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Review

Applications and Future Perspective of Pulsed Electromagnetic Fields in Foot and Ankle Sport-Related Injuries

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Abstract: Foot and ankle injuries are common in many sports. One of the main athletes issues is the time for sport resumption after trauma. Recently, extensive efforts have been made to speed up the athletes' return-to-sport and to prevent joint degeneration. Among the conservative treatment options, biophysical stimulation with pulsed electromagnetic fields (PEMFs) is listed. This narrative review aims to outline current applications of PEMFs in main foot and ankle sport-related injuries, in particular in the treatment of bone marrow edema, osteochondral defects, fractures, and nonunions. Despite further high-quality studies on foot and ankle injuries are needed, PEMFs seem to be a valid aid to enhance the endogenous osteogenesis, to resolve the bone marrow edema, to inhibit the joint inflammation, preserving articular cartilage degeneration, and to relieve pain.

Keywords: pulsed electromagnetic fields; pain; bone marrow edema; fractures; nonunion; physical therapy; sport; foot and ankle

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Citation: Mazzotti, A.; Langone, L.; Artioli, E.; Zielli, S.O.; Arceri, A.; Setti, S.; Leigheb, M.; Samaila, E.M.; Faldini, C. Applications and Future Perspective of Pulsed Electromagnetic Fields in Foot and Ankle Sport-Related Injuries. *Appl. Sci.* **2023**, *13*, 5807. https://doi.org/10.3390/app13095807

Academic Editor: Daniel X. B. Chen

Received: 5 April 2023
Revised: 3 May 2023
Accepted: 5 May 2023
Published: 8 May 2023

1. Introduction

Foot and ankle injuries are common in many sports [1]. These injuries often lead to a significant time to sport resumption and a variable rate of sequelae with persisting symptoms.

Extensive efforts have been made to improve the management of sports injuries, to speed up the athletes' return-to-sport, and to prevent pathological conditions: nonsteroidal anti-inflammatory drugs, Hyaluronic-acid, Platelet Rich Plasma (PRP), different formulations of stem cells' injection, and biophysical stimulation [2,3].

Several biophysical stimulation devices have a consolidated role in the treatment of many musculoskeletal disorders, and already shown positive effects on articular cartilage, subchondral bone, and synovium [4]. These devices are classified into electrical energy applied directly to the skin by adhesive electrodes (capacitively coupled electric field, CCEF), by ultrasound probe (low-intensity pulsed ultrasound system, LIPUS), by transient pressure disturbances (extracorporeal shock wave therapy, ESWT), by low-frequency continuous laser (Low-Level Laser Therapy LLLT), or by pulsed electromagnetic energy applied by coils (pulsed electromagnetic fields, PEMFs) [4].

Among these conservative treatment options, biophysical stimulation with PEMFs consists in the application of nonionizing physical energy to a biological system in order to exert an anti-inflammatory effect and anabolic activity, acting mainly at the level of the cell membrane, and to increase and facilitate tissue regeneration [4].

PEMFs have shown positive effects on articular cartilage, bone, and synovium, as the musculoskeletal system is highly responsive to its physicochemical environment [4].

Thanks to these features, PEMFs have found several applications in sport-related injuries, in order to reduce joint inflammation and swelling, resolve bone marrow edema (BME), limit cartilage degeneration, and promote tissue healing. In addition, PEMFs may play a role as a post-surgical treatment to avoid chronic pain, and functional limitations, to enhance tissue regeneration, and to preserve the mechanical and biological properties of the repaired cartilage. PEMFs are also used as an adjuvant surgical treatment to initialize and finalize the osteogenic process in cases of fractures, delayed union, and nonunions [5].

This narrative review aims to outline current applications of PEMFs in foot and ankle sport-related injuries.

2. Applications

Current PEMFs applications derived from several laboratory and clinical investigations. Different studies reported the use of PEMFs therapy in the treatment of various pathological conditions. Regarding foot and ankle sport-related injuries, main applications of are represented by BME, osteochondral defects (OCD), fractures, and nonunions. Moreover, other conditions such as fasciae and tendon pathologies appear to theoretically benefit from PEMFs therapy.

