostic tool in more severe cases in which surgical treatment is used to resolve the clinical picture [2]. Finally, as the presence of BME is found both before and after the sports season, the assessment of BME by MRI could be used as a tool to monitor the health of high-performance athletes in Olympic programs. However, it is not clear whether the BME is the direct cause of the pain; thus, finding a possible causal connection should be addressed by future studies.

## 8. Limitations of This Review

BME is generally a clinical condition with a multifactorial and highly variable etiology. This makes it very difficult to make a correct diagnosis and to choose an appropriate treatment. In athletes, pain symptoms may or may not occur and the condition may therefore be detected on MRI at too late a stage, compromising the healing process. The limitations of our review are due to the small number of studies in the literature and their heterogeneity, as the results shown are related to different types of sporting activity and different associated BME patterns. Therefore, further studies are needed to better delineate this clinical picture in the athlete population, to facilitate the clinician's diagnosis and in their choice of the most correct therapeutic treatment.

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# Complex Regional Pain Syndrome in Athletes: Scoping Review

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**Abstract:** *Background and Objectives:* Complex regional pain syndrome (CRPS) is a chronic condition characterized by disproportionate regional pain, usually affecting distal limbs, that follows trauma or surgery. Athletes may develop CRPS because of exposure to traumatic or overuse injuries. The aim of the present study is to review the available literature about CRPS type 1 in athletes. *Materials and Methods*: We searched two online databases (PubMed and Web of Science), selecting papers aiming at investigating CRPS type 1 (algodystrophy) in athletes. The analysis of databases was made considering original articles published until 30 June 2021, written in English. *Results:* Fifteen papers (12 case reports, 3 case series) were selected for a total of 20 clinical cases (15 females, 5 males), aged between 10 and 46 years (mean age 18.4 ± 9.8 standard deviation years). Patients included practiced different types of sport (soccer, athletics, gymnastics, basketball). The most involved anatomical sites were lower limbs, and time to diagnosis ranged from 2 days to 4 years. The most used treatments were pharmacological and physical therapies, but sometimes invasive approaches, as regional nerve, or lumbar sympathetic blocks, were provided. The main assessed outcomes were return to activity and pain. *Conclusions*: Our review suggests a higher prevalence of CRPS type 1 in younger people and in lower limbs than in general population but confirms the higher prevalence in females. However, the number of studies addressing CRPS in athletes is limited, as well as the number of involved patients, considering that only few and heterogeneous case reports were published about this topic. Moreover, the high prevalence of old studies (only 5 available studies in the last 10 years) might have influenced the choice of both assessment tools and management strategies. Despite these limitations, athletes showing disproportionate pain after sport-related injury should be promptly evaluated and treated through a multidimensional approach to avoid long-term consequences of algodystrophy.

**Keywords:** complex regional pain syndromes; athlete; sport; pain



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## 1. Introduction

Complex regional pain syndrome (CRPS) is a rare clinical condition, usually occurring after appendicular trauma or surgery, characterized by extremely variable signs and symptoms of the affected limb [1,2]. The main CRPS patients' complaint is continuing pain, often burning, that is disproportionate to its underlying cause, usually accompanied with sensorimotor (muscle weakness, tremor, dystonia, hyperesthesia, and/or allodynia), vasomotor (temperature and color changes of skin), sudomotor (edema and/or sweating), and trophic changes of the affected site, and often localized at the upper or lower limb extremities [1,3]. Nowadays, different forms of CRPS, with overlapping clinical features, have been defined [4]: CRPS type I (algodystrophy), CRPS type II (causalgia), CRPS not otherwise specified (NOS), and CRPS with remission of some features (CRSF). In algodystrophy, clinical findings have a non-dermatomal pattern (regional) in the distal region of the affected limb, while causalgia can develop after a clearly detectable nerve injury. CRPS-NOS partially reproduces the clinical scenario of other forms, and it is not better

explained by any other condition. CRSF is a new type of CRPS, with partial remission, whose characteristics are still not well defined [4].

CRPS is considered among the most painful diseases even though the causes and pathogenic mechanisms of pain are mostly unknown [5,6]. CRPS can occur after crash injuries, fractures, or surgery, but in younger people it can follow minor accidents, as strain, sprain, or bone bruise [7].

According to presentation of all CRPSs, it has been described as having two phenotypes, inflammatory or warm and chronic or cold form. Current diagnosis of CRPS type I is based on clinical features (Budapest criteria) [8], while the role of imaging techniques is still debated [9].

Considering that the precipitating event in CRPS is often represented by an injury, such as fractures or sprains, this condition could be relevant for athletes, even if a direct relation between sport activity and CRPS risk has not been defined [7]. Indeed, in this context, sport-related injury could be a driving cause of CRPS in young people, due to trauma and/or aberrant exaggerated inflammatory processes. Athletes experiencing worsening conditions after common trauma should be assessed for excluding CRPS [10]. The intensity and frequency of sport activity may be linked to augmented risk of injury and CRPS. To the best of our knowledge, a comprehensive review on CRPS in sport practice is not available so far. The aim of the present study is to review the available literature about algodystrophy (CRPS type I) in athletes.

## 2. Materials and Methods

We searched two online databases: PubMed (PM) and Web of Science (WoS). The selection of articles was made through the following search string: ("Athlete" OR "Sport" OR "Player") AND ("Complex Regional Pain Syndromes" [Mesh] OR "Algodystrophy"). Moreover, we checked the reference list of all the screened full-text articles.

The analysis of databases was made through the following criteria: (i) articles published from inception until 30 June 2021; (ii) original articles, excluding reviews, commentaries, posters, and proceeding papers; (iii) only full paper written in English. After applying the research process (A.P.), two authors (A.M. and A.P.) independently reviewed the titles and abstracts of available articles to check the matching with the research aim and inclusion criteria. They selected papers aiming at investigating CRPS type 1 in athletes and combined the articles obtained from the two databases, excluding duplicates. Single-case studies, case series, and cohort studies were selected. After full text reading, they excluded (i) articles dealing with CRPS type 2, NOS or CRSF; (ii) review articles; (iii) articles dealing with patients not practicing any sport at any level. Moreover, additional papers matching the inclusion and exclusion criteria were found by screening the reference list of the articles found through the research process.

From the selected papers, the following data were extracted: (i) author(s) and year of publication; (ii) participant characteristics (number, age, sex); (iii) sport practiced; (iv) time to diagnosis; (v) affected site; (vi) comorbidity; (vii) treatment; (viii) outcome(s).

## 3. Results

The review process results are shown in Figure 1, according to the PRISMA guidelines for scoping reviews (PRISMA-ScR) [11].

After applying the paper selection criteria, we checked 21 full texts and excluded 2 articles dealing with CRPS type 2, 2 review articles, and 3 articles dealing with patients not practicing any sport. Finally, the selected articles were 15. Table 1 shows main characteristics of each study.

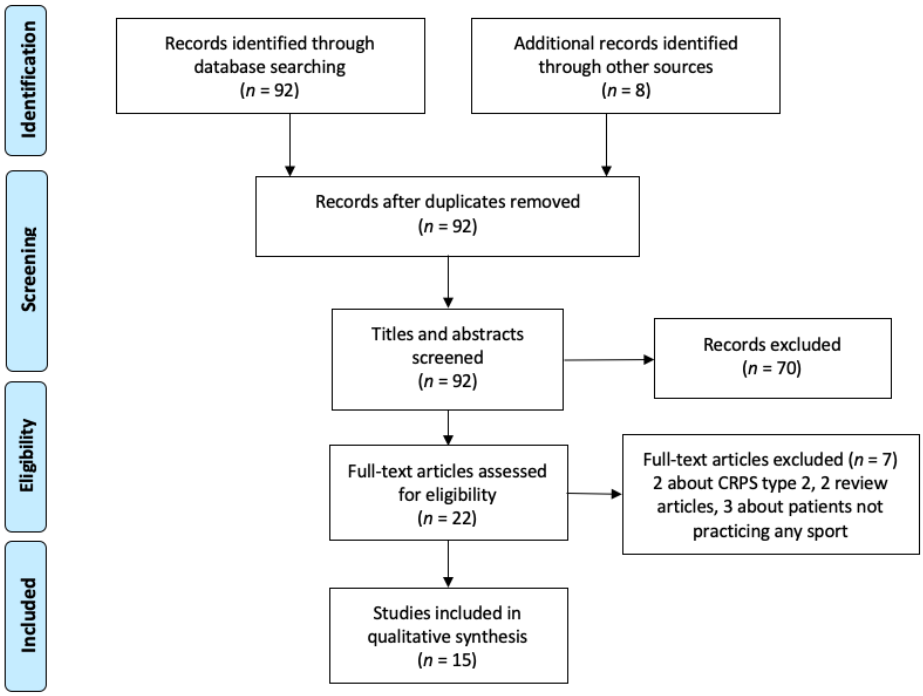


**Figure 1.** Flow diagram of the literature review process.

**Table 1.** Main characteristics of selected articles.

| Author and Year | Number of Patients | Gender | Age | Sport Practiced | BC | Imaging | Cold/Warm Type | Site |
|---|---|---|---|---|---|---|---|---|
| Carayannopoulos et al., 2009 [12] | 1 | F | 12 | Soccer, basketball, field hockey | No | US | n.a. | Ankle |
| Collins, 2007 [13] | 1 | M | 13 | Baseball, soccer, handball, basketball | No | XR, MRI, BS | n.a. | Ankle |
| Feldman et al., 2009 [14] | 1 | F | 37 | Triathlon | Yes | MRI | n.a. | Lower extremity |
| Hind et al., 2014 [15] | 1 | M | 29 | Powerlifting | Yes | DXA | n.a. | Leg |
| Khadavi et al., 2014 [16] | 1 | F | 17 | Athletics | No | MRI | Cold | Calf |
| Ladd et al., 1989 [17] | 3 | 1 M, 2 F | 18, 20, 31 | Athletics, swimming, hockey | No | No | n.a. | Ankle and knee |
| Martìnez-Silvestrini et al., 2006 [18] | 3 | F | 11, 13, 14 | Athletics, Volleyball | No | XR | n.a. | Foot, ankle, knee |
| McAlear et al., 2021 [19] | 1 | F | 18 | Soccer | No | No | n.a. | Foot |
| Middlemas, 2007 [20] | 1 | F | 10 | Soccer | No | XR, US | Warm | Foot |
| Myers, 2013 [21] | 1 | F | 46 | Running | No | XR | Warm | Knee |
| Rand, 2009 [22] | 1 | F | 10 | Gymnastics | No | MRI | n.a. | Knee |
| Suresh et al., 2002 [23] | 2 | F | 11–15 | Gymnastics, volleyball | No | No | n.a. | Foot and wrist |
| Takahashi et al., 2018 [24] | 1 | M | 12 | Soccer | No | XR, CT | n.a. | Ankle |
| Walia et al., 2004 [25] | 1 | M | 13 | Wrestling | No | XR, MRI, BS | n.a. | Ankle |
| Weber et al., 2002 [26] | 1 | F | 18 | Field hockey | No | XR, BS | Warm | Ankle |

Abbreviations. BC: Budapest criteria; BS: bone scan; CT: computer tomography; MRI: magnetic resonance imaging; n.a.: not available; US: ultrasound; XR: X-ray imaging.

Most of the available studies are case reports. Indeed, only three studies involve, respectively, 2 and 3 patients, for a total number of 20 patients. The 3 patients from Ladd et al. [17] were extracted from a cohort of 11 patients, 4 of whom were not practicing any sport and the others were excluded for data unavailability. The selected studies were published from 1989 to 2021. Sex prevalence is in favor of females (15 F: 5 M). The participants' age ranged from 10 to 46 years (mean age 18.4 ± 9.8 standard deviation years). The patients practiced different types of sport: soccer (5 studies), athletics or running (5 studies), hockey (3 studies), gymnastics (2 studies), basketball (2 studies), volleyball (2 studies), swimming, triathlon, baseball, handball, powerlifting, and wrestling. Table 2 provides detailed information about the selected studies. Only two studies [14,15] followed Budapest diagnostic criteria. Imaging, including X-ray, ultrasound, magnetic resonance, computer tomography, and bone scans, was often used for differential diagnosis. Only four studies reported details about warm- [20,21,26] or cold-type [16] CRPS in the considered clinical case.

**Table 2.** Detailed information of the selected studies, including time to diagnosis, site, comorbidity, treatment, and outcomes.

| Authors and Year | Time from Inciting Event | Time to Diagnosis | Comorbidity | Treatment | Main Findings |
|---|---|---|---|---|---|
| Carayannopoulos et al., 2009 [12] | Unknown time after ankle sprains | 2 years | Not reported | P, PT, OT, CBT, RNB | Pain relief, increased ankle RoM and functional independence |
| Collins, 2007 [13] | 15 months from ankle sprain | 2 months | Not reported | P, PT | Pain relief, improvement of gait cadence and pattern, endurance, weight bearing tolerance, ankle RoM and strength (+) |
| Feldman et al., 2009 [14] | 6 weeks after femoral fracture | 6 weeks | Osteopenia, amenorrhea, depression | P, PT, LSPB | Reduced discomfort, normalization of local color and temperature |
| Hind et al., 2014 [15] | Years after orthopedic surgery | 4 years | Calve–Perthes disease | LSPB, P, SCS | Not reported |
| Khadavi et al., 2014 [16] | Months after gastrocnemius strain | 6 months | Type 1 von Willebrand disease | P, PT | Improvement of passive RoM (knee extension and ankle dorsiflexion) and gait distance, reduced device usage and increased weight-bearing tolerance |
| Ladd et al., 1989 [17] | 3 months after ACL reconstruction; weeks after overuse; 10 days after ankle sprain | 10 days–3 months | Sprain and osteoarthritis | LSPB, P, PT | Return to activity (3–27 months) |
| Martìnez-Silvestrini et al., 2006 [18] | 1 day after ankle sprain; 3 days after overuse; 2.5 months after ankle sprain | 2 days–2.5 months | Depression | P, PT | Reduced edema and pain, improvement of RoM |
| McAlear et al., 2021 [19] | 2 weeks after tarsal tunnel release surgery | 2 weeks | Depression | LSPB | Return to activity |
| Middlemas, 2007 [20] | No leading cause | 2–3 weeks | Not available | P, PT | Improvement of weight bearing tolerance and independence in ADL, return to activity |

**Table 2.** *Cont.*

| Authors and Year | Time from Inciting Event | Time to Diagnosis | Comorbidity | Treatment | Main Findings |
|---|---|---|---|---|---|
| Myers, 2013 [21] | No leading cause | 10 days | Not available | P, PT | Pain relief and increased RoM |
| Rand, 2009 [22] | 7 weeks after knee injury | 6 weeks | Migraine | PT, LSPB, P, CBT | Return to activity (8 weeks) |
| Suresh et al., 2002 [23] | 1 year after metatarsal avulsion; 2 months after wrist injury | 2 months–1 year | Not available | P, PT, RNB | Return to activity (3 months), pain relief |
| Takahashi et al., 2018 [24] | 5 days after ankle sprain | 10 days | Not available | P, PT | Return to activity (35 days), pain relief |
| Walia et al., 2004 [25] | Unknown time after ankle sprain | Not known | Not available | P, PT, LSPB | Pain relief and gait improvement |
| Weber et al., 2002 [26] | 16 days after ankle sprain | 1 month | Not available | PT, LSPB | Improvement of symptoms, return to activity (2 months) |

Abbreviations. ADL: activities of daily living; CBT: cognitive behavioral therapy; LSPB: lumbar sympathetic plexus blocks; OT: occupational therapy; P: pharmacological treatment; PT: physical therapy; RNB: regional nerve blockade; RoM: Range of Motion; SCS: Spinal Cord Stimulation.

Time to diagnosis varies from a few days to several months, reaching up to 4 years in Hind et al. [15]. The most frequent triggering events were sprains, while CRPS presentation timing from trauma even varied from days to months. The most involved site was the lower limb, including calf, knee, ankle, and foot. Only one study [23] reported a wrist involvement. Athletes often presented previous traumatic or overuse injuries, clinical conditions (such as osteopenia or amenorrhea, or depression) that could be directly or indirectly (e.g., predisposing to stress fractures [14]) trigger CRPS, or other comorbidities (such as type 1 von Willebrand disease, or migraine). It is noteworthy that a single study reported Calve–Perthes disease as a comorbidity [15], which likely contributed to poor bone strength and lean mass. Treatments included drugs (gabapentin, pregabalin, tricyclic antidepressants, selective serotonin reuptake inhibitors, steroids, opioids, or local medication with lidocaine), physical therapy (including desensitization techniques and transcutaneous electrical nerve stimulation (TENS)), occupational therapy (OT), psychological counseling, regional nerve blockade (RNB) using ketorolac and lidocaine or ropivacaine and clonidine, and lumbar sympathetic block (LSB) using bupivacaine or guanethidine. Invasive approaches, such as RNB and LSB, were used to treat patients unresponsive to non-invasive therapies and to facilitate the execution of physical therapy when it was limited by pain. The main outcomes used to evaluate treatment response were joint range of motion (RoM) of the affected joints, gait parameters (pattern, distance, and assistive device needs), weight-bearing tolerance, symptoms (most of all pain), and return to activity. The investigated treatments showed positive effects on the reported outcomes, even if with different timing. Moreover, Hind et al. [15] revealed a possible contribution in CRPS diagnostic investigation by dual-energy X-ray absorptiometry to highlight regional body composition differences. The authors found reduced bone strength and lean mass in the affected region compared to the unaffected limb and with age-matched pairs, showing lower Z-scores. This may be also due to a long-lasting CRPS with non-use of the affected region.

## 4. Discussion

Even if large epidemiological studies of CRPS type 1 in athletes are not available, it seems that this condition has different characteristics from those of the general population. CRPS has a higher incidence between 60 and 70 years [27], particularly affecting older people after surgery, fractures, or other traumatic injuries, while it seems to mostly affect young people in reported cases, probably due to the higher incidence of sport-related injury in this population [7,28]. Even if previous studies showed that in general pop-

ulation CRPS incidence in young people is lower than that of adults (1.16/100,000 vs. 26.2/100,000) [27,28], in the present study, apart from four studies [14,15,17,21], most of the participants ranged from 10 to 18 years. As for sex distribution, the higher prevalence in females confirms previous findings about the epidemiology of CRPS in both adults and children [9,27,28]. As regards the involved site, the upper extremity is more frequently affected than lower one [27] in the general population, while almost all involved regions are in the lower limb in athletes. This may be explained by the higher prevalence of lower limb injuries (as sprains, fractures, bruise) in sport practice [29,30]. Different comorbidities were found in the described clinical cases. Some of them, as menstrual alterations, or migraine, have already been found as predisposing factors for CRPS [14,31]. Other conditions, such as psychiatric comorbidities, are often found in CRPS patients, but their relationship has not been clarified yet [32]. Moreover, pathogenic hypothesis has been done to link other comorbidities to the CRPS occurrence, such as microvascular damage in von Willebrand disease [16].

Even if sport-related injuries are suggested as inciting event in patients with CRPS, we cannot define more hazardous ones for developing CRPS, because of the scarcity of literature to corroborate their role as risk factor.

It is worth noting that only two studies followed Budapest criteria for CRPS diagnosis and that imaging was often used for confirming diagnosis or excluding other pathologic conditions. Moreover, a clear definition of the cold or warm subtypes of CRPA cannot be found in most of the included papers.

As for the general population, the delayed diagnosis of CRPS might be a crucial issue for athletes, too. A person can procrastinate even for years before achieving a correct CRPS diagnosis, as reported also in our review. This is important, particularly in athletes, because a delayed diagnosis can lead to a worse therapeutic response and prognosis [33], thus implying a late or incomplete return to sport activity.

In the studies included in our review, pain and physical function were mostly assessed, while emotional well-being, the participants' ratings of global improvement and satisfaction, and adverse events were not investigated [34]. Positive effects on the reported outcomes were obtained by treatment administration with different timings. Considering the huge variability in clinical scenarios and treatment response of patients with CRPS, the management of this condition should be based on a bio-psycho-social model [35] through a comprehensive assessment of impairments and activity limitations to guide multimodal interventions, including pharmacological and non-pharmacological treatments.

Concerning the treatment options for athletes developing CRPS, pharmacological therapy was often combined with physical therapy. It should be underlined that no study reported bisphosphonate use in this population (e.g., neridronate), considering that this drug class seems effective in the management of algodystrophy and is supported by moderate quality of evidence [36,37]. As for physical therapy, athletes with CRPS were treated with desensitizing techniques, early mobilization, and TENS. Early and progressive mechanical loading by avoiding muscle wasting and bone loss due to non-use could represent a key point in CRPS rehabilitation, especially in athletes [15].