2.1. BME

BME is defined as a condition characterized by an area of low signal intensity in T1- weighted and high signal intensity findings on T2-weightd on Magnetic Resonance Imaging (MRI) [6]. In the foot and ankle, the talus is the most affected foot bone [7].

This condition represents a nonspecific finding with multiple etiologies. Under physiological circumstances, high-intensity exercise triggers bone remodeling process. However, a repeated mechanical overload beyond a certain intensity can result in an incomplete remodeling process, and in an imbalance between bone apposition and absorption, with an alteration of the physiological trabecular bone architecture. This bone stress reaction results in pain and disability [8].

If adequately treated, BME resolves; in other conditions, it can also evolve towards bone necrosis.

The rational for the use of PEMFs in the treatment of BME are based on two fundamental mechanisms of action: (1) PEMFs can play a role in the local inflammation control [9,10] and (2) can enhance the healing process by stimulating neovascularization and new bone formation [11,12].

Martinelli et al. [7] investigated the effectiveness of PEMFs on patients with talar BME, determining their effect on MRI findings. BME reduced after 1 month of treatment and completely resolved within 3 months. Normal signal intensity and no signs of progression to avascular necrosis were reported, associated with a significant decrease in pain after 3 months. The mean American Orthopaedic Foot and Ankle Society (AOFAS) score improved from 59.4 (range, 40–66) before treatment to 94 (range, 80–100) at the last follow-up. The Visual Analog Scale (VAS) score decreased significantly from 5.6 (range, 4–7) before treatment to 1 (range, 0–2) at the last follow-up.

This study confirms the evidences already reported on other joints. At the hip level, different authors described the use of PEMFs in the management of avascular necrosis of the femoral head in adults with positive results [13]. Results were evaluated using the Ficat classification. The Ficat classification stages osteonecrosis of the femoral head using a combination of plain radiographs, MRI, and clinical features: five different stages of bone necrosis are recognized, from Stage 0 to Stage 4 [14]. Al-Jabri et al. [13] performed a systematic review reporting that early Ficat stages show the best responses to treatment via PEMFs with improvements in both clinical and radiographic parameters.

Similarly, good outcomes were reported at the knee level: Marcheggiani Muccioli [15] et al. reported the results on spontaneous osteonecrosis of the knee in the early stage.

Twenty-eight patients suffering from symptomatic Koshino I spontaneous osteonecrosis of the knee, confirmed by MRI, were treated with local PEMFs (6 h daily for 90 days). Pain, measured using the visual analog scale (VAS) (a 100-mm horizontal line, where the left end represents no pain, and the right end maximum possible or unbearable pain), significantly reduced at 6 months (from 73.2 ± 20.7 to 29.6 ± 21.3, $p < 0.0001$), which remained almost unchanged at the final follow-up (27.0 ± 25.1). Knee society score (KSS) significantly increased in the first 6 months (from 34.0 ± 13.3 to 76.1 ± 15.9, $p < 0.0001$) and was slightly reduced at the final follow-up (72.5 ± 13.5, $p = 0.0044$). Tegner median level increased from baseline to 6-month follow-up (1 (1–1) and 3 (3–4), respectively, $p < 0.0001$) and remained stable. EQ-5D (a standardized measure of health-related quality of life developed to provide a simple, generic questionnaire for use in clinical and economic appraisal and population health surveys) improved significantly throughout the 24 months (0.32 ± 0.33, baseline; 0.74 ± 0.23, 6-month follow-up ($p < 0.0001$); 0.86 ± 0.15, 24-month follow-up ($p = 0.0071$)). Significant reduction in the total Whole-Organ Magnetic Resonance Imaging Score (WORMS) mean score ($p < 0.0001$) and mean femoral bone marrow lesion's area ($p < 0.05$) were observed. This area reduction was present in 85% and was correlated to WORMS grading both for femur, tibia, and total joint ($p < 0.05$). Four failures (14.3%) at the 24-month follow-up were reported.

Current applications of PEMFs for BME and osteonecrosis are summarized in Table 1.

Table 1. Summary of studies related to BME.

Disease	Study	Characteristics	Results
BME	Martinelli et al. [7]	Talar BME. Duration: 8 h/d for 30 days. Time of pulse (rise time): 1.3 ms Frequency: 75 Hz. Induced voltage of 3.5 ± 0.5 mV.	Significant BME area reduction associated with a significant decrease in pain within 3 months of beginning treatment
	J.L. Cebrián et al. [16]	Osteonecrosis of the head in pre-collapse bone stages Duration: 8 h/d for 6 months. Time of pulse (rise time): 1 at 3 ms Frequency: 75 Hz Intensity: 400 mA	PEMFs reduce the incidence of radiographic progression of symptomatic osteonecrosis of femoral head in early stages and provide successful clinical results
	Marcheggiani Muccioli et al. [15]	Spontaneous osteonecrosis of the knee. Duration: 6 h/d for 90 days. Frequency: 75 Hz Duty-cycle: 10%. Peak magnetic field: 1.5 mT	PEMFs stimulation significantly reduced knee pain and necrosis area in Koshino stage I spontaneous osteonecrosis of the knee
	L. Massari et al. [17]	Osteonecrosis of the femoral head. Duration: 5 ± 2 months. Time of pulse (rise time): 1.3 ms. Frequency: 75 Hz Induced voltage: 2 ± 0.5 mV	The study confirms that PEMFs treatment may be indicated in the early stages of osteonecrosis of the femoral head
	C. Windisch et al. [18]	Osteonecrosis of the femoral head Duration: 6- and 12-month postoperative follow-up Frequency: ~20 Hz Flux density: ~5 mT Induced voltage: ~700 mV	No better clinical results and does not offer better prophylaxis for the avoidance of total hip arthroplasty over all ARCO stages

Table 1. *Cont.*

Disease	Study	Characteristics	Results
	Bassett et al. [19]	Femoral head osteonecrosis. Helmholtz-aiding coils Duration: 8–10 h/day Frequency: 15 Hz Single pulse frequency: 72 Hz	PEMF patients have experienced long-term improvements in symptoms and signs, together with a reduction in the need for early joint arthroplasty
	R.K. Aaron et al. [20]	Osteonecrosis of the femoral head. Duration: 8 h/day Single pulse frequency: 72 Hz 380 ms	Exposure to pulsing electromagnetic fields appears to be more effective in hips with Ficat II lesions than in hips with more advanced lesions.

2.2. OCD

ODC are focal areas of damaged articular cartilage and subchondral bone. OCD are common sport-related injuries and can often deeply affect the patient's quality of life [21].

Intra-articular injuries are known to occur more frequently in an athletic population: compared with the general population, athletes place a higher demand on the joint surfaces and, as a result, are more likely to develop pathological conditions.

Repetitive high-intensity loading during pivoting and twisting and acute contact trauma, especially in association with joint instability or deformities, can lead to OCD and/or rapid progression of cartilage injury [22].

This might explain why it is reported that osteoarthritis has a higher prevalence in former athletes [23].

Due to its poor restorative capacity, articular cartilage should be preserved in all its components: cells and extracellular matrix, together with subchondral bone.

The primary treatment for talar OCD up to 1.5 cm in diameter is surgical [24]: even if well treated, these lesions may require as much as one year to obtain clinical improvement in the symptomatology. PEMFs can support surgical treatment to speed up functional recovery and achieve better outcomes.

At the joint level, PEMFs perform a strong anti-inflammatory action and have a chondroprotective effect. In human osteoarthritic synovial fibroblasts, PEMFs inhibit the release of prostaglandin E2 (PGE2) and the pro-inflammatory cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8), while stimulating the release of interleukin-10 (IL-10), an anti-inflammatory cytokine. These effects are mediated by the PEMFs-induced up regulation of adenosine A2A, 3 adenosine receptors [25]. Moreover, PEMFs counteract the interleukin-1β (IL-1β) effect, thus increasing the synthesis of proteoglycans and proliferation of chondrocytes acting in concert with insulin-like growth factor-1 (IGF-1) present in both synovial fluid and articular cartilage; this plays a key role among the anabolic growth factors that control articular joint metabolism [26]. In addition, in human articular chondrocytes [27], PEMFs stimulation increase extracellular matrix component synthesis, such as collagen II (COLL II), glycosaminoglycan (Gags), and proteoglycans (PGs) [28].

Several studies have been published specifically reporting the use of PEMFs in surgically treated OCD.