The main limitations to provide reliable conclusion are the limited number of studies addressing CRPS in athletes as well as the limited number of involved patients. Moreover, the high prevalence of old studies (only 5 available studies in the last 10 years) might have influenced the choice of both assessment tools and management strategies.

## 5. Conclusions

The available findings show that CRPS can be found in young athletes. Physicians should investigate clinical findings characterizing this condition in the context of a sport-related injury with pain disproportionate to its cause, even in young people, as an early diagnosis influences the effectiveness of interventions and the prognosis. However, the best treatment to minimize symptoms and to allow a fast but safe return to activity in athletes with CRPS is not well established. Indeed, return to activity in athletes should be

careful, so that tissue recovery is reached before starting activity, to avoid relapses, but it should be started as soon as possible, as the progressive stimuli and weight bearing could represent therapeutic strategies for CRPS. Future studies may focus on the comparison or combination of different types of treatments to assess which one could maximize benefits. In our opinion, an interdisciplinary and multidimensional management should be proposed to athletes with CRPS to allow adequate pain relief and promote early and safe return to play.

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# Pharmacological Treatment for Acute Traumatic Musculoskeletal Pain in Athletes

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**Abstract:** Pain management is a crucial issue for athletes who train and compete at the highest performance levels. There are still evidence gaps for the use of analgesics for sports injuries despite the growing interest in training and competition settings. However, high-quality research is needed to determine the most appropriate and optimal timing and formulations in non-steroidal anti-inflammatory drug and opioid management, particularly given the strictness of anti-doping regulations. Indeed, the role of pharmacological therapy in reducing acute traumatic pain in athletes should still be addressed to minimize the timing of return to sport. Therefore, the aim of this comprehensive review was to summarize the current evidence about pain management in the setting of acute injury in elite athletes, providing the most informed strategy for pain relief and performance recovery.

**Keywords:** pain management; athletic injuries; trauma; return to sport; sport medicine; rehabilitation

## 1. Introduction

Growing attention has been paid to the promotion of physical activity and a healthy lifestyle over the past decades, with an improved number of initiatives promoting sports in both healthy subjects and patients suffering from various diseases [1–4]. As a result, a constant increase has been registered in the prevalence of both elite and recreational athletes, particularly in youth [5,6]. Apart from the widely noted positive effects of physical activity on cardiovascular and musculoskeletal health [1], the increase in the number of athletes has increased the incidence of sport-related musculoskeletal injuries, with relevant issues on sanitary costs and time lost from sport [7–9].

The International Olympic Committee (IOC) has recently defined sports injuries as new or recurring musculoskeletal complaints occurred during competition or training and requiring medical attention [10]. However, acute sport-related musculoskeletal injuries are characterized by a large heterogeneity in epidemiology and clinical presentation based on the sport performed [11,12]. Additionally, it has been reported that acute traumatic

musculoskeletal injuries represent the 10–19% of all acute injuries treated in the emergency department [13,14]. Sports-related injuries still represent a critical issue in sports medicine, despite the large attention paid to prevention programs [15,16]. To date, the negative effects of pain on training and physical function lead to a psychological and economic burden for athletes and their teams [17,18].

In this situation, an individualized and patient-tailored approach, including pain management, physical therapy, and rehabilitation, has been recommended to manage sports-related musculoskeletal injuries [10,19–23]. In 2016, Ahmadi et al. [24] assessed the pharmacological approach to traumatic injuries, highlighting the need for an age-specific individualized treatment. However, it should be noted that sports athletes usually require a tailored management to enhance the rehabilitation and the return to play (RTP) [24]. Accordingly, Zideman et al. [23] confirmed that a multitarget approach is crucial for elite athletes in terms of pain management. However, the authors included both nonpharmacological and pharmacological approaches, without focusing on acute traumatic injuries [23].

To the best of our knowledge, the role of pharmacological therapy in reducing acute traumatic pain in sportsmen should be addressed to optimize pain management, minimizing the timing of RTP.

Thus, by the present comprehensive narrative review, we aimed to summarize the state of the art about the pharmacological treatment for acute traumatic musculoskeletal pain in athletes, in order to enhance knowledge on this subject, and to guide physicians in the common clinical practice, management, and rehabilitation of these subjects.

## 2. Main Acute Traumatic Musculoskeletal Pain in Athletes

Musculoskeletal injuries represent the most common sports-related injuries [25], though the characteristics of specific sports and the physical stresses related to sports activities significantly affect the prevalence of the different types of injuries [14]. Therefore, an adequate assessment of sport-specific demands is particularly important to guide physicians not only in specific diagnoses but also in the prescription of a multitarget and multimodal therapeutic plan including pain management, sport-specific rehabilitation, and prevention of re-injuries [26].

Conversely, several athletes' characteristics should be taken into consideration to provide a precise diagnosis, including the main risk factors affecting injury risks such as age, gender, and level of play [27–29]. In particular, it has been reported that ankle sprains and knee injuries are more common in women, probably due to higher estrogen levels, higher body fat mass, lower muscle mass, greater flexibility, and a wider pelvis [27,28,30]. At the same time, chronic and overuse injuries are most common in older athletes, given the loss of elasticity and the less effective reparation mechanisms in tendons and muscles [31]. Accordingly, the level of play might significantly affect injury risk due to the number of hours of play per week, and the intensity of training and competitions [32]. Therefore, clinicians should be aware of the potential implications of a patient's characteristics, guiding a precise diagnostic process aimed at supporting a precise diagnosis that represents the starting point for an individualized and tailored pain management.

In these scenarios, acute traumatic musculoskeletal injuries are characterized by a sudden trauma to the tissue, commonly related to a specific identifiable event during the sports activity. Acute sport-related injuries might be classified according to the tissues involved in the injury (e.g., bone, ligament, muscle, tendon, joint,) and the type of injury (e.g., fracture, dislocation, sprain, or strain) [33] (See Figure 1 for further details on ankle injuries as an example).

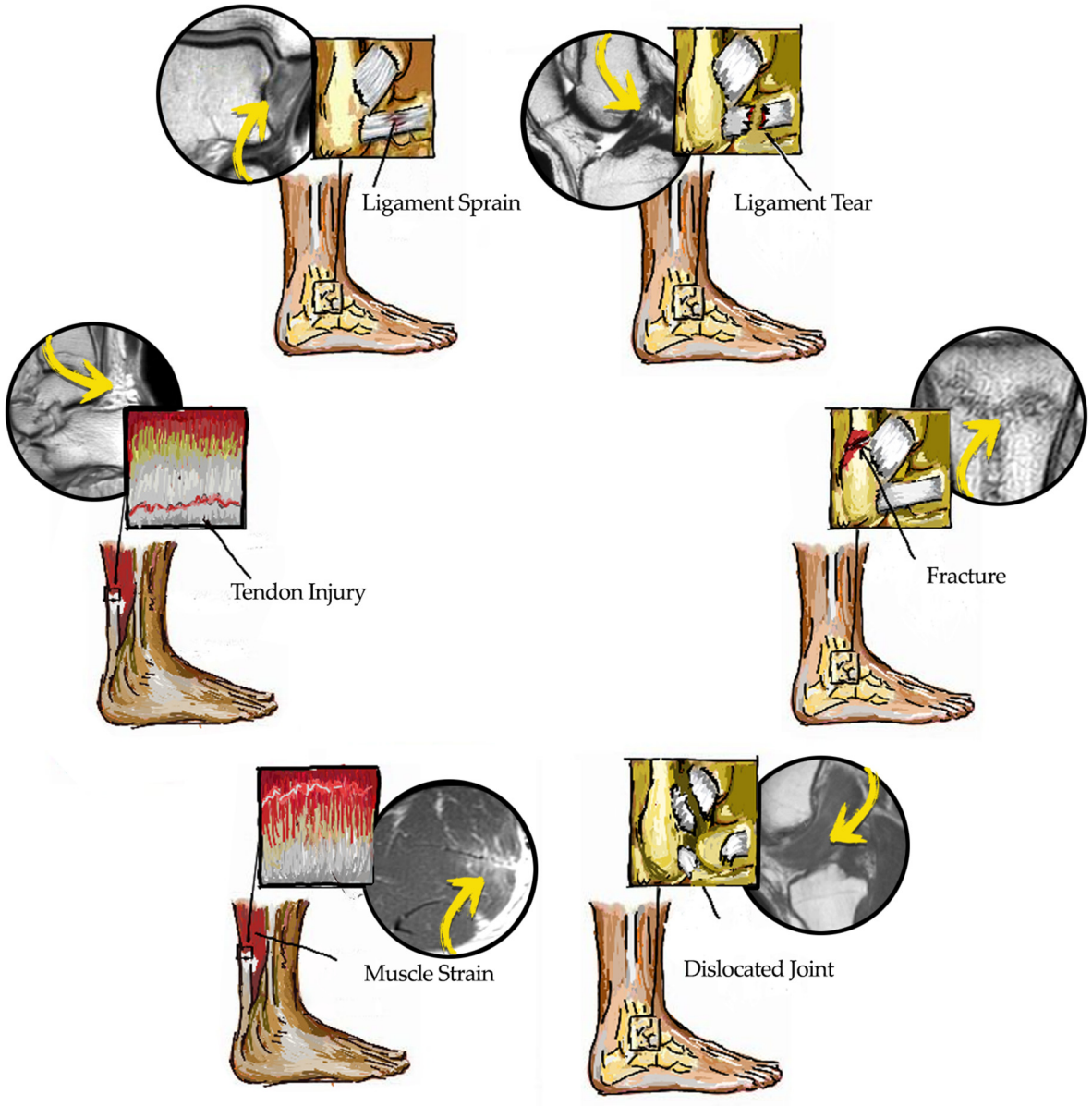


**Figure 1.** Main sports-related traumatic musculoskeletal injuries (graphical model and magnetic resonance imaging).

In further detail, the main painful sports-related traumatic injuries could include:

- *Ankle sprains:* These represent very common sports-related musculoskeletal injuries, especially in team sports [34]. An incidence of 3.1 per 1000 ankle sprains per season in elite athletes [35,36] is estimated. Recovery time and type of rehabilitation protocol are structured based on the severity of the injury. Unfortunately, the injury significantly predisposes the athlete to recurrent ankle sprains [37].
- *Knee injuries*: Anterior cruciate ligament (ACL) injuries are among the most disabling sports-related issues and occur in a range of 29 to 38 per 100,000 athletes [38,39]. However, other structures might be torn or overstretched during a knee sprain, resulting in injuries of posterior cruciate ligament, medial collateral ligament, lateral collateral ligament, or capsular sprain [40]. Nonetheless, meniscus injuries represent 8% of all seasonal injuries in professional football, since it is a sport characterized by pivoting and cutting movements [41].
- *Muscle injuries*: Muscle injuries represent one-third of sport-related injuries in soccer players and 92% of them affect hamstrings, adductors, quadriceps, and calf mus-

cles [42]. The pathological process can be characterized by direct trauma (muscle contusion) caused by a direct impact on soft tissues [43], or by indirect trauma (contraction-induced injury) due to severe mechanical stress on muscle fibers. In particular, the principal cause of indirect injuries is an excessive eccentric contraction or overstretching of the muscle, frequently related to rapid acceleration or deceleration [33,44]. To date, several classifications have been proposed to better characterize these injuries, and treatment and prognosis are based on the following classification [45–47].

- *Tendon injuries*: the most common acute tendon injury is the tendon rupture, due to an acute traumatic single event that leads to a singular macro-trauma on previously healthy tissue, not involved in chronic inflammation or a degenerative process [48]. The most common tendon involved is the Achilles tendon [49], and male and older athletes seem to be the most affected, reaching an incidence of approximately 40/100,000 persons per year [50]. Despite several approaches being proposed, surgical intervention is the most used in clinical practice, followed by an early functional rehabilitation program with evidence of a significant reduction in risk of recurrence [51].
- *Upper limb injuries*: Shoulder dislocations represent relatively common sports-related injuries, consisting 3.6% of all injuries in high school athletes, with an overall rate of 2.04 per 100,000 athletes [52]. They may occur when two or more bones are forced out of their normal position resulting in an abnormal and permanent separation in the joint. The shoulder dislocation represents 54.9% of dislocation in athletes [52,53]. Due to their traumatic etiology, dislocations are more frequent in sports with high risk of falling, such as rugby, hockey, and wrestling [54]. On the other hand, in the elite athlete, rotator cuff injuries can occur with acute episodes of direct contact trauma, a fall on an outstretched arm, and represent almost half (47%) of overall shoulder injuries per single season [55]. Medial ulnar collateral ligament (MUCL) injuries are described primarily as chronic progressive injuries but are underestimated as acute lesions in young athletes who play overhead sports [56].
- *Fractures*: Sport-related fractures, 5–10% of injuries in athletes, are very painful conditions, commonly resulting from a sudden trauma especially in contact sports or in sports with high risk of falls [57,58]. In this context, pain management plays a key role and requires specific strategies depending on the site of the fracture [59].

Therefore, alongside an adequate pain management, an optimization of the functional recovery and a safe RTP should be taken into consideration for athletes with sports-related injuries.

## 3. Analgesic Pharmacological Approach

The analgesic pharmacological approach historically represents the cornerstone of pain management for acute traumatic musculoskeletal injuries [25,60]. However, it should be noted that the pharmacological approach should be considered just one component in an integrated and multidisciplinary approach aimed at reducing physical impairment and optimizing functional recovery and RTP [61–64]. The IOC Consensus Statement [10] recommended that analgesic drug prescription should be performed targeting the lowest effective dose for the shortest period. Therefore, particular attention should be paid to minimize adverse risks and to achieve pain relief; furthermore, in the case of ineffective or intolerance to treatment, the drug should be discontinued [10].

Tissue location, type of injury, and pain severity significantly influence the treatment approach [65]. In this context, a recent review [23] underlined those minor injuries that might often be treated by non-opioid analgesic medication and non-pharmacological treatment; however, the effectiveness of this approach in different pathologies has not been deeply studied. In minor injuries, when same-day RTP is considered, oral or local analgesic drugs are routinely used according to the scientific literature that showed a positive effect [25,66–75].

Furthermore, when prescribing analgesic drugs, it is necessary to carefully consider different mechanisms of action and safety, as different pharmacological agents may be associated with different side effects [76]. According to the World Health Organization (WHO) pain ladder [77], non-narcotic analgesics may be used to manage mild to moderate pain. Nevertheless, the combination with narcotic analgesics may be performed to manage severe pain to obtain synergic effects [76]. To date, several options are currently available in the pharmacological non-invasive approach in acute traumatic injury, including paracetamol [78–81], non-steroidal anti-inflammatory drugs (NSAIDs) [80,82–85], and opioids [79–81,86–88].

- *Paracetamol*: one of the most common drugs routinely used for mild and moderate pain alone or combined with other pharmacological and non-pharmacological interventions [89]. In accordance with the WHO Pain Ladder Recommendations [89], it should be considered as a first-line treatment in mild pain. Furthermore, the safety of paracetamol at up to 3 g per day is well documented with studies reporting adverse effects compared to placebo [90,91]. In addition, studies comparing paracetamol to NSAID for treating pain after acute sport-related injuries did not report significant differences in term of effectiveness [92]. Similarly, a combination of paracetamol and NSAIDs might be more effective in pain relief, even if side effects might be more frequent [93].
- *NSAIDs*: This pharmacologic treatment is highly supported by the literature for pain management [80,82–85,94–96]; however, specific interventions including the exact time, dose, and duration of specific NSAIDs targeting a specific acute traumatic injury are still lacking. Apart from these limitations, NSAIDs are currently the most prescribed drugs in sport-related injuries, but another crucial issue is represented by the administration modalities.

In this context, a recent Cochrane review showed that topical diclofenac and ketoprofen could be effective in pain relief of acute sprains and strains [97]. Moreover, the intradermal absorption significantly minimizes the risk for adverse events, and the approximate benefit of 50% of pain relief after 1 week makes this treatment suitable as a first-line treatment for minor acute injuries [97,98]. To date, ketorolac is the most supported NSAID in acute pain management, as confirmed by a recent meta-analysis [99] highlighting the role of ketorolac in severe pain relief and an adequate safety profile if dismissed in 5 days. On the other hand, no randomized controlled trials (RCTs) have been performed supporting the ketorolac effects when compared to different NSAIDs. A recent report underlined a potential increase in the risk of post-traumatic hemorrhage and acute traumatic injuries, underlining that NSAIDs should be carefully administered in these subjects [100]. NSAIDs should be avoided in the first 72 h from brain concussion given the increased risk of bleeding [101]. In accordance, since inflammation has a crucial role in the first processes at the basis of tissue healing in the skeletal muscle system [68,102–105], the anti-inflammatory pharmacological approach has been recently questioned [68]. Moreover, NSAIDs mediate their pharmacological effects by the inhibition of prostaglandin synthesis in the COX pathway; therefore, a careful prescription of these drugs should consider the evidence highlighting the potential negative effects in bone, muscle, ligament, and tendon healing [68,102–105]. However, no studies assessed the long-term effects of NSAIDs in athlete global health, tissue overload on the kinetic chain continuum, injury recurrence, or complications related to pain relief effects [23].

- *Opioids:* These drugs should be prescribed in sports for major traumas that could be related to a high risk of bleeding and severe pain. Indeed, in these cases, NSAIDs did not represent a suitable option according to the WHO pain ladder recommendations [89]. In this context, the NICE guideline for major trauma in adults [106] supported the use of intravenous morphine as the first-line analgesic in the hospital or pre-hospital setting to achieve adequate pain relief without affecting blood coagulation. The IOC recommended that opioids should be considered for athletes only in case of severe

pain with the initial prescription not exceeding 5 days [107]. However, longer prescriptions have been reported despite the critical issue of risks of opioid dependence or addiction.

Rehabilitation might play a crucial role as a synergistic approach with the pharmacological therapy to reduce acute traumatic musculoskeletal pain. In this situation, instrumental physical therapies might be considered a complementary approach in both acute and chronic pain [108,109]. In addition, optimal pain management is a cornerstone of a proper rehabilitation plan, thus avoiding the psychological burden related to musculoskeletal pain and minimizing the fear of movement that might significantly affect the time of RTP and reinjury risk [110–112].

Moreover, treatment reducing deconditioning and enhancing physical performance should be considered even in the early stages of acute traumas [113]. Thus, the term "rehabilitation pharmacotherapy" has been recently introduced to characterize a specific pharmacological approach aimed at achieving the highest physical performance, physical function, and quality of life; a rehabilitative intervention that aims to influence the therapeutic approach, calming the multi-drug management [114]. Despite the studies supporting this approach mainly focused on older people [114,115], "rehabilitation pharmacotherapy" should be seriously considered in the pain management of sports athletes. Therefore, the pharmacological approach should not interfere with rehabilitation and RTP [114,115]. However, more evidence is needed to fully support this approach in athletes.

## 4. Invasive Pain Management: What Role for Infiltrations in Athletes?

Mini-invasive procedures are commonly used in clinical practice for chronic pain [109,116–118], but they are still not adequately investigated and performed for acute traumatic sports-related injuries [72,119,120]. In this situation, local anesthetic injections are frequently performed to ensure an anticipated or immediate RTP in elite athletes [121]. Drakos et al. [121] reported the effects of ultrasound-guided local anesthetic injections within 1 h of competition in patients suffering from muscle injuries and ankle sprains, demonstrating a high safety profile, and supporting their role in anticipated RTP.

To date, there is a lack of evidence on the impact of local anesthetic injections in acute sports-related injuries [122]. It is crucial that the type of the treatment should depend on the site of the injury [123–125]. However, the majority of evidence supporting corticosteroid injections for musculoskeletal pain involves non-athletes [126–130]. In addition, the corticosteroid effects in pain relief in acute sport-related injury are not fully supported by the current literature due to the potential interaction in physiological molecular pathways underpinning tissue healing [122,131,132].

Hyaluronic acid (HA) injection, notably, represents an effective and safe option in the treatment of articular pain in athletes, with recent evidence suggesting a potential effect in accelerating RTP [122,133]. To date, the Osteoarthritis Research Society International classification [134] reported that HA injections might be a recommended mini-invasive procedure to treat even early osteoarthritis in older athletes [122].

On the other hand, in young athletes, HA injection might have a role in multifactorial pain syndromes involving articular damage or cartilage involvement. In particular, the recent review by da Costa [135] supported HA injection in a multimodal treatment of patellar chondropathy. Moreover, given the lack of doping issues [136], HA injection represent a feasible and safe therapy for sport-related injuries in elite athletes [122,133]. However, in severely injured athletes, who have no benefit from conventional therapies, mini-invasive procedures should be taken into consideration [131,132].

Another technique that might be performed for acute pain in athletes is regional anesthesia, a procedure strictly linked to the type of injury; in particular, forearm nerve blocks or axillary blocks might be effective in pain management of hand and forearm fractures [137,138]. In addition, distal radius fracture management during reduction might involve hematoma block (achieving good results in pain relief) [58]. Similarly, sciatic nerve

blocks, adductor canal nerve blocks, fascia iliaca nerve blocks, and femoral nerve blocks have been demonstrated to be effective in specific pathologies to achieve adequate analgesia and reduce opioid medications after acute traumatic injuries requiring surgery [58,139–142]. Despite the promising effects of nerve block injections, some authors reported that regional anesthesia might mask compartment syndrome onset, therefore these procedures should be carefully performed [58].

However, it should be noted that, though nerve block might improve pain management and reduce oral medication [143–145], multimodal analgesia has been strongly recommended [146]. Therefore, mini-invasive procedures should be considered in a combination of pharmacological strategies to potentially reduce the side effects of monotherapy and improve pain management in acute injuries [146].

Moreover, infiltrations should always be framed within a comprehensive, multidisciplinary approach, including not only other pharmacological approaches but also non-pharmacological ones. Indeed, physical therapy might play a key role in pain control with growing evidence supporting its effects if combined with mini-invasive rehabilitative approaches [109,112,117,147]. To date, several reports suggested that physical activity might modulate pain perception modulating central nervous system excitability, and improving psychological constructs associated with pain [148,149].

On the other hand, rehabilitation might have several synergic effects with mini-invasive procedures, especially in athletes [150]. In more detail, pain control during rehabilitation might improve muscle tension, encourage realignment of the body, and prevent the fear of movement that affects functional outcomes and reinjury risk, potentially enhancing rapid recovery and RTP [151–153]. At the same time, physical therapy might induce pain relief by decreasing inflammation, increasing mobility, and decreasing overall pain levels with a high safety profile [112,154,155]. Moreover, considering the crucial issue of RTP in athletes, any therapeutic pathway should be integrated with treatment that enhances physical conditioning, including physical therapy, and retraining exercise [156,157].

In conclusion, rehabilitation represents a suitable therapeutic option in multimodal pain management (including infiltrations) for the management of musculoskeletal pain in athletes. However, these mini-invasive approaches should be safe, appropriate, and patient-tailored to optimize functional recovery and RTP in a comprehensive multimodal rehabilitation plan.

## 5. Return-to-Play after Trauma

RTP is crucial for elite athletes after an acute trauma, given the economic and competitive entanglements associated with absence for professional players [158]. Injury management should include proper pain management as a key step of a tailored intervention to enhance the RTP program [159]. Therefore, an evidence-based epidemiological report might guide physicians in the prognostic assessment to approach concerns from players, coaches, managers, media, and agents regarding RTP [160].

RTP may change according to the anatomical site and severity of the acute traumatic pain:

- *Ankle sprains:* Physicians should evaluate specific movements to determine appropriate RTP following an ankle sprain. Athletes should use a drop test to estimate the sportive gesture evaluation, considering muscle strength, proprioceptive balance, and joint range of motion [161]. In summary, appropriate RTP must be based on objective and scalable assessments that inform professionals about the future risk of injury. The experts' consensus indicates that RTP must focus on the sport gesture that the athlete requires in practice [161]. Unfortunately, due to the lack of evidence, each practitioner needs to establish an objective threshold for assessing a tailored RTP [162].
- *Knee injuries:* About half of athletes return to competitive sport after primary ACL reconstruction [163]. Regardless of treatment, the RTP rate is affected by factors including specific sport demands and regional differences. RTP rates are lower after revision

ACL reconstruction than after primary surgery [164]. Interestingly, the duration of RTP after an ACL reconstruction has a high variability in male professional football players, but, independent of this time, only a minority of athletes return to their pre-injury level 1 year after surgery [165]. However, the mean lay-off time in professional football for all Medial Collateral Ligament (MCL) injuries is 23 ± 23 days [166] given that MCL injuries can be managed conservatively, though grade III MCL injuries or involvement of the deep MCL and/or the posterior oblique ligament are associated with longer recovery time. Lastly, athletes requiring lateral meniscus treatment have longer recovery times and lower RTP rates than athletes who require medial meniscus treatment [167].

- *Muscle injuries:* Acute hamstring injury is the most frequent non-contact muscle injury in sports involving high-speed running, with a consistently high incidence and high reinjury risk [42,168,169]. Given the high heterogeneity of injury location and severity, time to RTP after acute hamstring injuries varies substantially from an average of 11.3 days to 50 weeks [170]. Among professional football players, the mean lay-off time was shown to be around 20 days [167]. On the other hand, total proximal hamstring ruptures might represent the highest grade of muscle injury, requiring surgery; therefore, RTP duration sensibly increases and is generally allowed after 6–9 months [171]. Intriguingly, there is currently no strong evidence that Magnetic Resonance Imaging (MRI) could be a predictive factor for RTP [172,173]. However, RTP is not a major issue in acute hamstring injuries because close to 100% of athletes RTP after an injury [174].
- *Tendon injuries:* The Achilles tendon is one of the most injured tendons in athletes involved in running and jumping activities [174]. It has been estimated that between 10 and 86% of athletes have RTP after 12 weeks of treatment for Achilles tendinopathy. However, up to half of athletes have a recurrence of Achilles tendinopathy after RTP [174]. After Achilles tendon rupture, 29–87% of athletes return to their pre-injury level [175]. Nevertheless, rehabilitation exercises are the cornerstone of RTP in Achilles tendinopathy, given that those who follow a standardized load progression have fewer incidences of recurrence compared with those who do not follow a progressive loading program [176]. Apart from these findings, permanent deficits in calf muscle strength and tendon elongation can be very common after Achilles tendon rupture [177]. Therefore, it is particularly important that athletes with Achilles tendinopathy undergo a full progressive loading program prior to clearance to RTP [176]. On the other hand, there are no milestone-based criteria for RTP following Achilles tendon rupture. The time-based criteria for non-contact sports are resumption from 16 weeks following injury and for contact sports from 20 weeks after injury [178].
- *Upper limb injuries*: Shoulder dislocations represent the most common site of dislocation in athletes. Nevertheless, little evidence exists regarding the physical RTP criteria of the shoulder after injury [179]. In more detail, nonoperatively treated shoulder instabilities that sustained shoulder subluxations returned after an average of 3.6 weeks, compared with 7.6 weeks in those who sustained a shoulder dislocation [179]. Players experiencing shoulder dislocations were found to miss more time before RTP and were more likely to undergo surgical intervention compared with those who experienced a subluxation [180]. A recent review [181] demonstrated no overall difference in the rate of RTP or patient-reported outcomes following arthroscopic Bankart repair, the Latarjet procedure, and open stabilization [182]. Return to the same level of play after surgical repair of full-thickness tears in professional overhead athletes has been unpredictable and often this kind of injury is career-ending; arthroscopic repair of full-thickness tears in professional baseball players allowed 83% to return to play, but few with pre-injury levels of competition [55]. Regarding MCUL, it is well known that operative treatment represents the gold standard for professional players, but, to date, there is no consensus on which approach (i.e., conservative or surgical) represents

the best choice for high-performance-demand athletes given the poorly predictable RTP [56].

- *Fractures*: Sports-related fractures may have critical implications for athletes. Fracture management tends toward preserving soft tissue, which is critical for an early recovery in the athletic population [58,183]. Given the breadth of circumstances faced during athletic activity, there is no patterned algorithm for defining a player's readiness to RTP after a fracture. Nevertheless, an athlete should be pain-free, neurologically unimpaired, and without deficits of strength or range of motion before returning to sport [184,185].

## 6. Antidoping Issues in the Pain Management of Athletes

Pain management has constantly influenced athletic conditions, thus making necessary the publication of a prohibited substances list by the World Anti-Doping Agency (WADA) [186].

In this context, doping indicates the presence, use, possession, or trafficking of a prohibited substance. Evidence suggests that currently banned narcotic analgesics (opioids) and cannabinoids are not ergogenic but ergolytic [84,186]. Indeed, both can be prescribed by a physician for pain control, but both can be obtained illegally and carry potentially serious health risks, including addiction.

In contrast, the most used analgesics, including non-steroidal anti-inflammatory drugs, acetaminophen, local anesthetics, and tramadol are not forbidden according to the WADA list of prohibited substances [84,186]. However, potential ergogenic effects of NSAIDs in sports performance have been recently reported, and, unfortunately, a significant difference between the use of NSAIDs in-competition vs. out-of-competition has been demonstrated, probably related to the postulated effects in improving physical performance [186–191]. Interestingly, performance enhancement seems to be related to the widely noted antalgic effect, which might improve exercise-induced pain level tolerance with consequent positive effects in sports performance [190]. Despite these considerations, the ergogenic effects of NSAIDs have not been supported by strong evidence and these molecules are still not considered forbidden [186].

Moreover, one of the most used methods to control pain is the injection of a local anesthetic, which raises little controversy in sport compared to opiate management, a currently contentious topic perhaps given the epidemic of opiate abuse in some regions of the world [190]. Indeed, although tramadol is not on the list, it may sometimes be abused, such as in cycling [191]. There is a solid argument that all opioids and cannabinoids should be available to the practitioner, but with a remarkably close window for managing these substances in elite competitors [192,193].

## 7. Conclusions and Future Perspectives

In this comprehensive review, we summarized the state-of-the-art in pharmacological intervention efficacy on the pain management of acute sport-related injuries in athletes. Moreover, we highlighted the need for an effective assessment and management of musculoskeletal disorders to obtain a prompt RTP. Intriguingly, there is still a large gap of knowledge in drug-induced pain relief in athletes in terms of kinematic and physical performance.

However, the optimal strategy to manage sport-related injuries should include not only pharmacological interventions but also tailored exercise prescription and load management and rehabilitation. These interventions should be performed by medical, sports science, and technical staff to provide the most effective management of sport-related acute injuries.

To date, evidence about the impact of pharmacological approaches on acute traumatic injuries in terms of kinematic outcomes, RTP, and long-term well-being of athletes is far from being fully established. Therefore, further high-quality studies (both systematic reviews and RCTs) focusing on the most effective rehabilitative and pharmacological interventions to treat acute sport-related injuries are warranted. This could provide evidence to

guide physicians in the comprehensive clinical and rehabilitative management of acute traumatic sports-related injuries.

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# Muscle Regeneration and Function in Sports: A Focus on Vitamin D

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**Abstract:** Muscle is one of the main targets for the biological effects of vitamin D. This hormone modulates several functions of skeletal muscles, from development to tissue repair after injury, through genomic and non-genomic mechanisms. Vitamin D deficiency and supplementation seem to significantly affect muscle strength in different populations, including athletes, although optimal serum 25(OH)D3 level for sport performance has not been defined so far. Additionally, vitamin D deficiency results in myopathy characterized by fast-twitch fiber atrophy, fatty infiltration, and fibrosis. However, less is known about regenerative effects of vitamin D supplementation after sport-related muscle injuries. Vitamin D receptor (VDR) is particularly expressed in the embryonic mesoderm during intrauterine life and in satellite cells at all stages of life for recovery of the skeletal muscle after injury. Vitamin D supplementation enhances muscle differentiation, growth, and regeneration by increasing the expression of myogenic factors in satellite cells. The objective of this narrative review is to describe the role of vitamin D in sport-related muscle injury and tissue regeneration.

**Keywords:** vitamin D; satellite cells; skeletal muscle; muscle fibers; skeletal; return to sport; sports; athletes



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## 1. Introduction

Since its identification as an effective cure for nutritional rickets, much of the scientific research on the biology of vitamin D is directed at its role in controlling the homeostatic mechanisms of calcium. The discovery that the vitamin D receptor (VDR) is widely expressed in many tissues has prompted a series of studies aimed at understanding its roles in physiological responses unrelated to calcium homeostasis. In the last few decades, huge attention was paid to the biological functions of this secosteroid on skeletal muscle physiopathology, from contraction to tissue regeneration after immobilization or injury [1,2]. The physiological effects of vitamin D, in muscle as in other tissues, involve genomic and non-genomic mechanisms that are related to each other in crosstalk in the intracellular signaling mechanisms of vitamin D [3,4]. Thousands of vitamin D-responsive genes were identified (e.g., calbindin-D9K, osteocalcin, osteopontin), many of which are key players in skeletal muscle health being involved in protein synthesis and muscle performance [5]. Experimental data showed that serum 25(OH)D3 and vitamin D supplementation significantly affect muscle strength in several populations, such as older and younger people [6–12]. Indeed, vitamin D receptor (VDR) is widely expressed on the skeletal muscle cells, with potential effects on the de novo protein synthesis, thus contributing to the muscle hypertrophy [13]. Moreover, among the non-genomic effects of VDR, an improvement of muscle contraction was observed, due to the modification of intracellular calcium fluxes and enhancement of the interaction between myosin and actin in the sarcomere, a crucial event for muscle function [14].

Vitamin D deficiency was also observed among athletes, not only in those practicing indoor activities (e.g., basketball and dance) [15], but also in football and soccer players [16].

In athletes, vitamin D deficiency may be attributable not only to training settings (indoor vs. outdoor), but also to timing of training (early- or late-day), geographic location, skin pigmentation, and sunscreen use [16].

In this context, a key issue is the definition of both vitamin D status (i.e., serum 25(OH)D3.) and optimal levels, particularly among the athletes.

In the general population, concentrations of >30 ng/mL are considered acceptable in terms of benefits on bone health. On the other hand, the specific threshold for reaching optimal sport performance is not established in athletes [17]; although, vitamin D supplementation is required for values below 12 ng/mL [14,18].

Historically, it was well known that vitamin D deficiency is characterized by myopathy (i.e., rickets-associated myopathy) with muscle fiber atrophy accompanied by fatty infiltration and fibrosis, particularly affecting fast-twitch muscle fibers (i.e., type II), with consequent slow peak muscle contraction [19]. Moreover, immunomodulatory effects of vitamin D might be also useful to counteract increased pro-inflammatory cytokines (e.g., TNF-α) after intense exercise [20].

Although evidence suggests multiple benefits of vitamin D supplementation for skeletal muscle to improve athletic performance [16], less is known about the muscle regenerative effects of this hormone after sport-related injuries. Athletes are the individuals most exposed to muscle damage, considering its occurrence after bruising or because of high-intensity resistance training, particularly eccentric exercise [21,22]. Therefore, this narrative review aims to elucidate the role of vitamin D in the pathophysiology of muscle injury and tissue regeneration with a focus on sport.

## 2. Vitamin D and Skeletal Muscle: Basic Concepts

The striated muscle represents about 40% of the total body mass and is critical for the posture and global and selective body movements [23]. Muscle fiber is the basic functional unit of striated muscle and is composed of syncytium of multinucleated cells. Muscle fibers have different properties and are classified according to their metabolic activity and the consequent contraction type and speed. Type I fibers are characterized by an oxidative metabolism that produce energy to support a protracted and fatigue-resistant contraction. Fast twitch (type II) fibers can be glycolytic and oxidative (fast-twitch oxidative, FOG) or glycolytic only (fast-twitch glycolytic, FG) and are involved in faster contraction [24,25]. Striated muscles contain different percentages of fiber type which determine huge differences in contraction speed and muscle strength [26,27]. Furthermore, the functional activity of the muscle fibers changes over time since they can change in size and even convert from one type to another to adapt to different functional requirements [28]. Muscle responds to various biochemical stimuli. Due to its characteristics as an organ that produces and responds to various substances present in the blood circulation, the muscle is now identified as an endocrine organ [29]. In fact, it modifies its structural and functional features in response, for example, to changes in the serum levels of insulin, GH (growth hormone), glucocorticoids, thyroid hormones, and vitamin D [1,30–33]. In turn, the muscle produces some substances with endocrine activity (i.e., myokines) which have systemic effects modulating glucose uptake, fat oxidation, gluconeogenesis, bone mass and fracture healing [34]. Among several hormones affecting striated muscle, vitamin D influences its structure and function during the different stages of life, starting from embryonic development up to ageing, and it is involved also in the mechanisms of muscle repair after trauma [2,7–10].

Vitamin D receptor is localized both in the cytoplasm and in the nucleus of muscle fibers, to mediate non-genomic and genomic actions [35,36]. Moreover, the amount of VDR is significantly higher in immature myoblasts and muscle cell precursors than in differentiated myotubes or mature muscle fiber [37]. It should be emphasized that in adult animals that suffered muscle injuries, or that were subjected to stressful physical exercise, there was a significant upregulation of the VDR on the muscle fibers being repaired, confirming a prominent role of vitamin D both on cellular precursors and on

muscle fibers during tissue regeneration [38]. Vitamin D acts on muscle tissue mainly through two mechanisms, by activating specific areas of the genome (genomic pathway) with consequent structural and functional plastic modifications of the muscle in the long-term, and by a faster mechanism (non-genomic pathway) that affects muscle contraction through the modification of intracellular calcium fluxes [3]. In more detail, through the genomic pathway, vitamin D stimulates the proliferation and differentiation of muscle cells by modulating gene transcription in myoblasts, resulting in an increase in the synthesis of specific muscle proteins, such as myosin and calcium-binding protein. 1α,25(OH)2D3 enhances muscle differentiation, growth, and regeneration by increasing the expression of several myogenic factors (i.e., MYOD, MYOG, MYH1, and MYC type II, muscle troponin I and T) in satellite cells as well as of other key factors involved in muscle growth and regeneration (i.e., IGF, FGF, and TGF-β) [39].

In addition to modulating calcium absorption, vitamin D participates in the metabolism of phosphate for cellular energy needs [40]. Through the non-genomic pathway, vitamin D regulates the calcium-mediated action of second messengers to enhance muscle contraction. The 1,25-(OH)2D3 acts on the SOC/TRPC3 dependent voltage channels to regulate the intracellular levels of calcium and, therefore, the excitation–contraction coupling [3]. The beneficial effects of vitamin D on the skeletal muscle depend also on other mechanisms that significantly affect muscle microarchitecture and physical performance. This hormone inhibits the differentiation of myogenic precursors into adipocytes thus limiting the accumulation of intra- and intermuscular fat [41]. Moreover, vitamin D modulates the main negative regulator of muscle growth, the myostatin [42]. In particular, 1α,25-(OH)2D3 increased the expression of follistatin (FST), an inhibitor of myostatin, and reduced the expression of myostatin in satellite cells [39].

## 3. Vitamin D and Sport-Related Muscle Injury: From Biology to Clinical Practice

The role of vitamin D in muscle development is clearly suggested by the early presence of VDR in the embryonic mesoderm and in muscle precursor cells (i.e., satellite cells) at all stages of life [43]. It is evident that this hormone must necessarily play a leading role both in the formation and growth of the muscular system during intrauterine life and in the clinical recovery of the skeletal muscle after a trauma that has altered its structure and/or function. If we consider that the increased expression of VDR in cultured C2C12 cells (myoblasts) treated with 1α,25(OH)2D3 and 25(OH)D3 alters their proliferation and differentiation [44], it might be hypothesized that vitamin D deficiency can cause an impairment in the healing process in patients who have suffered a direct trauma or have sustained a damaging functional stress (e.g., eccentric exercise). The expressions of VDR and 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) were demonstrated in myoblasts and myotubes [45]. VDR is localized in nuclei of myoblasts, and in cytoplasm of myotubes, probably because of the increased expression of RXR in myotubes that is associated with increased cytoplasmic localization of VDR [46]. However, increased nuclear VDR was documented in myotubes treated with calcitriol. 25(OH)D3 inhibited myoblasts proliferation and increased VDR expression, suggesting the conversion of 25(OH)D3 to 1α,25(OH)2D3. However, the growth-suppressive effect of 25(OH)D3 on the myoblasts was dropped after the inactivation of the CYP27B1, suggesting a key role of 1α- hydroxylase in modulating the proliferation of muscle cells by 25(OH)D3. Moreover, VDR and CYP27B1 were significantly upregulated in myonuclei and cytoplasm, respectively, of the regenerating muscle fibers [45].