Cadossi et al. reported the results of a prospective comparative study on patients with grade III and IV Outerbridge talar OCD managed with a collagen scaffold seeded with bone marrow-derived cells who randomly received postoperative biophysical stimulation with PEMFs (1.5 mT, 75 Hz, 4 h/day). Only one stimulation regime was used. A superior and significant clinical outcome was found in the PEMF group, with more than 10 points higher AOFAS score at the final follow-up. Authors concluded that PEMFs started soon after surgery-aided patient recovery, leading to pain control and better clinical outcomes [29].

Reilingh and colleagues in a double-blind, randomized controlled trial evaluated the use of PEMFs (1.5 mT, 75 Hz, 4 h/day) after arthroscopic debridement and microfracture of talar OCD in athlete patients [30]. Although no differences in sport resumption one year after surgery between the treated and control groups were reported, in the PEMF-treated group, 96% of patients returned to sport by week 30, while in the control group the same percentage was achieved at week 52 [31].

These findings are in agreement with other papers in which the use of PEMFs in other anatomical districts after surgery was related to a faster functional recovery [29,32–34].

When dealing with PEMFs, exposure time in terms of hours/day, intensity peak value of the magnetic field, and frequency of pulses are essential in order to obtain satisfactory results. Schmidt-Rohlfing and colleagues used a physical signal with different physical parameters (magnetic field peak intensity, frequency, signal waveform) and dosage and suggest that PEMFs and sinusoidal magnetic fields have no effect on the cellular metabolism of human osteoarthritic chondrocytes cultivated in a collagen gel in vitro [35]. However, researches performed ex vivo on bovine articular cartilage explants made it possible to identify the most effective parameters and treatment conditions to be used in in vivo and clinical studies for the joint: 1.5 mT, 75 Hz, 4 h/day [36].

Current applications of PEMFs for OCD are summarized in Table 2.

Table 2. Summary of studies related to OCD.

Disease	Study	Characteristics	Results
Osteochondral defects	Cadossi et al. [29]	Peak intensity: 1.5 mT Frequency: 75 Hz Duration: 4 h/day for 60 days starting within 3 days after surgery	Pain control and a better clinical outcome after surgery
	Reilingh et al. [30]	Peak intensity: 1.5 mT vs. placebo peak\0.05 mT Frequency: 75 Hz Duration: 4 h/day for 60 days	Earlier resumption of sports after arthroscopic debridement and microfracture of talar OCDs

2.3. Fractures

Sports traumas, because of high-intensity forces, may lead to complex foot and ankle fractures.

PEMFs are generally known for accelerating fresh fractures healing by stimulating growth factors and cytokines production, [36] and increasing angiogenesis and perfusion [37].

Aleem et al. [38] conducted a meta-analysis of randomized controlled trials with sham group to determine the efficacy of electrical stimulation for bone healing, identifying only those trials in which patients were randomized into the stimulated or placebo group. Patients treated with electrical stimulation as an adjunct for bone healing have less pain (mean difference (MD) on 100-mm visual analogue scale = −7.7 mm; 95% CI −13.92 to −1.43; p = 0.02) and are at reduced risk for radiographic nonunion by 35% (95% CI 19% to 47%; number needed to treat = 7; p < 0.01).

More recent results were reported in a systematic review and meta-analysis of randomized controlled trials performed by Peng et al. [39]. On 1131 participants, PEMF treatment increased overall healing rate with a risk ratio of 1.22 (95% CI = 1.10–1.35), but only marginal significance in healing time (SMD = −1.01; 95% CI = −2.01 to −0.00; I 2 = 90%). PEMFs showed better pain relief (SMD = −0.49; 95% CI = −0.88 to −0.10; I 2 = 60%) [39].

Up today, there are no studies evaluating the role of PEMFs in the setting of acute foot and ankle fractures.

However, there are studies that have evaluated the role of PEMFs after metatarsal osteotomies. As a matter of fact, osteotomies can be considered a good repeatable fracture model in order to reduce variability.

Breccia et al. [40] conducted a study in 60 patients percutaneously treated with osteotomies for hallux valgus and metatarsalgia and stimulated with PEMF. The treated group showed better radiographic healing rates and pain control with less edema. The author concluded that early application of PEMF would appear particularly beneficial to selected patients with high activity levels by reducing pain, disability, convalescence time, and return to work after surgery. A faster recovery could be also a cost-saving solution.