Even negligible muscle injuries, such as acute microinjury during resistance training, increase VDR and CYP27B1 suggesting the enhanced sensitivity of injured and healing muscle to vitamin D [47]. Morphological changes occur in muscle fibers after acute trauma or during eccentric contraction, such as myofiber necrosis and inflammatory responses that result in the widening of perimysium among fascicles, and the separation of myofibers within the same fascicles [48]. Muscle regeneration is a complex process based on the activation, differentiation, and formation of new myofibers from muscle-specific stem cells (i.e., satellite cells) under the control of the myogenic and mitogenic regulatory factors [49].

The satellite cells are located between the muscle fibers and the basal membrane, and they can be activated when necessary, making the muscle able to heal after tissue damage. After trauma, satellite cells are activated and guide muscle repair. Their activation and differentiation are regulated by complex paracrine signals from neighboring cells (e.g., fibroblasts, endothelial cells, and macrophages), intracellular signals (e.g., Wnt and Notch) [50,51], myogenic regulatory factors (e.g., myf5 and myoD) [52]. After activation, the satellite cells can replicate and some of them differentiate into myoblasts, based on the expression of Pax7 compared to myf5 [49]. Activated satellite cells differentiate into myoblasts and myocytes that express specific markers (i.e., (Pax7+, Myf5+, and MyoD+ in myoblasts, and Pax7−, MyoD+, myogenin+, and MRF4+ in myocytes) [53]. Finally, fused myocytes form multinucleated myotubes that mature into myofibers. To specifically address muscle repair after exercise-related tissue injuries, Hyldahl et al. investigated satellite cell activity and inflammatory milieu in human skeletal muscle following eccentric (ECC) or concentric contractions (CON). They found that only ECC induced high levels of Xin (i.e., striated muscle-specific protein) in the sarcolemma, and inflammatory cytokines, such as interferon gamma-induced protein 10 (IP-10) and monocyte chemotactic protein 1 (MCP-1). Moreover, ECC-induced muscle damage significantly increased satellite cell proliferation (+27%) compared to CON in the early phase of injury (24 hrs) [54]. After muscle damage, several growth factors are released activating nuclear pathways in quiescent satellite cells [55].

Vitamin D modulates muscle repair by regulating satellite cell proliferation and differentiation as well as mitochondrial density and function [56]. VDR and Pax7 are colocalized in the nuclei of satellite cells. After muscle injury, overexpression of both VDR and Pax7 occurs, resulting in inhibition of proliferation and stimulating differentiation of satellite cells [46,57,58]. Increased expression of VDR after muscle injury also positively affects mitochondrial health by increasing biogenesis and reducing oxidative stress. Moreover, administration of vitamin D inhibits proliferation and increases differentiation of myoblasts as well as oxygen consumption in mitochondria, that might be the fuel for myotube formation [59]. Whereas vitamin D deficiency adversely affects mitochondrial function by reducing adenosine triphosphate (ATP) production and increasing oxidative stress, as demonstrated in VDR-knockout myoblasts [60], thus hindering muscle regeneration. Mitochondrial function is critical for muscle repair after injury considering its role in modulating satellite cells activity [61], as demonstrated by reduced oxidative capacity in quiescent satellite cells [62]. Moreover, modulation of mitochondrial mitophagy seems to be necessary to satellite cell function, as demonstrated in mouse models knock-out for Parkin, an E3 ubiquitin ligase [63], that showed reduced differentiation of satellite cells and, consequently, poor muscle regeneration. These data confirm that mitophagy favors the increase and maintenance of the satellite cells pool.

Traditionally, the role of vitamin D in calcium metabolism was widely investigated, whereas the effect of this hormone on phosphorus metabolism was not addressed so extensively and dates back mainly to the 1970s and 1980s, although the effects of vitamin D on skeletal muscle were attributed to the modulation of phosphate metabolism [64,65]. Phosphate is an essential substrate for ATP production and protein synthesis. The treatment of vitamin D deficient rats and chicks with 25(OH)D3 resulted in a significant increase in phosphate uptake and stimulation of ATP synthesis in muscle cells [64]. The active form of vitamin D [i.e., 1α,25(OH)2D3] seems to significantly affect mitochondrial health in muscle cells by modulating calcium metabolism. Animal (i.e., chicks) and human models of vitamin D deficiency demonstrated both impaired oxidative phosphorylation and calcium uptake in muscle mitochondria [66,67]. On the other hand, muscle cells exposed to 1α,25(OH)2D3 increased oxygen consumption and ATP production, while no effect was reported by administrating 25(OH)D3. However, these effects were not observed after the direct treatment of mitochondria with 1α,25(OH)2D3, suggesting a VDR-dependent mechanism [68].

Vitamin D supplementation also mitigates the effects of muscle damage secondary to high intensity exercise as demonstrated in both animal and human studies (on Sprague–Dawley rats and young men, respectively) [69,70]. During a muscle injury, administration of vitamin D reduces the production of stress-related proteins (p38 MAPK, ERK1/2, IKK, IkB), inflammatory cytokines (TNF-α, IL-6) and oxidative stress [69]. Moreover, a more rapid recovery of the contractile force of the damaged muscle after vitamin D supplementation was reported [71], whereas, in an experimental model of C57BL/6 mice with an induced muscle injury, excessive doses of 1α,25(OH)D3 or its intramuscular administration did not have beneficial effects on muscle regeneration but can even negatively affect the activity of satellite cells thus compromising the formation of muscle fibers [57].

In Figure 1 is reported a summary of multiple vitamin D-mediated mechanisms affecting skeletal muscle health.

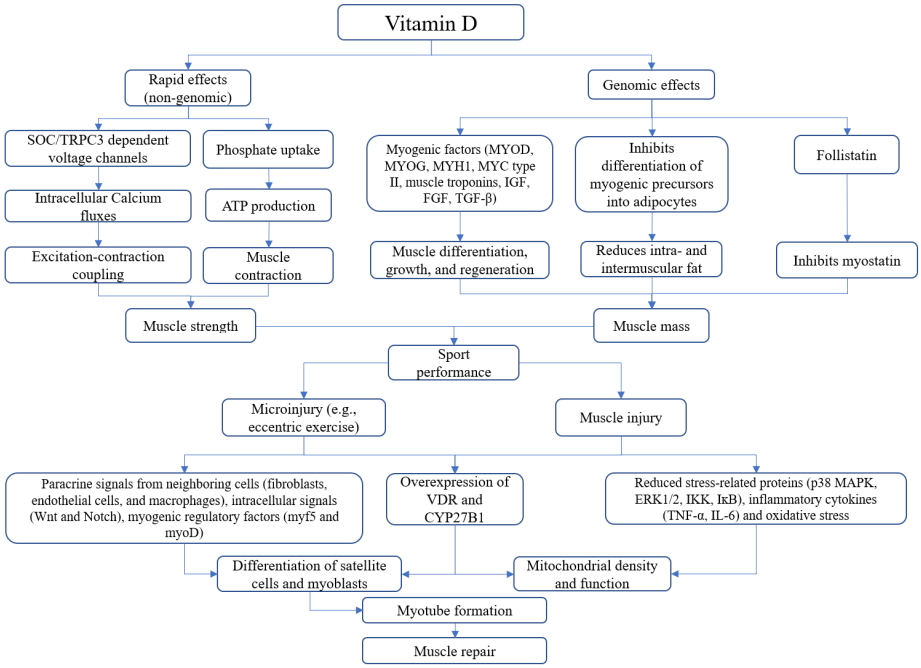


**Figure 1.** Vitamin D-mediated mechanisms affecting skeletal muscle performance and healing. Vitamin D produces non-genomic effects that affect calcium and phosphate uptake within muscle to sustain contraction, while long-term effects (genomic) of this hormone influence the release of myogenic factors and reduce the accumulation of fat tissue within muscle fibers as well as muscle catabolism. After direct or indirect muscle injury, three main events occur: paracrine signals by neighboring cells stimulate the release of myogenic mediators, overexpression of VDR and CYP27B1 and reduction of oxidative stress.

Even in humans, vitamin D status significantly affects muscle repair after injury. It was documented that the serum levels of 25(OH)D3 before exercise are inversely related to post-exercise muscle weakness in a healthy adult male population [71]. Interventional studies have reported a beneficial effect of vitamin D supplementation on muscle recovery in adult males exposed to muscle injury from repetitive eccentric contractions [71]. As is known, vitamin D deficiency contributes to muscle wasting by promoting oxidative stress, mitochondrial dysfunction, reduction of superoxide dismutase (SOD), and favoring the production of free radicals within muscle fibers [72]. Normalization of the vitamin D status in severely deficient subjects significantly improves mitochondrial function and oxidative phosphorylation of muscle fiber after exercise [66]. Furthermore, vitamin D supplementation might reduce muscle fatigue since serum levels of 25(OH)D3 are inversely correlated with those of lactic acid, creatine kinase (CK) and total antioxidant activity after exercise [73].

Another issue to be clarified is the effect of initiation timing of vitamin D treatment after injury, as suggested by experimental data. Subcutaneous administration of cholecalciferol to male Wistar rats soon after crush injury resulted in enhanced proliferation of immune cells, such as macrophages, as well as satellite cells, along with a reduction of cell apoptosis that preserved muscle structure [74]. However, delayed intramuscular administration of calcitriol decreased satellite cells differentiation and increased muscular fibrosis [57].

The serum 25(OH)D3 is a key issue to be considered in the context of vitamin D treatment. Young males with vitamin D deficiency undergoing exercise-induced muscle injury received cholecalciferol (4000 IU daily for 6 weeks) showed significant recovery of peak torque at 2- and 7-days post exercise [75]. Moreover, myoblasts from biopsies of the same population received mechanical injury and were cultured with calcitriol. This intervention improved myotube fusion and hypertrophy at 7- and 10-days after injury. These findings suggest potential benefits of treating vitamin D deficiency in athletes. Interestingly, vitamin D status seems to be involved also in the occurrence of sport-related muscle injury, as suggested by a study including National Football League (NFL) players [76]. In this cohort, vitamin D deficiency significantly increased the risk of strain at lower limb or core muscles (Odds Ratio, OR 1.86), particularly at hamstrings (OR 3.61) compared to athletes with normal serum 25(OH)D3. Similar findings were reported also in swimmers, where low serum 25(OH)D3 levels increased the risk of muscle injuries (+77%) [77]. Vitamin D supplementation reduced the risk of muscle injury also in elite ballet dancers [78]. These athletes received oral supplementation of cholecalciferol (2000 IU per day) for 4 months during winter, reporting fewer muscle injuries compared to controls that did not receive vitamin D [78]. Moreover, increasing serum 25(OH)D3 reduces muscle weakness after exercise-induced muscle injury, thus reducing recovery times [79]. Finally, the vitamin D status should not be overlooked also during periods of inactivity due to the sport-related injury. Experimental data suggest that vitamin D deficiency worsens immobilization-induced muscle wasting. In VDR-knock-out mice models, limb immobilization resulted in more severe muscle atrophy than controls. Interestingly, more pronounced muscle atrophy and increased expression of pro-inflammatory cytokines promoted by immobilization (i.e., TNF-α) were reported in mice with neural crest-specific VDR-deficiency compared to those with muscle-specific VDR-deficiency. This finding opens new scenarios on the role of the vitamin D system as a regulator of muscle mass through its action on the central nervous system [80].

## 4. Conclusions

Vitamin D has documented effects on muscle regeneration through mechanisms and biological pathways that mainly depend on the interaction with the pool of satellite cells within muscle and that are particularly active during recovery from a traumatic event to enhance the structural and functional restoration of the muscle. However, the number of studies addressing the role of vitamin D on muscle repair in athletes is relatively small and well-designed randomized controlled trials are lacking. Therefore, future research should be directed to improve knowledge about the clinical benefits of vitamin D supplementation in sport-related muscle injury.

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# Therapeutic Exercise and Conservative Injection Treatment for Early Knee Osteoarthritis in Athletes: A Scoping Review

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**Abstract:** *Background and Objectives*: Recent evidence highlighted a higher prevalence of knee osteoarthritis (kOA) among young and former ex-professional athletes. Although the practice of a highly demanding sport is considered a predisposing factor for the knee joint cartilage degeneration, articular cartilage seems to positively respond to a moderate load increase. We aim to investigate recent evidence on the conservative management of early kOA in athletes, with a particular emphasis on therapeutic exercise and injection treatment, in order to highlight whether there are any indications that can influence clinical and rehabilitation practice. *Materials and Methods*: A scoping review was conducted, screening MEDLINE and PEDro databases for studies published over the past twenty years on the topic. Studies in English, with accessible abstracts, were included in the review. The PICO framework was used (P—patient: athletes, I—Intervention: conservative treatment with therapeutic exercise or injection therapies, C—Comparison: not needed, O—Outcomes: clinical outcomes). Clinical trials, randomized controlled trials, and longitudinal studies were considered. *Results*: Four studies were finally included in the review. Therapeutic exercise seems to have beneficial effects on prevention of cartilage degeneration, on pain reduction, and on physical function enhancement. On the other hand, in mild to moderate stages of kOA the intra-articular viscosupplementation with Hyaluronic Acid showed a medium to long-term improvement in joint pain and function. The Platelet Rich Plasma treatment also showed a significant improvement in pain and function up to 12 months. *Conclusions*: Despite the heterogeneity of the studies considered, a multimodal treatment combining therapeutic exercise and moderate aerobic activity (such as running) should be indicated to prevent kOA development. In cases of symptomatic kOA it may be indicated to add minimally invasive injection therapy that seems to contribute to the improvement of motor function and symptomatology.

**Keywords:** sport; professional athletes; early osteoarthritis; therapeutic exercise; physical activity



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## 1. Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease of an inflammatory nature that is characterized by changes in the articular cartilage, the presence of fibrillation area, and cracking and thickening of the subcondral bone [1]. It is considered as the most common form of arthritis [2] and it represents a major cause of disability worldwide, affecting more than 240 million of people and causing symptomatic and activity-limiting concerns [3]. OA is strongly associated with aging and typically affects the knee, hip, spine, and hands, having a considerable impact on costs and mortality rate.

In particular, people affected by hip and knee OA have approximately a 20% higher mortality rate compared with age-matched controls [1]. It has been calculated that in the United States, direct medical costs OA-related exceed 100 billion dollars [4].

Knee osteoarthritis (kOA) is present in 30% of individuals older than 45 years, presenting radiographic evidence of knee OA, of which about a half suffer from OA symptoms [5].

Risk factors for kOA include older age, obesity, and female gender [2,6,7]. However, OA is increasingly being reported in the young and in athletic populations [8].

Luyten et al. first proposed the definition and the classification criteria of early OA [9]. This condition is characterized by knee pain, radiographic evidence of Kellgren–Lawrence grade 0 or 1 OA, and at least one of the two following structural criteria: arthroscopic findings of cartilage lesions, MRI findings of articular cartilage degeneration and/or meniscal degeneration, and/or subchondral bone marrow lesions [9]. This is particularly detectable in active and sportive individuals, since signs and symptoms often become manifest only after long periods (and mostly in high-impact loading activities such as running, jumping sports, etc.) [9].

The intensity and the duration of active participation in sport activities seem to be related to the risk of developing OA [10]. Particularly, athletes who practice sports including rapid acceleration with instant deceleration or continuous training with high impact on joints, or those who compete at a professional level for prolonged periods of time, present a greater risk of developing OA [11].

Tran et al., in an extensive systematic review, suggested that the risk of OA may be associated with the type of sport [12]. The occurrence of early kOA, both in amateurs and in professional athletes, has been widely described [13–15]. Since previous studies demonstrated that an active lifestyle could protect against the risk of OA development, the Osteoarthritis Systematic International Review and Synthesis Organization (OASIS) stated that the risk of OA is more likely associated with sport trauma rather than with sport activity [10,16]. The anterior cruciate ligament (ACL) and the menisci are the two intra-articular structures more frequently injured following sports trauma and their damage represents a predisposing factor for the risk of OA development [17]. Although post-traumatic osteoarthritis (PTOA) following acute injuries is well recognized, it is assumed that repetitive microtraumas of the joint surface could also be a leading cause of OA, an excessive mechanical stress that can directly damage the articular cartilage and, consequently, negatively alter chondrocytes' function [18].

The diagnosis of kOA can usually be made by anamnesis and clinical examination revealing knee pain, stiffness, and functional limitation. Radiograph evaluations confirm the physical exam demonstrating the presence of joint space narrowing, marginal osteophytes, subchondral bone sclerosis, and cysts. However, previous studies demonstrated that the damage of the cartilage commonly begins when limited and sporadic symptoms are present, and radiographs alterations are not still detectable [19]. Therefore, since the outcomes may be different depending on the stage of disease evolution, identifying and treating subjects at risk for progression at the early stages could guarantee a better result.

The treatment of kOA requires a multimodal approach including non- pharmacological, pharmacological, and surgical interventions on the basis of disease's severity and patient's symptoms [20]. However, most guidelines agree in "core" treatment recommendations for all subjects affected by kOA [21]. Early management requires patient's education and lifestyle changes with the aim of reducing the mechanical joint load [22,23]. Clinicians are encouraged to provide their patients with necessary information about OA disease progression and self-care techniques, including muscle strengthening, weight management, knee braces for support [24]. Moreover, behavioral intervention represents a useful tool to manage pain, fear, stress, depression, and anxiety in selected individuals [25].

Despite poor evidence in the literature, physical therapies are widely used as additional strategies for the management of kOA. Based on the data of a recent systematic review, hich analyzed the effectiveness of physical agents in the management of patients with early OA, transcutaneous electrical nerve stimulation (TENS) and pulsed electromag-

netic fields stimulation (PEMFS) demonstrated a pain-relieving action and a beneficial effect on joint function, quadriceps strength, physical performance, and quality of life [26]. Moreover, especially in early-stage OA, functional orthoses could play a role in the management of pain symptom. Both soft-braces and kinesio taping have shown to reduce pain and improves knee joint stability by stimulating cutaneous mechanoceptors and enhancing muscle performance in subjects with kOA [27,28].

Guidelines highlight the importance an active lifestyle by limiting sedentary behavior and promoting physical exercise [23,29,30]. However, methods concerning how to achieve this are still unclear.

To the best of our knowledge, there are no comprehensive reviews focused on therapeutic exercise and conservative injection treatment in athletes with early OA. We therefore investigated the most recent research on the conservative management of early kOA in athletes, with a particular emphasis on therapeutic exercise and injection treatment, in order to highlight whether there are any indications that can influence clinical and rehabilitation practice.

## 2. Materials and Methods

### *2.1. Search Strategy*

The authors, having clinical and research experience on the topic, formulated a research question defined as follows: What is the most recent evidence for the role of therapeutic exercise or injection therapies in athletes with early OA or predisposing conditions for OA?

The authors followed the procedures of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) 2020 statement.

The PICO framework was used to answer the research question (P, patient, problem, or population: athletes; I, intervention: conservative treatment with therapeutic exercise or injection therapies; C, comparison, control, or comparator: not needed; O, outcomes: clinical outcomes such as motor function, symptom relief, changes in gait analysis, or imaging tests).

Clinical trials, randomized controlled trials, and longitudinal studies were considered.

After the research issue was identified, two independent researchers performed a search on the MEDLINE (PubMed) and PEDro database, using the following keywords: "knee osteoarthritis", "early osteoarthritis", "athlete", "sport", "treatment", "soccer", "running", combined with Boolean operators, looking at OA in the most popular sports, according to Tran's extensive analysis [12]. A comprehensive process of identifying and selecting appropriate studies was then performed.

### *2.2. Study Selection*

Articles published within the past 20 years, with available abstracts, written in English that answered the question formulated by the authors were included in the review.

Articles that did not report a conservative intervention, those that reported a post-surgical intervention, those that did not describe clinical outcomes, reviews and metanalysis, and articles written in languages other than English were omitted from the analysis.

### *2.3. Data Extraction*

Once the articles meeting the criteria for inclusion in the review were chosen, the complete texts were downloaded and examined in depth.

Data were extracted and charted. Authors, year of publication, type of sport, study design, population, sample size, age, intervention and the main results were all extracted and gathered as reported in Table 1.

**Table 1.** Characteristics of the included studies. RCT, randomized controlled trial. i.a., intra-articular.

| Authors (Publication Year) | Study Design | N (M/F) Mean (Years) | Sport | Intervention | Outcomes | Evaluation Times | Main Conclusions |
|---|---|---|---|---|---|---|---|
| Papalia et al., (2016) | RCT | 47 (M) 37.2 (range 34–39) | Soccer | 3 i.a. injections of HHA (3.2% 64 mg/2 mL, 32 mg High-MW 1100–1400 kDa + 32 mg Low-MW 80–100 kDa) at one week interval or 3 i.a. injections of 5.5 mL PRP | VAS, IKDC, KOOS | Baseline, 3, 6 and 12 months | Both treatments showed to be effective in relieving patients' symptoms |
| Tamburrino and Castellacci (2016) | Single arm clinical trial | 30 (M) 30.7 (range 17–39) | Soccer | 2 i.a. injections of HYADD4-G (3 mL of 8 mg/mL) at one-week interval | VAS, KOOS | Baseline, 1, 3 and 6 months | Significant improvement on symptoms, ADL performance, KOOS and VAS ($p < 0.05$) |
| Van Ginckel et al., (2010) | Longitudinal | 19 (F) 25.5 (range 22–34) | Running | 10-week STR program | MRI dGEMRIC index | Baseline and at the end of the program | Significant positive change of the median dGEMRIC index compared to sedentary controls (+11.66 ms (95% CI: 25.29, 44.43) vs. 9.56 ms (95% CI:29.55, 5.83), $p = 0.006$) and with increasing physical activity ($p = 0.014$) |
| Willy et al., (2016) | RCT | 30 (16/14) 20.99 years (range 18–35) | Running | In-filed running retraining program using mobile biofeedback | Derived peak and cumulative tibiofemoral joint contact force estimated by gait analysis | Baseline, at the end of the program, 1 month | 7.5% increase in step rate during running with a significant reduction in tibiofemoral and medial tibiofemoral joint contact forces per stance phase (9.1% and 8.1%, respectively) |

HHA, hybrid hyaluronic acid; MW, molecular weight; PRP, platelet rich plasma; ADL, activities of daily living; VAS, visual analogue scale; IKCD, international knee documentation committee; KOOS, knee injury and osteoarthritis outcome score; STR, start to run; MRI, magnetic resonance imaging; dGEMRIC, delayed gadolinium enhanced magnetic resonance imaging of cartilage.

## 3. Results

### *3.1. Selected Studies*

The search yielded 636 studies in total. A total of 95 abstracts were evaluated after an initial screening of titles. Finally, four studies that satisfied the review's eligibility criteria were chosen. Two of them considered an exercise regimen, while the other two considered injection therapy (Table 1). Figure 1 shows the study selection procedure.

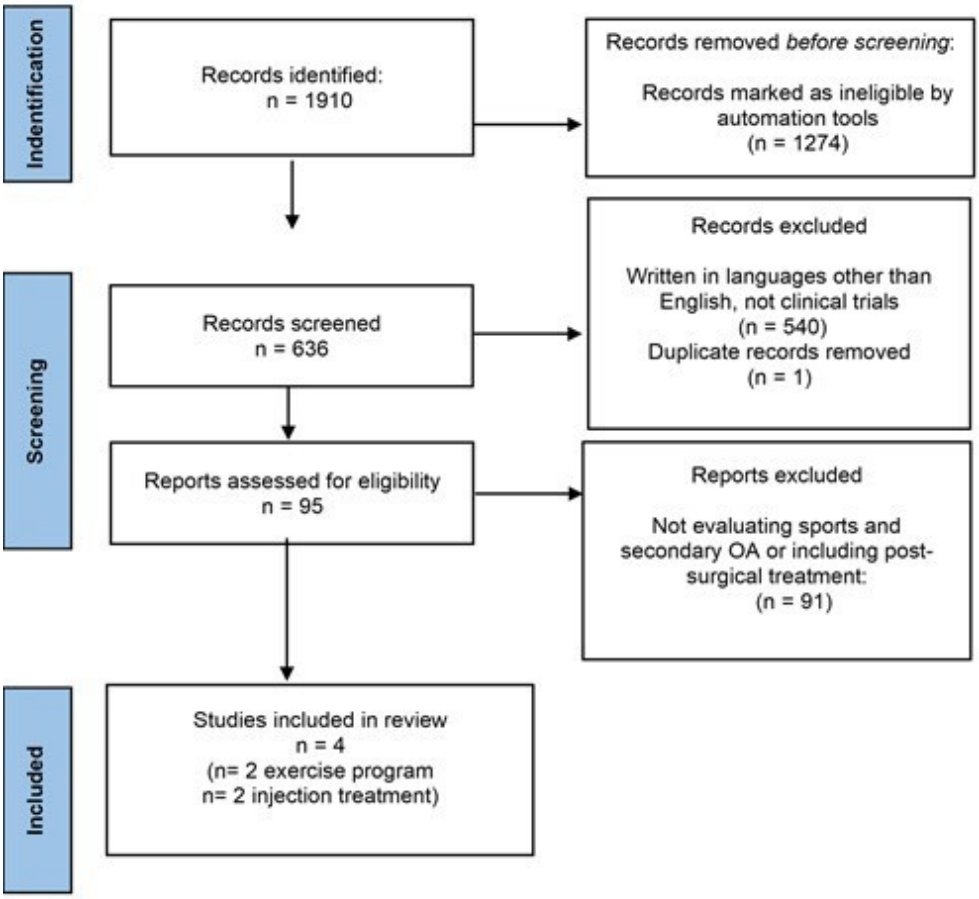


**Figure 1.** PRISMA Statement flow-chart describing the studies selection strategy.

### *3.2. Therapeutic Exercise*

Van Ginckel et al., estimated changes in glycosaminoglycan content of knee cartilage measured by gadolinium enhanced magnetic resonance imaging of cartilage (dGEMRIC) imaging, in asymptomatic untrained female novice runners participating in a start to run program (STR), compared to sedentary controls. SRT aimed at jogging for approximately 5 km within a training period of 10 weeks. dGEMRIC index estimates glycosaminoglycan (GAG) content using the anionic contrast agent gadolinium diethylene triamine penta-acetic acid (Gd-DTPA2), that distributes inversely to the fixed negative charge associated with the GAG content.

Before and after the 10-week period, both groups were subjected to dGEMRIC and it was found that the STR contributed to a significant positive change of the median dGEMRIC index compared to sedentary controls (+11.66 ms (95% CI: 25.29, 44.43) vs. 9.56 ms (95% CI: 29.55, 5.83), $p = 0.006$]. Moreover, the change in dGEMRIC index showed a significant improvement with increasing physical activity ($p = 0.014$) [31].

Another study analyzed the effect of an in-field gait retraining program, using mobile biofeedback through a wireless accelerometer and a small wrist mounted running computer [32]. The proposed program reduced cumulative and peak tibiofemoral loads during running in high impact runners with an average age of 251.88 months (20.99 years).

The in-field gait retraining, causing a 7.5% increase in step rate during running, resulted in a significant reduction in tibiofemoral and medial tibiofemoral joint contact forces per stance phase, by the 9.1% and 8.1%, respectively. The reductions in tibiofemoral joint contact forces, noted during the acute gait modification trial, persisted at one-month post-retraining. However, despite the increase in the number of gait cycles needed to cover a given distance, there was no change in cumulative tibiofemoral joint loads [32].

### *3.3. Injection Treatment*

In a study evaluating thirty professional male soccer players with a diagnosis of kOA, who underwent two intra-articular injections of a hexadecylamide derivative of hyaluronic acid (HYADD4-G) at one-week interval, and one, three and six months following the treatment, a significant improvement on symptoms, performance of daily activities, local pain, as well as in all of the clinical endpoints was shown. A significant improvement was also found in the knee osteoarthritis and injury outcome score (KOOS) and visual analogue scale (VAS), at one, three, and six months compared to the pre-injection value ($p < 0.05$) [33].

In a randomized controlled trial involving professional soccer players with clinical and radiographic (grade I or II Kellgren-Lawrence scale) evidence of degenerative changes in the knee, both Hybrid Hyaluronic Acid (HHA) viscosupplementation and Platelet Rich Plasma (PRP) injections, demonstrated improvement in the clinical outcomes tested at the 3-, 6- and 12-months follow-ups. At the intergroup analysis, HHA group showed better outcomes at the 3- and 6-month follow-ups compared to PRP, losing significance at the 12 months follow-up [34].

## 4. Discussion

Both nonpharmacological and pharmacological treatments are used in the management of OA [30]. Exercise is generally recognized for its benefits in the therapy of OA: it is regarded as an effective, non-pharmacological treatment for improving OA symptoms such as pain and stiffness [24]. Structured land-based exercise regimens, comprising strengthening, aerobic, and balance training, are strongly suggested for the non-surgical care of kOA according to the most recent OARSI guidelines [35]. Mind-body exercises, such as Tai Chi or yoga, are also beneficial and recommended [19].

Moreover, aquatic exercises are recommended for individuals with kOA presenting no other comorbidities, as well as for individuals with cardiovascular or gastrointestinal comorbidities or with pain disorders and/or depression [35].

Regular weight-bearing physical exercise has been shown to have a modulating action in OA molecular pathways through a periarticular trophic effect on bone, muscles, and tendons [36]. Furthermore, chondrocyte biosynthetic activity is susceptible to mechanical stimuli and can influence cartilage morphology and composition [37]. In particular, several experimental research investigating the effect of physical exercise in OA have reported increased synthesis of GAG, anti-inflammatory cytokines, and bone morphogenic proteins, and reduced levels of pro-inflammatory cytokines and MMPs in joint tissues [38]. Therapeutic exercise has also been shown to ameliorate the lubrication of the joints and modulate the production, the viscosity, and the composition of the synovial fluid [39].

Early OA in young and former athletes represents a growing problem with about one third of cases involving the knee joint, particularly considering the rising prevalence of intensive sports practice among the general population [13].

Based on the limited benefits of pharmacologic therapy, and the indications that nonpharmacologic techniques are more effective in relieving symptoms in the long term, preventing or delaying function deterioration, there has been a gradual transition from pharmacologic to nonpharmacologic interventions for kOA treatment [40]. Among nonpharmacological strategies, an individualized therapeutic exercise protocol, personalized according to outcome expectations, pain severity, patient's preferences, and fear of movement, seems to represent an essential component of the comprehensive and multimodal management of kOA [30].

In our review, despite the heterogeneity of the included studies, due to the study design, the interventions used, and the type of sports examined, some important suggestions should be considered.

A gradually built-up running scheme seems to contribute to a chondroprotective effect of the knee, modulating cartilage GAG content [31].

It has been reported that moderate daily physical activity may have a positive effect on cartilage matrix composition, thus contributing to cartilage healing and reducing risk

for knee injury [34]. Several studies conducted in animal models of knee PTOA revealed that exercising exerts beneficial effects both at the bone and cartilage level. Treadmill walking has shown to increase bone morphogenic protein expression and to prevent the progression of cartilage and subchondral bone lesions in rats [41]. In addition, aerobic exercise training reported notable results in modulating degenerative process of cartilage and downregulating IL-1β, caspase-3, and MMP-13 expression in ACL transection rat models [42]. In the same experimental model, reduced IL-1β, TNF-α, MMP-13, and caspase-3 expression and enhanced IL-10, IL-4 lubricin, and Hsp70 expression have been detected in articular tissues after moderate physical activity, thus underlying anti-inflammatory, chondroprotective, and anti-apoptotic effects [43,44].

Long-distance runners seem to have less musculoskeletal disability, to retain higher functional capacity than age-matched controls, and demonstrated improved cardiovascular fitness [19]. However, a history of long-distance running may cause cartilaginous volume reductions in the tibia, patella, and medial and lateral menisci, possibly as a response to the repeated and continuous load [36]; in ex middle- and long-distance runners a higher incidence of tibiofemoral and patellofemoral OA was found [45].

Therefore, in agreement with the preexisting literature, running activity appears to have a beneficial role on cartilage when appropriately dosed.

A small increase in step rate may help to minimize peak and impulse contact pressures per step for the tibiofemoral joint while running, thus lowering the incidence of OA. It is noteworthy that the reduction in peak and impulse contact force on medial tibiofemoral compartment is predominant in the medial joint compartment, the most affected during running [32]. Since total tibiofemoral contact force impulse per unit distance is not different between running and walking, cartilage seems to be highly sensitive to peak loads, particularly when applied at a high rate as would be expected in runners with high impact forces [46]. Therefore, a training exercise aimed to reduce peak and impulse tibiofemoral contact forces per stance could represent a relevant tool in preventing early OA in these individuals.

Among the injection treatments, intra-articular (i.a.) viscosupplementation with hyaluronic acid (HA) represents a valid therapeutic strategy for people who regularly practice sport activity and who are diagnosed of mild to moderate kOA [47].

HA is a glycosaminoglycan, a natural component of the synovial fluid and the extracellular matrix of articular cartilage, with lubricating, viscoelastic, and "shock absorber" properties. These actions are carried out through the increase of the hyaluronate content in the chondrocytes, the synthesis of proteoglycans, the inhibition of production and activity of pro-inflammatory mediators and MMPs [48,49].

The main international guidelines recommend viscosupplementation with intra-articular (i.a.) HA in the management of kOA as a second-choice conservative treatment in non-responders (or those who have contraindications) to non-steroidal anti-inflammatory drugs. In the case of joint effusion, preventive arthrocentesis has an anti-inflammatory effect thanks to the removal of cytokines, neuropeptides and other inflammatory mediators. This procedure also allows to optimize the therapeutic action of HA by preventing its i.a. dilution [29,30].

The two studies included in our review regarding the injection treatment showed a medium to long-term improvement in joint pain and function in a population of young professional football players (age ranges 34–39 and 17–39, respectively) with early kOA. However, the hydrogel solution and the treatment protocols were extremely different.

In the study by Tamburrino et al., patients underwent two i.a. injection of a HYADD4-G hydrogel at one week intervals with no control group [33]. Hexa-decylamide derivative of HA is a highly viscoelastic hydrogel that recovers its original structure even after repetitive mechanical stress. Therefore, it could represent a valid therapeutic option in the integrated treatment of athletes affected by post-traumatic or degenerative early kOA. However, the lack of a control group, and the small sample size, makes the results poorly generalizable.

In the study by Papalia et al., subjects underwent three i.a. knee injections administered at a weekly interval with a HA hybrid formulation (intervention group) or a PRP solution (control group) [50]. In this study clinicians used a hybrid HA solution with a peculiar profile distribution into the joint due to the combination of both high and low molecular weight fractions. These characteristics seem to guarantee good rheological properties with an anabolic activity on chondrocytes, thus stimulating extracellular matrix production [51].

At the 3, 6, and 12-month follow-ups, HHA showed improvement in the clinical outcomes assessed. The PRP group also showed a significant improvement in pain and function recovery up to the 12 month follow up.

Although the exact mechanism of action of the PRP has not yet been clarified, it is hypothesized that there is a stimulating effect on the cell proliferation of chondrocytes, synoviocytes and mesenchymal cells and on the production of cartilage matrix, with an increase in the synthesis of type II collagen and proteoglycans. Furthermore, PRP seems to intervene in the regulation of the chronic inflammatory process by inhibiting the activation of the nuclear transcription factor NF-kB (a regulator of inflammation) and the expression of pro-inflammatory MMPs enzymes, cyclooxygenases 2 and 4, and disintegrins [52].

According to the results obtained from our review, therapeutic exercise seems to represent an appropriate strategy for the management of conditions at risk of developing OA (sports with joint loading or repeated microtraumas). From this perspective, exercise conducted at the right doses, according to a personalized prescription, could not only be employed for rehabilitative programs in patients with kOA at early stages but also for prevention protocols.

Although different exercise training has been proposed, lower limbs strengthening and general aerobic exercises are recommended by most international guidelines for the treatment of kOA with the main goals of restoring impaired muscle function, resulting in a decreased joint load and a reduced stress on articular cartilage [53]. Previous studies have also demonstrated the role of muscular weakness on the early onset of kOA [54].

Emerging topics include the use of technology supports and remote delivering of therapeutic exercise protocols [55].

An adequate muscle-strengthening rehabilitation program allows a faster recovery of the athlete, prevents the risk of injury recurrence, and slows down the degenerative process of the articular cartilage. Therefore, a strengthening program of knee extensor and hip abductor muscles could also be suggested to prevent kOA development.

A multimodal treatment, based on the identification of subjects at risk, the implementation of preventive interventions with sport-specific programs, and the recourse to minimally invasive interventions in the more severe conditions, could be an appropriate treatment strategy for kOA in athletes.

In young or former athletes with symptomatic kOA, the combination of viscosupplementation and muscle-strengthening exercises and aerobic training with moderate load (e.g., running with an individualized dose of exercise) appears to be a suitable rehabilitation strategy, since a low-impact training seems not to expose to OA worsening [40].

*Limitations*

This scoping review presents some methodological limitations. In fact, although we deliberately used broad inclusion criteria, in order to avoid excluding relevant articles, the literature research provided only a few studies. Moreover, the selected articles were heterogeneous in study design, study populations, sport considered, and the type of intervention proposed (therapeutic exercise, mini-invasive treatment).

Having conducted the research on a small number of databases may be another limitation of our research. In particular, gray literature was not considered since it is not peer-reviewed and therefore difficult to determine as reliable.

Excluding case reports from the review may be another limitation. Rehabilitation protocols may have been described in these types of manuscripts and thus were not found by our search.

## 5. Conclusions

Currently there are no rehabilitation or prevention protocols for athletes with early kOA or conditions at risk of developing it. From the literature review, it seems desirable to combine therapeutic muscle-strengthening exercise and moderate aerobic activity to prevent kOA development. In cases of already developed and symptomatic early kOA it may be necessary to add minimally invasive injection therapy which, from early evidence, seems to contribute to the improvement of motor function and symptomatology. Future studies should be conducted to define specific treatment protocols.

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# Biophysical Stimulation in Athletes' Joint Degeneration: A Narrative Review

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**Abstract:** Osteoarthritis (OA) is the most prevalent degenerative joint disease and the main cause of pain and disability in elderly people. OA currently represents a significant social health problem, since it affects 250 million individuals worldwide, mainly adults aged over 65. Although OA is a multifactorial disease, depending on both genetic and environmental factors, it is reported that joint degeneration has a higher prevalence in former athletes. Repetitive impact and loading, joint overuse and recurrent injuries followed by a rapid return to the sport might explain athletes' predisposition to joint articular degeneration. In recent years, however, big efforts have been made to improve the prevention and management of sports injuries and to speed up the athletes' return-to-sport. Biophysics is the study of biological processes and systems using physics-based methods or based on physical principles. Clinical biophysics has recently evolved as a medical branch that investigates the relationship between the human body and non-ionizing physical energy. A physical stimulus triggers a biological response by regulating specific intracellular pathways, thus acting as a drug. Preclinical and clinical trials have shown positive effects of biophysical stimulation on articular cartilage, subchondral bone and synovia. This review aims to assess the role of pulsed electromagnetic fields (PEMFs) and extracorporeal shockwave therapy (ESWT) in the prevention and treatment of joint degeneration in athletes.

**Keywords:** PEMF; ESWT; biophysical stimulation; extracorporeal shock wave therapy; cartilage; bone; osteoarthritis; athletes



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## 1. Introduction

Athletes, due to the physical demands necessary for chasing sporting results, put significant stress on their joints and it is usual for them to suffer from articular cartilage defects. Chondral defects are linked to discomfort and physical weakness, the limiting of athletic activity and have been implicated as a potential risk factor in the development of early-onset osteoarthritis (OA).

However, cartilage pathology is not always symptomatic: more than half of the asymptomatic athletes have a full-thickness defect [1].

Chondral injuries are often present in sports subjects; the incidence rate in the knee is 36% compared to 16% in the general population [2].

Concomitant ligament instability, misalignment, and previous injury may facilitate chondral lesions.

Chondral damage can lead to an excessive load on the subchondral bone and therefore to bone edema, which can manifest itself with painful symptoms and limit sports participation.

Over time, bone edema can resolve if adequately treated or can evolve towards bone necrosis (spontaneous osteonecrosis of the knee, SONK), which, however, can also be secondary to vascular pathologies, or towards arthritic evolution.

Non-operative strategies aim to improve effective hyaline cartilage regeneration by delivering growth factors or reducing inflammation [3].

Many conservative therapies are available, such as chondroprotective drugs and nonsteroidal anti-inflammatory drugs (NSAID), Hyaluronic-acid or Platelet Rich Plasma (PRP) or staminal cells' injection or biophysical stimulation.

Biophysical stimulation is a non-invasive therapy currently employed in orthopaedics and traumatology practice to enhance the reparative abilities of the musculoskeletal system. Biophysical stimulation refers to the application of physical energy to a biological system to increase and facilitate tissue regeneration and anabolic activity [4].