Despite there is still a moderate quality evidence in the current literature [39], PEMFs can be beneficial in the treatment of acute fractures regarding time to radiological and clinical union (Table 3), therefore, should be considered as a valid option, in particular when dealing with athlete patients [41].

Table 3. Summary of studies related to fractures.

Disease	Study	Characteristics	Results
Fractures	Aleem et al. [38]	- (meta-analysis)	Less pain and lower rates of radiographic nonunion or persistent nonunion
	Peng et al. [39]	- (systematic review and meta-analysis)	Moderate increasing in healing rate and relieved pain of fracture
	Breccia et al. [40]	Peak intensity: 2.5 mT Frequency: 75 Hz Duration: 8 h/day until the 42nd postoperative day	Better radiographic healing rates and pain control with less edema

2.4. Nonunions

The definition of nonunion is a fracture that persists for a minimum of 9 months without healing signs for three months [42].

Delayed unions or nonunions have a substantial clinical, economic, and quality of life impact.

Due to their characteristics, PEMFs have been applied to the treatment of nonunions

Gupta and al. conducted a study on 45 tibial fractures with established atrophic nonunion treated by PEMFs [43]. All patients had abnormal mobility and no or slight gap at the fracture site with no evidence of callus formation. PEMFs was given using above-knee plaster cast (0.008 Weber/m^2 magnetic field was created for 12). The average duration for PEMFs therapy was 8.35 weeks, with the range being 6–12 weeks. About 35% of cases (n = 16) showed union in 10 weeks, and 85% (n = 38) of cases showed union in 4 months. Authors concluded that PEMFs are a useful noninvasive treatment option for difficult nonunion of long bones.

As reported by Adie S et al., PEMFs are an effective treatment for delayed unions and nonunions, but their efficacy in preventing healing complications in patients with acute fractures is largely untested [44].

In a double-blind randomized trial, 259 participants with acute tibial shaft fractures were randomized by means of external allocation to externally identical active and inactive PEMFs devices. Participants were instructed to wear PEMF for 10 h/day for 12 weeks. The primary outcome was the proportion of participants requiring a secondary surgery because of delayed union or nonunion within 12 months after the injury. Secondary outcomes included surgical intervention for any reason, radiographic union at 6 months, and the Short Form Health Survey 36 (a 36-item, patient-reported survey of patient health), Physical Component Summary, and Lower Extremity Functional Scales at 12 months. Two hundred and eighteen patients (84%) completed the follow-up. One hundred and six patients were allocated to the active device group, and one hundred and twelve to the placebo group. Compliance was reported to be 6.2 h/day of average. Overall, 16 patients in the active group and 15 in the inactive group experienced a primary outcome event (risk ratio, 1.02; 95% confidence interval, 0.95 to 1.14; p = 0.72). According to the per-protocol analysis, there were 6 primary events (12.2%) in the active, compliant group and 26 primary events (15.1%) in the combined placebo and active, noncompliant group (risk ratio, 0.97; 95% confidence interval, 0.86 to 1.10; p = 0.61). No differences between-groups were found with regard to all the considered parameters. Authors concluded that adjuvant PEMFs stimulation does not prevent secondary surgical interventions for delayed union or nonunion and does not improve radiographic union or patient-reported functional outcomes.

For what it may concern foot and ankle nonunions, main applications of PEMs involve proximal fifth metatarsal fractures, especially Jones fractures, and diaphyseal stress fractures [45].

Holmes et al. [46] treated 9 delayed unions and nonunions of the proximal fifth metatarsal with PEMFs. All fractures healed in a mean time of 4 months (range 2–8 months), with no refractures, nor recurrence of symptoms and no further requirements of additional interventions. Three patients after receiving PEMF fields were placed in a non-weight bearing cast and healed in a mean time of three months. Authors compared the healing time of delayed unions and nonunions proximal fifth metatarsal treated in other ways such as cast with non-weight bearing, bone graft, and screw fixation in other studies and concluded that the use of PEMFs provided for healing in a comparable or shorter time and without complications when compared with immobilization alone or surgery [45,47–49].