Biophysical stimulations act mainly at the level of the cell membrane. It plays a fundamental role in recognizing and transferring the physical stimulus to the various intracellular signalling pathways.

Several types of non-invasive electrical stimulation devices have received US FDA approval for orthopaedic application and are classified into: electrical energy applied directly to the tissue by adhesive electrodes (capacitively coupled electric field, CCEF), ultrasound energy (low-intensity pulsed ultrasound system LIPUS) and electromagnetic energy applied by coils (pulsed electromagnetic fields, PEMFs) or extracorporeal shock wave therapy (ESWT) or Low-Level Laser Therapy (LLLT) [5].

Pulsed electromagnetic fields and extracorporeal shockwave therapy have strong evidence in the literature, so this narrative review aims to assess the role of PEMFs and ESWT in the prevention and treatment of joint degeneration in athletes.

## 2. PEMF

Several preclinical and clinical trials of PEMFs have shown positive effects of biophysical stimulation on articular cartilage, subchondral bone and synovia. After initial studies performed on animal cartilage cells, such as bovine or equine or guinea pigs' cells [6–8], studies were conducted on human mesenchymal cells (MSCs): it was found that chondrogenic differentiation of MSCs is facilitated when exposed to PEMFs' magnetic fields of varying amplitude and intensity [9].

The transmembrane signal recognition processes of PEMF were reported for the first time by Varani et al. [10]. They discovered that Adenosine Receptors (AR) were the primary target of PEMF stimulation in inflammatory cells; ARs play an important role in the control of inflammatory processes, with both pro-inflammatory and anti-inflammatory effects. PEMF exposure has been shown to increase the density of $A_{2A}$ and $A_{3AR}$ on the cell membranes of osteoblasts, chondrocytes and synoviocytes [11], and inhibited cytokine IL-6 and IL-8 while stimulating the release of the anti-inflammatory cytokine IL-10 and inhibited Prostaglandin E2 (PGE2) production with an upregulation of A (2A) receptors [12]. IL-1β is a pro-inflammatory cytokine that promotes ECM cartilage degradation in healthy and osteoarthritic-joint-derived cells. It is reported that PEMFs inhibit the negative effect of the cytokine IL-1β in a study on cartilage explants [13].

PEMF stimulation increased chondrocytes' proliferation in patients without OA [14], and increased the expression of growth factors and cytokines, ECM component synthesis, such as collagen II (COLL II), glycosaminoglycan (Gags) and proteoglycans (PGs) [15–18].

Furthermore, some authors evaluated how PEMFs could influence the replication of chondrocytes cultured from subjects with OA. Stolfa and colleagues conducted three experiments with different PEMF signal parameters and different concentrations of chondrocytes and showed that this type of PEMF stimulated the metabolic activity of chondrocytes but there were no significant effects on cell proliferation. These results were not achieved in all experiments [19]; Schmidt-Rohlfing and colleagues do not suggest any effect of PEMF and

sinusoidal magnetic fields on the cellular metabolism of human osteoarthritic chondrocytes cultivated in a collagen gel in vitro [20].

The sound frequency of PEMF is also debated; frequencies of 37 and 75 Hz were able to preserve the structural parameters of both cartilage and bone in the advanced phase of knee osteoarthritis. However, PEMF stimulation at 75 Hz compared to 37 Hz significantly improved cartilage preservation [21].

The combined effect of PEMF and bone marrow concentrate (BMC) in the healing of osteochondral defects treated with a scaffold has been assessed in animal models by different authors. Both cellular and cartilage matrix parameters improved with the addition of PEMF stimulation compared to using the scaffold alone—the combination with BMC also facilitated osteochondral regeneration [22].

In clinical practice, biophysical stimulation can be used proactively as: (*i*) a post-surgical treatment to quickly control local inflammation of the joint, and, over the long term, to maintain the mechanical and biological properties of the cartilage or engineered tissue, which can be used after arthroplasty to attenuate inflammatory processes involving periarticular tissues and reduce the chances of developing chronic pain or functional limitations [23,24]; (*ii*) a conservative treatment to limit the progression of the osteoarthritis degenerative process or the development of bone edema, or in association with surgery for risk fractures, delayed union and non-unions.

Damage to articular cartilage is increasingly identified as a source of joint limitation and reduced athletic performance in athletes, whether isolated or in conjunction with ligament or meniscal or tendon tears [25]; therefore, surgical treatment must be supported by biophysical therapy to facilitate functional recovery and achieve better outcomes.

Few authors have evaluated the role of PEMFs in chondral and osteochondral damage in athletes; for example, van Bergen and colleagues in a double-blind, randomized controlled trial of 68 young and athletic patients evaluated the effectiveness of PEMFs used for sixty days in the management of osteochondral ankle lesions after arthroscopy, considering the simple technology and ease of use and for the high potential to provide a safe and effective adjunct treatment option for talus osteochondral defects [26].

In the literature, in studies that evaluate the PEMFs' efficacy in patients with osteochondral lesions, it is not specified whether the sample under examination is from athletes [27].

Initially, in 2009, Vavken et al. in a meta-analysis evaluated the positive effects of PEMF associated with some conservative therapies on the quality of life in patients with osteoarthritis of the knee [28].

Later, Gobbi and colleagues also evaluated their use in the treatment of early osteoarthritis (Kellgren Lawrence < 2) and age < 60 for 2 years; the results were mixed as they showed an improvement in pain symptoms and KOOS and Tegner scores after one year of treatment and a worsening, instead, at two years [29]. The author concluded that an annual repetition of the treatment may result in sustained symptomatic improvement for the patient.

The same author in a prospective level IV study enrolling 22 patients with a mean age of 48.4 years and with early OA, found at 1 year follow up a statistical improvement of KOOS, EQ-5D, Tegner score and IKDC after PEMF treatment for 45 days [30].

Satisfactory results were also highlighted by Iammarrone and colleagues despite the small sample examined from young patients with patellofemoral pain syndrome (PFPS) [31].

Marchegiani Muccioli et al., in a study on 28 patients with spontaneous osteonecrosis of the knee (SONK), assessed the clinical MRI effectiveness of PEMF therapy performed 6 h daily for 90 days. At 6-month follow up, a clinical improvement and a reduction of the SONK area were detected with MRI [32].

PEMF therapy, with the same treatment protocol in 31 patients with focal knee chondral tears who were undergoing arthroscopy with chondroabrasion and/or perforations, involved a reduction from 75% to 26% with the use of NSAIDs, a higher KOOS at 90 days

and a large number of patients that returned to normal daily sports activity at 3 years follow up [33].

Collarile et al., in a prospective comparative study recruiting thirty patients, affected by grade III and IV International Cartilage Repair Society chondral lesions of the Knee treated with matrix-assisted autologous chondrocyte implantation (MACI), reported the patients who randomly received postoperative stimulation with PEMFs had a better clinical outcome both in the short- and long-term follow-up [34]. These findings suggest biophysical stimulation is an effective tool, able to ameliorate clinical results of regenerative medicine [34].

Similar results have been also reported by Cadossi et al., in a prospective comparative study recruiting thirty patients with grade III and IV Outerbridge osteochondral lesions of the talus (OLT) managed with a collagen scaffold seeded with bone marrow-derived cells (BMDCs), showed the patients who randomly received postoperative biophysical stimulation with PEMFs revealed a better clinical outcome–assessed using the American Orthopaedic Foot and Ankle Society (AOFAS) score; Visual Analog Scale (VAS) and Short Form-36 (SF-36)- at 12-months after surgery [35]. Therefore, the authors concluded stating PEMFs are useful in fastening the patient's recovery after BMDCs transplantation [35].

Benazzo and colleagues also showed a reduction in the use of NSAIDs and faster functional recovery compared to the control group in patients who, after cruciate reconstruction, had been treated with a pulsed magnetic field; however, there was no statistical improvement in IKDC and SF-36 [36].

Some authors, such as Gremion et al. and Ozgüçlü et al., found that a different pulsed signal therapy improved the clinical state of treated patients but there was no significant statistical difference to other conservative treatments such as physiotherapy and therapeutic ultrasound [37,38].

Nelson et al. and Bagnato et al., in a double-blind pilot clinical study with respectively 34 and 60 patients with OA treated with PEMF, showed that the VAS pain score decreased versus baseline and a reduction in the intake of NSAIDs [39,40]. Bagnato's treatment scheme consisted of 12 h daily treatment for 1 month.

Wuschech, after a twice a day treatment for 5 min over a period of 18 days in patients with OA, found a significant reduction in stiffness ($p = 0.032$) and a significant reduction in disability in daily activities according to the WOMAC score, compared to the placebo group [41].

Biophysical therapy, with specific and tested parameters of PEMF, must be considered a valid aid to arthroscopic surgical treatment considering the role of cell stimulation and the reduction of inflammation and pain after treatment. Its use would allow the athlete a more rapid functional recovery and therefore an early return to sporting activity. However, unlike the bone edematous pathology, in which it occupies a prominent place in association or not with bisphosphonates and load reduction, there are no studies in the literature on sportsmen that evaluate whether biophysical therapy alone can replace surgical treatment in the case of mild/moderate chondral damage.

## 3. ESWT

For more than 25 years, extracorporeal shockwave therapy (ESWT) has been routinely utilized to treat soft tissue and bone-related musculoskeletal diseases and has been manifested clinically to be effective in plantar fasciitis [42], lateral epicondylitis of the elbow [43], calcific tendonitis of the shoulder [44], and nonunion or delayed fracture healing [45]. Shock waves, which are used in ESWT, are acoustic waves produced from different sources such as electro-hydraulic, electromagnetic, piezoelectric, or pneumatic generators. This pressure disturbance propagates in space, and the progression of the wave can be described by a positive phase showing a rapid increase in pressure followed by a negative phase of a slow return to starting levels [46,47]. Concerning medical applications, many authors talk about low energy ESWT with an energy dose, expressed in EFD (Energy Flux Density),

equal to or less than 0.28 mL/mm$^2$, and high energy when EFD is equal to or more than 0.6 mL/mm$^2$ [48].

The exact mechanism by which cells recognize an acoustic wave, converting it into biological responses, is currently largely unknown. According to the mechano-transduction theory, shockwaves induce the cellular mechano-transduction process, through which cells convert the shockwave mechanical signals into biochemical responses; mechanical stimulation of the cell membrane induces a conformational change of membrane proteins including integrins and ion channels. The activation of pathways, such as MAPKs and PI3K-Akt-eNOS, influences the transcription and expression of the genome [49–51]. Activation of the Akt-eNOS pathway caused by exposure to ESWT determines an increase in the release of NO and VEGF at the bone tendon junction, improving vascularization and tissue healing [52].

Human osteoblasts exposed to shock waves show a dose-dependent increase in differentiation and growth secondary to the increased expression of the Transforming Growth Factor β1 (TGF-β1), which plays a fundamental role in osteogenesis and osteoblastic lineage differentiation [53–55]; similarly, Hausdorf et al. demonstrated an increase in FGF-2 in human osteoblasts and fibroblasts. Lyon et al. showed a response to ESWT on a rabbit's knee with smaller denudation on cartilage and enhanced density and chondrocytes formation; a decreased level of TNF-α on chondrocytes after shockwave application may partially explain the mechanism by which ESWT improves cartilage repair and chondroprotection [56]. Another investigation by Moretti et al. confirmed the chondroprotective effects of shock waves stimulation by restoring normal levels of Il-10 and TNF-α [57]. Wang et al., in a series of studies on osteoarthritic knees in rats, confirmed the effect on cartilage through histochemical examinations with Hematoxylin-eosin and Safranin-O stains, showing less cartilage fissuring and better chondrocyte vitality and concentration in the ESWT group compared with the untreated ones [58].

Similar results were also found in rabbit models with osteochondral defects after ESWT showed improvements in the macroscopic characteristics of hyaline cartilage [59]. The application of ESWT to knee OA in rats results in the decline of urinary levels of cartilage degradation markers such as CTX and MMP [58–60]. Several studies focused on the effect of ESWT on MSCs; all of them have shown that shockwaves improve stem cell recruitment and differentiation into chondrocytes in mouse models [61]; an augmented proliferation rate was also observed in equine ASCs treated with ESWT [62,63].

The role of subchondral bone throughout the early stages of OA showed that subchondral bone alteration might be a therapeutic focus in OA therapy [64,65]. Wang C. et al. observed improved tissue distributions, including cortical bone, cancellous bone, and fibrous tissue, in many studies using extracorporeal shockwaves to the subchondral bone of the medium tibia condyle. ESWT increased BMP-2 and osteocalcin expression in OA rats, which is usually linked with cell proliferation and extracellular matrix synthesis in healthy osteoblasts [66]. The immunohistochemical examination revealed that the expression of Dickkopf-related protein 1 (DKK-1)—a regulator of osteoblast activity—was considerably greater in OA and significantly decreased after ESWT therapy; these findings show that shock wave stimulation can boost subchondral bone anabolism and improve trabecular microarchitecture. Iannone et al. tests the effects of ESWT on subchondral osteoblasts in vitro and found a significant increase of IL-10 intracellular levels both in OA and healthy osteoblasts [67], in contrast to Moretti et al. who observed downregulation of IL-10 expression in human chondrocytes by applying the identical protocol of ESWT. The dissimilar responses of cartilage and subchondral bone in IL-10 expression after ESWT suggest that IL-10 may play a different role in each component of the OA joint. In a rat model, Hashimoto et al. proposed that ESWT might expedite the repair of meniscal injuries in avascular areas, which may contribute to OA development.

ESWT improved the healing of avascular tears by promoting meniscal cell proliferation and the upregulation of cartilage-repairing factors, such as CCN2, SOX9, aggrecan, and Col2a1, resulting in enhanced synthesis of a cartilage-specific extracellular matrix [68].

Liu et al. experimented with the combined use of ESWT and intra-articular hyaluronic acid in the early stages of OA; the analysis of functional evaluation scores, such as VAS WOMAC and KOOS, showed a superiority of the combined treatment compared to the use of hyaluronic acid alone. These results can be attributed to the ability of ESWT to increase the expression of hyaluronan cellular receptors CD44, which would lead to increased production of type 2A collagen, favouring the repair of cartilage lesions [69].

The efficacy of ESWT in human and animal models with OA has also been demonstrated in several clinical trials in which improvements were observed in functional outcomes and pain relief with a reduction of VAS and WOMAC scores [44,70–72]. In a retrospective study, ESWT outperformed laser therapy in terms of symptom reduction as measured by the WOMAC and Numeric Rating Scale (NRS) [73].

The beneficial effect on OA pain could be explained by nerve fibre responses to ESWT treatment. Ohtori et al. showed that ESWT caused nerve fibre degeneration and reduced the expression of calcitonin gene-related peptide (CGRP) in dorsal root ganglia (DGR) neurons. The analgesic effect and the functional ability enhancement may be time-limited because of nerve regeneration that occurs in fibres 14 days after ESWT [74,75]. The time limits of the benefits of ESWT were studied by Ochiai in rat models, showing an improvement in functional performance between 4 and 14 days after treatment; however, between 21 and 28 days, there were no differences compared to the placebo group [76].

Extracorporeal shock waves, used routinely for various musculoskeletal diseases, represent a valid therapeutic option for the treatment of the early stages of OA, resulting in an improvement in functional scores and pain; however, the benefits appear to be limited in time.

## 4. Conclusions

Biophysical therapies with PEMF or ESWT can act to improve the symptoms and function of joints, such as the knee in patients with non-advanced OA or those who have suffered a trauma that has led to cartilage damage or subchondral edema. This can be very useful in athletes for an early return to sport and, above all, for preventing this damage from causing an arthritic evolution of the joint. However, in the literature, few studies use exclusively sportsmen or athletes as a sample to study. Particularly concerning the treatment with ESWT, studies that evaluate the effectiveness of the treatment are mainly on animal models while studies on human models focus on musculotendinous pathology.

Further high-quality studies on athletes are needed to draw stronger conclusions.

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*Systematic Review*

# Physical Agent Modalities in Early Osteoarthritis: A Scoping Review

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**Abstract:** Early osteoarthritis (EOA) still represents a challenge for clinicians. Although there is no consensus on its definition and diagnosis, a prompt therapeutic intervention in the early stages can have a significant impact on function and quality of life. Exercise remains a core treatment for EOA; however, several physical modalities are commonly used in this population. The purpose of this paper is to investigate the role of physical agents in the treatment of EOA. A technical expert panel (TEP) of 8 medical specialists with expertise in physical agent modalities and musculoskeletal conditions performed the review following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) model. The TEP searched for evidence of the following physical modalities in the management of EOA: "Electric Stimulation Therapy", "Pulsed Electromagnetic field", "Low-Level Light Therapy", "Laser Therapy", "Magnetic Field Therapy", "Extracorporeal Shockwave Therapy", "Hyperthermia, Induced", "Cryotherapy", "Vibration therapy", "Whole Body Vibration", "Physical Therapy Modalities". We found preclinical and clinical data on transcutaneous electrical nerve stimulation (TENS), extracorporeal shockwave therapy (ESWT), low-intensity pulsed ultrasound (LIPUS), pulsed electromagnetic fields stimulation (PEMF), and whole-body vibration (WBV) for the treatment of knee EOA. We found two clinical studies about TENS and PEMF and six preclinical studies—three about ESWT, one about WBV, one about PEMF, and one about LIPUS. The preclinical studies demonstrated several biological effects on EOA of physical modalities, suggesting potential disease-modifying effects. However, this role should be better investigated in further clinical studies, considering the limited data on the use of these interventions for EOA patients.

**Keywords:** osteoarthritis; early osteoarthritis; rehabilitation; physical therapy modalities; physical agents; electric stimulation therapy; pulsed electromagnetic field; extracorporeal shockwave therapy; vibration therapy



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## 1. Introduction

Osteoarthritis (OA) is the most common degenerative and progressive joint disease, characterized by localized pain and impaired mobility, with relevant implications on both the quality of life of affected patients and socio-economic burden [1]. This condition is very challenging to manage, considering the extreme variability of clinical and instrumental findings of OA patients. Moreover, no available intervention can effectively counteract the structural changes of different tissues involved in the pathogenesis of OA, such as bone, synovium, and cartilage [2].

Much effort has been made to identify OA in the early stages to avoid the occurrence of major joint structural alterations. However, early OA (EOA) is a controversial condition due to the lack of an agreement on a unanimous definition, diagnosis, and, above all, of therapeutic intervention [3].

Several diagnostic criteria have been proposed for EOA. The first definition of EOA was provided by Luyten et al., stating that early knee OA (EKOA) is defined if three of the following criteria are met: two or more episodes of knee pain lasting more than 10 days, Kellgren and Lawrence (KL) grades 0–2, cartilage lesions in arthroscopy, magnetic resonance imaging (MRI) evidence of cartilage or meniscus damage, and/or bone marrow lesions (BMLs) of the subchondral bone [4]. More recently, Migliore et al. proposed diagnostic criteria of EKOA in patients over 40 years based on symptoms lasting for less than 6 months (knee pain without any recent trauma associated with joint stiffness), the presence of clinical risk factors (e.g., family history of OA, metabolic syndrome, malalignment and/or leg length discrepancy), and no radiological findings of OA (KL grade 0) [5]. Moreover, Luyten et al. proposed new EKOA classification criteria based on patient-reported outcomes (i.e., Knee Injury and Osteoarthritis Outcome score (KOOS) for defining pain and functional limitation), clinical examination (joint line tenderness and/or crepitus), and KL grade 0–1 [6].

Considering these uncertainties about a clear definition of EOA, various therapeutic approaches, both pharmacological and/or non-pharmacological, have been proposed in clinical practice, although no agreement has been reached on recommended interventions.

Pharmacological therapy (i.e., NSAIDs) is commonly prescribed to reduce pain and inflammation and might affect disease progression through immune-mediated mechanisms. Symptomatic slow-acting drugs, such as glucosamine, chondroitin sulfate, and diacerein, have also been suggested as early interventions for knee OA [7]. Intra-articular administration of corticosteroids and/or hyaluronic acid is widely used in clinical practice, although their roles are still debated [8].

Rehabilitation approaches are commonly prescribed in clinical practice and are supported by international guidelines for the management of OA, particularly exercise and assistive devices as well as physical agent modalities [9,10]. However, the effects of physical modalities on the joint environment as well as their clinical implications in the early stages of OA are poorly known. Therefore, an analysis of the literature is necessary to elucidate the mechanisms of action of this intervention in EOA, considering the huge variety of physical agents available and their applications in clinical practice. It is critical to study the effects of these interventions on not only pain management but also any changes induced to joint tissue, such as the articular cartilage and subchondral bone.

The purpose of this scoping review is to analyze the current knowledge regarding the biological effects and clinical effectiveness of physical agents in the management of patients with EOA.

## 2. Materials and Methods

This scoping review has been performed according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) model [11]. The technical expert panel (TEP) consisted of eight physicians, including four physiatrists with expertise in EOA (G.L.M, D.S., G.I., A.M.), three experts in scoping review methodology (F.G., M.P., S.L.), and one orthopedic surgeon (G.T.).

The TEP investigated the biological effects and clinical effectiveness of the following instrumental physical therapy on EOA: electric stimulation therapy, pulsed electromagnetic field (PEMF), laser therapy, magnetic field therapy, extracorporeal shockwave therapy (ESWT), cryotherapy, vibration therapy, and induced hyperthermia.

### *2.1. Search Strategy*

The TEP performed their research on PubMed (Public MedLine, run by the National Center of Biotechnology Information (NCBI) of the National Library of Medicine of

Bethesda, Bethesda, MD, USA), with a search string combining keywords for both EOA and physical therapy modalities (see Table 1 for further details on the search strategy).

**Table 1.** Search Strategy.

| |
|---|
| ("Electric Stimulation Therapy" [Mesh] OR "Pulsed Electromagnetic field" OR "Low-Level Light Therapy" [Mesh] OR "Laser Therapy" [Mesh] OR "Magnetic Field Therapy" [Mesh] OR "Extracorporeal Shockwave Therapy" [Mesh] OR "Hyperthermia, Induced" [Mesh] OR "Cryotherapy" [Mesh] OR "Vibration therapy" OR "Whole Body Vibration" OR "Physical Therapy Modalities" [Mesh]) AND ("Osteoarthritis" [Mesh] OR "Osteoarthritis, Spine" [Mesh] OR "Osteoarthritis, Knee" [Mesh] OR "Osteoarthritis, Hip" [Mesh] OR "Early Osteoarthritis") |

### *2.2. Study Selection*

The TEP considered, for eligibility, articles published from inception to 31 December 2020, including only those in the English language (see Table 2 for further details about eligibility criteria). All data extracted from full texts and findings from included studies were qualitatively analyzed.

**Table 2.** Eligibility criteria.

| **Inclusion Criteria** |
|---|
| - English language<br>- Reference period: from inception to 31 December 2020<br>- Study design: preclinical and clinical studies, including case reports, clinical trials, and observational studies.<br>- Studies including instrumental physical therapies for patients with EOA at any joint as intervention |
| **Exclusion Criteria** |
| - Books and documents, meta-analyses, reviews, systematic reviews, letters to the editor<br>- Population affected by osteoarthritis.<br>- Articles written in other languages.<br>- Studies investigating non-instrumental physical therapies as intervention |

## 3. Results

We initially found 3448 articles from the PubMed database. Based on the titles and abstracts and following our exclusion criteria, a total of 3432 papers were excluded. Further, eight articles were excluded after reading the full text because they did not meet our inclusion criteria. The remaining eight articles (published between April 2014 and December 2020) met the inclusion criteria (Figure 1).

All studies included in our analysis were focused on the effects of physical modalities on animal models of EKOA, except two studies investigating the efficacy and effectiveness of these interventions in patients with EKOA (Table 3). Six preclinical studies were included: five were conducted on the knees of rats and one on the knees of rabbits. One observational longitudinal study and one randomized, single-blind clinical trial were considered as clinical research. Among these studies, we found one randomized, single-blind trial concerning transcutaneous electrical nerve stimulation (TENS), three preclinical studies concerning ESWT; one preclinical study concerning low-intensity pulsed ultrasound (LIPUS); two articles concerning PEMF (one preclinical study and one prospective case series); and one preclinical study concerning whole-body vibration (WBV). No articles regarding laser therapy, cryotherapy, or other forms of induced hyperthermia were found.

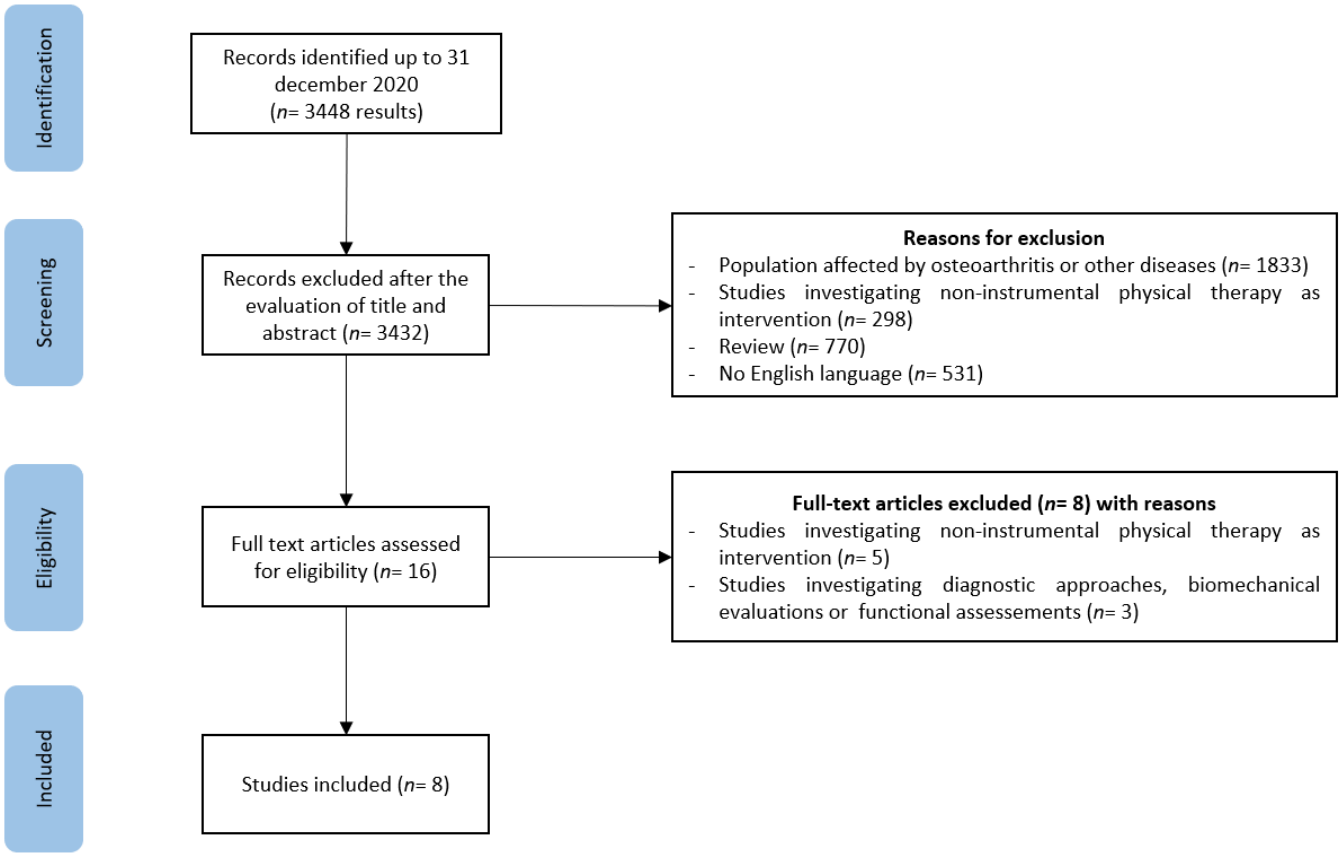


**Figure 1.** PRISMA-ScR flow diagram of the study selection process.

**Table 3.** Characteristics and findings of the included studies evaluating the effects, efficacy, and effectiveness of physical agent modalities in early osteoarthritis.

| Author, Year | Physical Therapy Modality | Study Design | Sample Size: Total (Group) | Administration | Main Findings |
|---|---|---|---|---|---|
| Cherian et al., 2015 [12] | TENS | Prospective, randomized, single-blinded trial, including EKOA patients (Kellgren–Lawrence grade 1) | *n* = 23<br>TENS group = 13<br>Control group = 10 | TENS: device included in a brace to wear for the entire day<br>Pulse waveform: asymmetric, biphasic, and simple modulated<br>Pulse rate: 12 s intervals of grouped pulses<br>Voltage current: 48–400 µs at 50% peak amplitude<br>Duration of the intervention: 3 months<br>Control: self-directed exercise therapy and/or corticosteroid injections | TENS significantly improved quadriceps strength, TUGT, objective KSS score, LEFS, and physical component of SF-36 compared to controls. |
| Chou et al., 2019 [13] | ESWT | Preclinical study on EKOA rat model (ACLT + MM) | *n* = 50<br>5 groups<br>(10 rats in each group) | Group I Sham: arthrotomy of left knee<br>Group II Meniscus: arthrotomy and ESWT applied to the medial edge of the meniscus<br>Group III OA: anterior cruciate ligament transacted (ACLT) and medial meniscectomy (MMx)<br>Group IV T(M): ACLT and MMx of left knee and ESWT applied to the proximal medial tibia plateaus<br>Group V Articular Cartilage: The animals received ACLT and MMx of left knee and ESWT applied to the articular cartilage surface of the proximal medial tibia plateaus<br>One ESWT at 1-week post-surgery with ultrasound guidance<br>ESWT: 800 impulses at 0.25 mJ/mm | ESWT applied to the subchondral bone has protective effects for articular cartilage, synovium, and subchondral bone. |

**Table 3.** *Cont.*

| Author, Year | Physical Therapy Modality | Study Design | Sample Size: Total (Group) | Administration | Main Findings |
|---|---|---|---|---|---|
| Hsu et al., 2017 [14] | ESWT | Preclinical study on EKOA rat model (ACLT) | *n* = 144 | Group I: normal control (NC)<br>Group II: EKOA induced by ACLT<br>Group III: EKOA induced by ACLT receiving ESWT (800 impulses at 0.18 mJ/mm$^2$, 4 Hz frequency) to the subchondral bone of the medial tibia plate.<br>12 rats in each group were sacrificed at 2, 4, 8, and 12 weeks post-surgery. Of the 12 rats at 2 weeks post-surgery, the articular cartilage and subchondral bone of tibia of 6 rats were used for proteome analysis and the joints of another 6 rats for immunohistochemistry analysis. | ESWT might affect chondrocytes' and osteoblasts' functions in the joint environment by modulating several factors of the rapid membrane signaling pathway, including Pdia-3, ERK1, OPG, ALP, and MMP13. These factors significantly increased at 2 weeks post-treatment, resulting in favorable histological changes. |
| Cheng et al., 2016 [15] | ESWT | Preclinical study on EKOA rat model (ACLT + MM) | *n* = 30 | Group I: sham<br>Group II: OA<br>Group III: OA + ESWT applied on the subchondral bone of the medial tibia plateau<br>One ESWT at 1-week post-surgery.<br>ESWT: 800 impulses at 0.22 mJ/mm and 4 Hz frequency<br>Histological and miRNA analyses were performed after 4 weeks.<br>A set of 729 miRNAs expressed in cartilage and subchondral bone was obtained. | ESWT induced expression of miRNA to control genes correlated with cartilage development and bone remodeling.<br>In the ESWT group, the articular surface damage was not obvious and only mild fibrillation was observed. |
| Xia et al., 2015 [16] | LIPUS | Preclinical study on rabbit EKOA model (ACLT) | *n* = 36 | Group I: early control (6)<br>Group II: early osteoarthritis (6)<br>Group III: early treatment (6)<br>Group IV: late control (6)<br>Group V: late osteoarthritis (6)<br>Group VI: late treatment (6)<br>The early and late treatment groups were exposed to low-intensity pulsed US 4 and 8 weeks after surgery | LIPUS protects cartilage from damage in early-stage osteoarthritis via the integrin/FAK/MAPK pathway |
| Yang et al., 2017 [17] | PEMF | Preclinical study on EKOA rat model (induced by low-dose of MIA) | *n* = 75 | Group I: OA (30)<br>Group II: pre-emptive PEMF (10) from day 0 to end of week 4<br>Group III: early PEMF (10) from week 4 to end of week 8<br>Group IV: delayed PEMF (10) end of week 8 to end of week 12<br>Group V: control (15)<br>After 1 week, rats in OA and PEMF groups were injected with 0.2 mg MIA through the infrapatellar ligament of the right knee only once. MIA was dissolved in sterile physiologic saline and administered in a 50 mL microsyringe. Control rats received a 50 mL sterile physiologic saline injection.<br>PEMF: Frequency of 75 Hz Intensity of 1.6 mT<br>Duration: 2 h/day for 1 months during the activities of daily life | Pre-emptive and early PEMF treatment significantly increased bone and cartilage synthesis and decreased bone and cartilage degradation<br>Pre-emptive PEMF treatment has a more beneficial effect on subchondral trabecular bone microarchitecture.<br>Delayed PEMF treatment only increased bone synthesis<br>The time point of treatment initiation is crucial for treating OA |
| Gobbi et al., 2014 [18] | PEMF | Prospective study (EKOA patients Kellgren–Lawrence grade 0–2) | *n* = 22 | PEMF (4 h per day) for 45 days<br>The maximum intensity of the magnetic field was 1.5 mT and the frequency was 75 Hz.<br>1- and 2-year follow-up. | PEMF reduced symptoms (pain and joint swelling) and improved knee function and activity level in EKOA patients at the 1-year follow-up, especially in young patients. These effects decreased at 2-year follow-up |

**Table 3.** *Cont.*

| Author, Year | Physical Therapy Modality | Study Design | Sample Size: Total (Group) | Administration | Main Findings |
|---|---|---|---|---|---|
| Wang et al., 2020 [19] | WBV | Preclinical study on EKOA rat model (induced by 0.15 mL mixture of 4% papain and 0.03 mmol/L l-cysteine into knee joint cavity) | $n$ = 40 | Group I: sham control (SC)<br>Group II: high frequency 60 Hz (HV1)<br>Group III: high frequency 40 Hz (HV2)<br>Group IV: middle frequency 20 Hz (MV)<br>Group V: low frequency 10 Hz (LV)<br>WBV (peak acceleration 0.3 g): 40 min/day and 5 days/week | WBV could alleviate the degeneration of articular cartilage. WBV regulates related gene expression at both mRNA and protein levels. HIF-2α could be a therapeutic target. The effect of WBV seems frequency-dependent: lower frequency shows better effects |

**Abbreviations.** TENS: transcutaneous electrical nerve stimulation; ESWT: extracorporeal shockwave therapy; EKOA: early knee osteoarthritis; KSS: Knee Society score; TUGT: Timed-Up-and-Go test; LEFS: Lower Extremity Functional Scale; SF-36: Short Form Health Survey-36 score; VAS: visual analog scale; PEMF: pulsed electromagnetic field therapy; ROM: range of motion; ACLT: anterior cruciate ligament transacted; MMx: medial meniscectomy; MIA: monosodium iodoacetate; Pdia-3: protein-disulfide isomerase-associated 3; OA: osteoarthritis; WBW: whole-body vibration; SC: sham control; HV1: high frequency 60 Hz; HV2: high frequency 40 Hz; MV: middle frequency 20 Hz; LV: low frequency 10 Hz; HIF-2α: hypoxia-inducible factor-2α; US: ultrasound; OPG: osteopontin; ALP: alkaline phosphatase; MMP-13: matrix metalloproteinase 13; qPCR: quantitative polymerase chain reaction.

### *3.1. TENS*

No preclinical study investigated the effects of TENS on EOA models.

A randomized, single-blind clinical trial was conducted by Cherian et al. [12] to assess the efficacy of TENS on 23 EKOA patients (KL grades 1 and 2) in terms of pain relief, muscle strength, functional improvements, and quality of life (QoL). Patients were randomly divided into two groups: one treated with TENS for three months and another one undergoing standard conservative therapy (exercise and/or corticosteroid injections; control group).

Despite some limitations of the study, related to the small sample size and the short-term follow-up (3 months), the authors reported that TENS compared to standard therapy resulted in significant improvements in the isokinetic muscle strength of quadriceps (+5.12 ft/lb vs. −4.64 ft/lb; $p = 0.0184$), Timed-Up-and-Go test (TUGT) (−7.2 s vs. +3.9 s; $p = 0.003$), Knee Society score (KSS) (+23.2 vs. +7.2; $p = 0.032$), SF-36 score (+11.4 vs. +1.7; $p = 0.030$), and Lower Extremity Functional Scale (LEFS) score (+20.8 vs. +7.5; $p = 0.042$). Moreover, significant pain relief (baseline VAS 5 vs. 3-month VAS 2.4; $p = 0.0027$) was reported in patients receiving TENS.

### *3.2. ESWT*

Three studies evaluated the effects of ESWT in animal models of EKOA. No clinical study on the role of ESWT in the treatment of EOA patients was found.

Chou et al. [13] conducted a comparative study on rats with EKOA to clarify the effects of ESWT on the articular cartilage of the medial compartment and the subchondral bone of the medial tibial plate. Fifty rats were randomly divided into five groups: Group 1 (sham group) received a simulated left knee arthrotomy without medial meniscectomy (MMx) and anterior cruciate ligament transection (ACLT); Group 2 (meniscus group) received a simulated arthrotomy of the left knee without ACLT and MMx but with ESWT applied to the medial rim of the meniscus; Group 3 (OA group) received ACLT and MMx of the left knee; Group 4 (T(M) group) received ACLT and MMx of the left knee in association with ESWT applied to the subchondral bone of the medial tibial plate; Group 5 (articular cartilage group) received ACLT and MMx of the left knee in association with ESWT applied to the articular cartilage surface of the medial tibial plate. The application of ESWT on the subchondral bone of the medial tibial plates compared to its application on articular cartilage resulted in statistically significant changes in terms of cartilage surface damage, loss of cellularity, loss of matrix staining, loss of tidemark integrity (modified Mankin score 1.60 ± 0.21 vs. 3.00 ± 0.23; $p < 0.05$), maximum extension angle of joint-surface damage (26.22 ± 4.00 vs. 57.36 ± 8.67; $p < 0.05$), bone mineral density (0.34 ± 0.03

vs. 0.29 ± 0.02; $p < 0.05$), and medial tibial plate injury (55.43 ± 8.32 vs. 87.04 ± 6.82; $p < 0.05$). The authors also analyzed the effects of ESWT on synovial tissue compared to OA and articular cartilage groups, demonstrating statistically significant differences in terms of the thickening of synovial cell lining (1.80 ± 0.20 vs. 2.60 ± 0.25 and 2.80 ± 0.20; $p < 0.05$), synovial hyperplasia (1.60 ± 0.25 vs. 2.80 ± 0.20 and 2.60 ± 0.25; $p < 0.05$), and cell infiltration (1.60 ± 0.25 vs. 2.80 ± 0.20 and 2.60 ± 0.25; $p < 0.05$), synovitis score (5.00 ± 0.40 vs. 8.20 ± 0.34 and 8.00 ± 0.40; $p < 0.05$) and IL1β expression (IL1β layer score 1.56 ± 0.24 vs. 2.22 ± 0.22 and 2.33 ± 0.20; $p < 0.05$). Moreover, the T(M) group showed significantly increased expression of chondrogenesis proteins such as TGF-β1 and DMP-1 compared to the OA and articular cartilage groups (70 ± 9.9% and 9 ± 3.9% vs. 46 ± 9.4% and 4 ± 1.9% vs. 52 ± 7.2% and 2 ± 2.5%; $p < 0.05$) as well as reduced expression of cartilage degradation enzymes such as matrix metalloproteinase 13 (MMP-13) and the A Disintegrin And Metalloproteinase with ThromboSpondin motif (ADAMTS-5) (7 ± 3.2% and 10 ± 4.1% vs. 14 ± 2.4% and 21 ± 5.2% vs. 12 ± 2.8% and 24 ± 7.9%; $p < 0.05$). Finally, authors reported that ESWT did not result in significant differences between the sham group and the meniscus group in terms of OA lesion score (0.00 ± 0.00 vs. 0.05 ± 0.05), maximum extension angle (19.12 ± 1.65 vs.19.91 ± 1.87), bone mineral density (0.35 ± 0.02 vs. 0.34 ± 0.04), and medial tibia lesion (0 vs. 0), suggesting a good safety profile of ESWT (at the dosage of 0.25 $mJ/mm^2$) for treating EKOA.

Hsu et al. [14] provided the first evidence that ESWT increased the expression of several factors modulating rapid membrane signaling pathways that affect the integrity and function of chondrocytes and osteoblasts in the joint environment in EKOA. A preclinical study was conducted on 144 rats, randomly divided into 3 groups. Group 1 (normal control, NC) received neither the transection of ACLT nor ESWT; Group 2 received ACLT (OA group), whereas Group 3 underwent ACLT and received ESWT on the medial tibial plate subchondral bone (OA + ESWT). ESWT determined an overexpression of the mRNA of protein-disulfide isomerase-associated 3 (Pdia-3), a key mediator of the 1α,25-dihydroxy vitamin D 3 (1α,25(OH)2D3) non-genomic pathway, and extracellular signal-regulated protein kinase 1 (ERK1), implicated in mechanical-stimulated bone formation, compared to the OA and NC groups ($p < 0.001$). An increase in bone formation markers, such as alkaline phosphatase (ALP), osteopontin (OPG), and MMP-13, was also observed compared to OA and NC ($p < 0.001$), resulting in improved osteogenesis and an improved turnover rate of the subchondral bone in the knees affected by OA. Additionally, compared to the OA and NC groups, a decrease in cartilage matrix loss was observed in the OA + ESWT group, with higher expression of collagen II (increased by about 3 times; $p < 0.001$) and aggrecan (increased by about 20 times; $p < 0.001$). Histological analysis revealed that Group 3 had significantly lower Mankin scores compared to Group 2 at all follow-ups (2-, 4-, 8-, and 12 weeks).

The chondroprotective role of ESWT was also evaluated by Cheng et al. [15], who performed a gene processing of microRNAs (miRs) found in articular cartilage and subchondral bone following ESWT. The authors conducted a preclinical study on 30 rats undergoing ACL resection in combination with MMx (ACLT + MMx) to induce EOA-like changes in joints (OA group). Following the application of ESWT to the medial tibial plateau subchondral bone (OA + SW group), histological samples were collected and processed to identify specific miRNA activated or suppressed by the intervention and correlated with OA-related changes. ESWT stimulates or inhibits the expression of several specific miRNA for cartilage and subchondral bone, controlling genes involved in cartilage development and bone remodeling. The histological analysis showed only mild fibrillation on the surface of articular cartilage in the OA + SW group at 4 weeks. In articular cartilage, 4 miRs were found to be increased and 10 miRs were decreased in OA vs. OA + SW groups, respectively, while in the subchondral bone, 3 miRs were increased and 9 miRs were decreased in OA vs. OA + SW groups. In this group, in both articular cartilage and subchondral bone, rno-miR-181a-5p was significantly up-regulated compared to the OA group.

### *3.3. LIPUS*

No clinical study about the role of LIPUS in the treatment of EOA patients was found.

Xia et al. [16] studied the chondroprotective effect of LIPUS on animal models of early and late OA. The authors conducted a preclinical study on 36 rabbits, randomly divided into 6 groups (i.e., early control, EOA, early treatment, late control, late OA, and late treatment). All groups were submitted to surgical procedures: control groups received sham operations with knee exposure, while all other groups received ACLT. Early treatment and late treatment groups were treated with LIPUS at 4 and 8 weeks after surgery, respectively. After treatment with LIPUS, the first group showed a slightly irregular cartilage surface and chondrocytes proliferation, but in the late treatment group, the cartilage damage remained almost unchanged. The Mankin score was significantly higher in the EOA group vs. the early treatment group, whereas no significant between-group difference was reported for histological changes in the late treatment vs. late OA groups. In addition, early use of LIPUS has been shown to significantly increase type II collagen expression ($p < 0.05$) and decrease MMP-13 levels ($p < 0.05$) compared to the EOA group, while no significant changes were reported in the comparison between late LIPUS vs. late OA. Authors have also investigated the effect of LIPUS on the integrin/focal adhesion kinase (FAK)/mitogen-activated protein kinase (MAPK) signaling pathway, which plays an important role in the pathogenesis of OA by targeting the ECM in articular cartilage. This study demonstrated that early application of LIPUS significantly increased the expression of integrin β1 ($p < 0.05$) and phosphorylated FAK ($p < 0.05$) and decreased the expression of ERK1/2 ($p < 0.05$) and phosphorylated MAPK 38 ($p < 0.05$) compared to the EOA group.

### *3.4. PEMF*

Two papers investigated the role of PEMF in EOA (one preclinical study and one case series).

In the preclinical study of Yang et al. [17], the effects of PEMF were assessed on cartilage and subchondral bone at different stages of knee OA. Seventy-five rats were divided into five groups: the control group (sterile saline injection), a group previously treated with PEMF (in the 4 weeks preceding injections of 0.2 mg iodoacetate monosodium (MIA) to induce OA), a group early treated with PEMF (4 to 8 weeks after MIA injection), a group late treated with PEMF (from 8 weeks to 12 weeks after MIA injection), and a group with OA. Preventive treatment with PEMF was shown to preserve subchondral trabecular bone microarchitecture compared to the OA group, with significant reductions of trabecular separation (Tb.Sp) in all knee compartments (medial tibia: 111.18 ± 13.21 μm vs. 143.27 ± 13.36 μm, $p = 0.003$; lateral tibia: 120.32 ± 8.80 μm vs. 151.47 ± 4.37 μm, $p < 0.0001$; medial femur: 93.85 ± 10.46 μm vs. 119.25 ± 7.92 μm; $p = 0.001$; lateral femur: 115.03 ± 8.48 μm vs. 95.67 ± 20.84 μm, $p = 0.002$. respectively) and significantly higher bone volume fraction (BV/TV) in the medial and lateral tibia (50.11 ± 6.28% vs. 36.84 ± 3.07%, $p = 0.001$; 38.85 ± 2.89% vs. 33.71 ± 2.36%, $p = 0.021$) and in the medial femur (52.08 ± 5.34% vs. 45.34 ± 2.25%, $p = 0.043$), trabecular thickness (Tb.th) in the medial tibia and femur compartments (118.21 ± 16.98 μm vs. 87.95 ± 5.09 μm, $p = 0.002$; 104.59 ± 12.81 μm vs. 86.71 ± 7.83 μm, $p = 0.044$), and trabecular number (Tb.N) in the lateral tibia and femur compartments (4.85 ± 0.27 l/mm vs. 4.35 ± 0.12 l/mm, $p = 0.007$; 5.21 ± 0.22 l/mm vs. 4.82 ± 0.11 l/mm, $p = 0.006$). Early treatment with PEMF resulted in a significant increase of Tb.N in the medial and lateral tibia (4.18 ± 0.09 l/mm vs. 3.78 ± 0.16 l/mm, $p < 0.0001$; 4.57 ± 0.09 vs. 4.14 ± 0.17 l/mm, $p = 0.0001$) and significant reduction of Tb.Sp in the medial tibia (114.21 ± 11.42 μm vs. 135.12 ± 14.83 μm, $p = 0.04$) compared to the OA group. Tb.N of the lateral tibia was also significantly higher in the group early treated with PEMF compared to the control group (4.57 ± 0.09 l/mm vs. 4.23 ± 0.14 l/mm, $p = 0.008$). The late treatment with PEMF resulted in significant improvements of BV/TV (56.48 ± 6.03% vs. 43.54 ± 5.45%, $p = 0.004$), bone mineral density (BMD) (862.99 ± 55.37 mg/cc vs. 743.52 ± 62.77 mg/cc; $p = 0.008$), and Tb.N (4.13 ± 0.17 l/mm vs. 3.74 ± 0.24 l/mm, $p = 0.016$) and significant decreases of Tb.Sp in

the medial tibia (109.46 ± 14.45 μm vs. 139.01 ± 18.80 μm, $p = 0.019$) compared to the OA group. Moreover, in the delayed PEMF group, compared to the control group, there was a significant decrease in Tb.N in the medial tibia (4.13 ± 0.17 l/mm vs. 4.55 ± 0.28 l/mm, $p = 0.043$) as well as significant increases of BMD in all knee compartments (medial tibial: 862.99 ± 55.37 mg/cc vs. 627.46 ± 44.96 mg/cc, $p < 0.0001$; lateral tibial: 762.60 ± 45.06 mg/cc vs. 583.75 ± 36.30 mg/cc, $p = 0.001$; medial femur: 657.70 mg/cc ± 61.51 vs. 845.04 ± 65.83 mg/cc, $p = 0.007$; lateral femur: 823.56 ± 41.71 mg/cc vs. 649.87 ± 40.09 mg/cc, $p = 0.003$). Furthermore, preventive and early treatment with PEMF also significantly increased the bone formation markers compared to the OA group, such as serum osteocalcin (OC) ($p = 0.003$ and $p = 0.001$, respectively), serum N-propeptide IIA of type II collagen (PIIANP) ($p < 0.001$, both), urine C-terminal telopeptide of collagen type I (CTX-I) ($p = 0.005$ and $p = 0.004$, respectively) and urine C-terminal telopeptide of collagen type II (CTX-II) ($p < 0.001$ and $p = 0.019$, respectively). Moreover, preventive and early PEMF significantly reduced cartilage degradation, whereas delayed PEMF only increased the markers of bone synthesis.

In the prospective study of Gobbi et al. [18], the effectiveness of PEMF in patients with symptomatic EKOA was investigated. Forty-eight patients were recruited, receiving PEMF for 4 h per day for a period of 45 days. Of these, only 22 patients met the study inclusion criteria (aged 30–60 years, symptomatic EKOA with KL grade 0–2) and were followed for 2 years. After the application of PEMF, improvements of pain, other symptoms (e.g., joint swelling and stiffness), participation in activities of daily living (ADL), QoL, and activity level (work and sport) were observed, and these results were maintained at 1 year, while they decreased in the 2-year follow-up. Furthermore, these results were greater in young patients (<45 years) than in those aged >45 years. At 1 year after treatment, significant improvements in KOOS Pain (52.4 ± 4.9 vs. 89.7 ± 4.4; $p = 0.006$), KOOS Symptoms (55.2 ± 5.0 vs. 87.5 ± 3.5; $p = 0.04$), KOOS ADL (53.3 ± 5.6 vs. 94.8 ± 2.9; $p = 0.002$), KOOS Sport (28.0 ± 5.9 vs. 75.4 ± 6.2; $p = 0.001$), KOOS QOL (35.6 ± 4.5 vs. 80.5 ± 4.7; $p = 0.008$), VAS (5.6 ± 0.3 vs. 1.3 ± 0.4; $p = 0.001$), and Tegner Activity scale (2.5 ± 0.5 vs. 4.5 ± 0.5; $p = 0.002$) were reported. At 2 years after treatment, the values remained higher than baseline, showing no significant improvement: KOOS Pain (52.5 ± 4.9 vs. 75.9 ± 3.6; $p = 0.422$), KOOS Symptoms (55.2 ± 5.0 vs. 72.2 ± 3.7; $p = 0.306$), KOOS ADL (53.3 ± 5.6 vs. 72.9 ± 3.9; $p = 0.971$), KOOS Sport (28.0 ± 5.9 vs. 75.4 ± 6.2; $p = 0.503$), KOOS QOL (35.6 ± 4.5 vs. 66.8 ± 6.1; $p = 0.224$), VAS (5.6 ± 0.3 vs. 2.2 ± 0.6; $p = 0.037$), and Tegner Activity scale (2.5 ± 0.5 vs. 3.8 ± 0.5). An improvement in ROM was observed both 1 year after treatment (0–131.1° ± 2.5°) and 2 years after treatment (1.2–127.2° ± 5.1°) compared to baseline (7.5–120.0° ± 4.2°). The authors also conducted a comparison of results between patients younger than 45 and those older than 45. From this comparison, statistically significant results emerged 1 year after treatment in patients younger than 45 years, particularly in terms of the Tegner Activity scale (6.1 ± 0.5 vs. 2.9 ± 0.5; $p = 0.01$)

### *3.5. WBV*

No clinical study about the role of WBV in the treatment of EOA patients was found.

Wang et al. [19] investigated the effects of different frequencies (10, 20, 40, and 60 Hz) of WBV in the progression of EKOA in animal models. Forty rats were divided into five groups: a control group; a group treated with high-frequency vibrations of 60 Hz; a group treated with high-frequency vibrations of 40 Hz; a group treated with medium frequency vibrations of 20 Hz; and a 10 Hz low-frequency vibration group. In all groups treated with WBV, the treatment lasted 8 weeks. Low-frequency WBV compared to higher-frequency WBV resulted in significant reductions in the expression of IL1β ($p < 0.001$), the inducible factor by hypoxia 2-α (HIF-2 α) ($p < 0.001$), and the catabolic enzyme MMP-13 ($p < 0.001$) and increased the expression of collagen type II α 1 (COL2A1) ($p < 0.001$). Low-frequency WBV also led to a greater reduction in the degeneration of articular cartilage, assessed by the Osteoarthritis Research Society International (OARSI) grading system, compared to high-frequency WBV ($p = 0.002$ and $p = 0.027$, respectively).

## 4. Discussion

To the best of our knowledge, this is the first review that specifically addresses the effects of physical agent modalities in EOA. According to PRISMA-ScR [11], our paper aims to synthesize evidence and identify gaps on a specific topic (how physical agents might work in EOA) "from a body of knowledge that is heterogeneous in methods or discipline", considering that EOA is still a debated topic. Indeed, our review also suggests that the studies included did not use any of the diagnostic criteria proposed for EOA so far [4–6].

This is a complex disease to deal with, considering that consensus about its definition, diagnosis, and treatment is still debated. Its management is even more intricate due to the high variability of clinical and instrumental findings. Therapeutic approaches recommended for managing OA [9,10], such as non-surgical interventions, including physical therapies, are usually also first-line interventions for EOA [20]. In clinical practice, physical agent modalities are widely used alone or in combination with other conservative treatments in all phases of OA [21]. However, their use is supported by a few studies with methodological limitations, particularly in dosage information, and their effects are usually based on short-term pain relief only. Moreover, for some physical agent modalities (i.e., TENS), recent international guidelines have recommended against their use in patients with knee or hip OA. Despite poor evidence available, physical therapies are widely used as adjuvant interventions for OA, also considering their optimal safety profile [21,22]. Another key issue concerns the timing of the intervention of physical agents in OA, as suggested by some experimental data. For example, LIPUS seems more effective in the early phases than in the late phases of joint degeneration.

As demonstrated by our review, several physical modalities have been studied for the treatment of EOA, such as TENS, ESWT, LIPUS, PEMF, and vibration therapy, although these interventions have been predominantly investigated in preclinical studies, all aimed at the treatment of EKOA. It should be emphasized that the clinical implications of the findings derived by the preclinical studies should be considered with caution, considering that in animal models, the EOA is mainly due to trauma (ACL injuries and/or meniscus injury). Moreover, the clinical studies included in our review used different diagnostic criteria for EOA (Kellgren–Lawrence grade 1 or 0–2) [12,18].

According to our scoping review, TENS showed pain-relieving action along with beneficial effects on joint function, quadriceps strength, physical performance, and QoL in patients with EKOA [12]. The functional benefits of TENS has opened interesting scenarios, supporting its use in combination with therapeutic exercise. Indeed, exercise is a core strategy in all stages of OA [10] and has been demonstrated to be also effective in EKOA in middle-aged adults, including high-risk populations (i.e., athletes) [23,24].

Emerging evidence supports ESWT as non-invasive therapy for OA [25], whereas data about the effectiveness of this physical modality for patients with EOA are lacking. Chou et al. [13] have shown on animal models that ESWT has protective effects for joint tissues (i.e., articular cartilage, synovium, subchondral bone), delaying the progression of OA. These effects were superior if ESWT was applied directly to the subchondral bone rather than to articular cartilage.

Cheng et al. [15] performed a gene analysis of miRNAs expressed in joint tissues after an application of ESWT, revealing rather conflicting data that do not allow us to reach clear and definitive conclusions regarding the role of ESWT in EKOA.

Significant up-regulation of miR-181a-5p was observed both in articular cartilage and subchondral bone in rats with EKOA receiving ESWT compared to the EKOA group [15]. It has been reported that the up-regulation of miR-181a-5p increases oxidation of the ECM by reducing the expression of selenoprotein glutathione peroxidase 1 (GPX1) and 4 (GPX4) through the inhibition of their target, selenocysteine insertion sequence binding protein 2 (SBP2), finally resulting in cartilage damage [26]. However, Cheng et al. [15] reported only negligible damage of the articular surface, with slight fibrillation in rat knees treated with ESWT.

The protective action of ESWT on the joint environment in EKOA could be attributable to the increased expression of mediators involved in the membrane signaling pathway, such as Pdia-3, ERK1, OPG, ALP and MMP-13, after only 2 weeks, resulting in favorable histological findings [14]. Pdia-3 is a protein that mediates the membrane response to 1$\alpha$, 25 (OH) 2D3, and it is involved in the regulation of protein kinase C (PKC) activation and the release of prostaglandin E2 (PGE2), following stimulation by phospholipase A2 (PLA2). In this way, Pdia-3 regulates the transcription of genes related to bone mineralization through the phosphorylation of transcription factors such as ERK 1/2 in cells with mitogenic functions, similar to osteoblasts. ERK-1 is a kinase that acts as a mediator for the differentiation and proliferation of osteogenic cells. Once activated by Pdia-3, following the application of ESWT, ERK-1 migrates to specific nuclear targets, causing an increase in bone formation in the areas of damage. Therefore, by modulating the expression of Pdia-3 in the subchondral bone, ESWT improves subchondral bone remodeling.

LIPUS stimulates the proliferation of chondrocytes and prevents cartilage damage in EOA through the integrin/FAK/MAPK pathway with an increase in type II collagen and a reduction in the expression of MMP-13 [16]. This occurs because the application of LIPUS in an early stage of OA determines a greater expression of β1 integrin and phosphorylated FAK and down-regulation of the expression of ERK1/2 and phosphorylated p38. On the contrary, in advanced OA, this intervention resulted in the down-regulation of β1 integrin and phosphorylated FAK and the up-regulation of ERK1/2 and p38, which might negatively affect the disease course. These findings indicate that the time schedule of physical modalities might play the main role in the management of OA.

PEMF seems a promising therapeutic option for EKOA, as it preserves subchondral trabecular bone microarchitecture, prevents subchondral bone loss, and increases bone and cartilage synthesis. These protective effects on the subchondral bone were more pronounced in animal models previously treated with PEMF compared to early or delayed interventions after the induction of OA [17]. From a clinical perspective, the effectiveness of PEMF has been investigated in a prospective study, including patients with EKOA. This intervention was demonstrated to be effective in terms of pain relief and improvement of knee function, physical performance, and QoL at both 1- and 2-year follow-ups, particularly in patients younger than 45 years, although a significant worsening of outcome measures between the first and the second year was observed [18]. These findings suggest the need to repeat PEMF after a certain period. Moreover, the age of the patient with EKOA can play a critical role in the effectiveness of PEMF, with better results generally obtained in patients at a younger age.

Experimental data suggest that exposure to low-frequency WBV has protective effects on the knee joint as it counteracts the degeneration of articular cartilage in rats [19]. Its main observed effects were the reduction of the expression of cartilage catabolic factors (HIF-2$\alpha$, MMP-13) and inflammatory mediators (i.e., IL1β), along with the increased expression of COL2A1, resulting in favorable histological findings.

Starting from preclinical studies conducted on animals, further implementation through research on clinical studies conducted on humans is essential to be able to identify a standard method based on exact dosages and time parameters.

The main limitation of our review is the search strategy, including only one (although the most used) database (i.e., PubMed), which might be a selection bias. Another limitation is due to the prevalence of preclinical scientific studies conducted on small animals (rats and rabbits), whose anatomy and physiology of the knee differ from that of humans. This could decisively influence the reproducibility of the results obtained in future studies in humans, where, in addition to the different dimensions, there are different anatomical and physiological characteristics. Further limitations are the lack of information on the safety of some physical therapies (e.g., WBV), the appropriate dosage recommended for humans, and the lack of data on pain and disease progression in most animal studies.

## 5. Conclusions

Identification of EOA is challenging because different diagnostic criteria have been proposed in the last decade. This issue must be solved to better define the role of the available therapeutic options for OA. Our review contributes to increasing knowledge about the mechanisms of action of several physical therapies in EKOA, suggesting their role in modifying disease progression, mainly thanks to its action on the subchondral bone and through gene modulation. In this context, experimental data suggest that the effects of physical modalities are affected by the timing of the intervention with physical modalities. In clinical practice, these interventions are widely used, with weak scientific support, particularly concerning the limited data available from clinical studies.

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