Adam Streit et al. [50] conducted a prospective, randomized, double-blind trial on 8 patients diagnosed with a fifth metatarsal delayed or nonunion, with no progressive signs of healing for a minimum of 3 months. Patients were randomized to receive either an active stimulation or placebo PEMFs device. All patients underwent an open biopsy of the fracture site and was fitted with the appropriate PEMFs device. The biopsy was analyzed for messenger-ribonucleic acid (mRNA) levels. The patients were followed at 2- to 4-week intervals with X-rays and were graded by the number of cortices of healing. After 3 weeks, the patients underwent repeat biopsy and open reduction and internal fixation of the nonunion site. A significant increase in placental growth factor (PIGF) level was found after active PEMF treatment ($p = 0.043$). Authors reported that all fractures healed, with an average time to complete radiographic union of 14.7 weeks and 8.9 weeks for the inactive and active PEMF groups, respectively. Results lead to the conclusion that the adjunctive use of PEMF for fifth metatarsal fracture nonunion produced a significant increase in local factors and faster average time to radiographic union compared to unstimulated controls.

The characteristics of PEMFs in the treatment of foot and ankle nonunion have been confirmed by other authors not only in the field of fractures. Martinelli et al. [51] reported the case of a 42-year-old woman affected by a nonunion of the first metatarsal bone after percutaneous distal osteotomy for hallux valgus deformity. The patient was surgically treated with debridement of the fibrous nonunion with plating followed by the application of PEMFs, and achieved bone consolidation within 3 months.

Current applications of PEMFs for nonunions are summarized in Table 4.

Table 4. Summary of studies related to nonunions.

Disease	**Study**	**Characteristics**	**Results**
Nonunions	Gupta et al. [43]	Intensity: 0.008 Weber/m^2 Duration: 12 h/day, 8.35 weeks	35% (n = 16) of cases showed union in 10 weeks
	Holmes et al. [46]	Intensity: burst consisting of 20 magnetic field pulses with anincreasingphase (0–20 gauss) of 200 psec duration and a decreasing phase of 20 gsec followed by a 5-psec pause Frequency: pulse burst of 4.5 msec duration repeated at 15 Hz Duration: 8–10 h/day	Healing in a comparable or shorter time course and with no complications

Table 4. *Cont.*

Disease	Study	Characteristics	Results
	Adie S. et al. [44]	EBI Bone Healing Duration: 10 h/day, within 2 weeks after the injury	No significant differences in preventing secondary surgical interventions for delayed union or nonunion
	Adam Streit et al. [50]	EBI Bone Healing Duration: 10 h/day	Significant increase in local factors and faster average time to radiographic union
	Martinelli et al. [51]	Intensity: 3.5 ± 0.5 mV for 1.3 ms Frequency: 75 Hz Duration: 7 days after surgery and was maintained until initial bone consolidation	Bone consolidation within 3 months

3. Discussion

Foot and ankle injuries are common in many sports. The main problem of most injuries in athletes is represented by the time taken for coming back to sports after trauma or surgery. In both cases, a possible way to shorten recovery time might be the application of PEMFs, for their capability of cell stimulation, inflammation reduction, articular cartilage preservation, and pain relief.

These features seem very important in athletes for an early return to sport and, moreover, for reducing other possible tissue damages, in particular regarding joints arthritic evolution.

The aim of this narrative review was to present some possible application of PEMFs in sport-related foot and ankle injuries, in particular BME, OCD, fractures, and nonunion.

The effect of PEMFs stimulation on BME has been shown to promote osteogenic activity, preventing trabecular fracture, and subchondral bone collapse.

Similarly, OCD seems to benefit from PEMFs application. In particular, PEMFs started soon after surgical OCD repair with bone marrow-derived cells transplantation, aided patient recovery leading to better clinical results.

Bone marrow-derived cells are known to be able to differentiate into mature hyaline cartilage cells in vitro; however, the effect of microenvironment in vivo may lead to different results, and PEMFs may play a positive role in this field, in particular by decreasing some of the most relevant pro-inflammatory cytokines releases [29,31].

It has to be also considered that any surgical procedure activates an inflammatory reaction, which is different for each patient. When inflammation is not controlled, it may negatively affect cartilage repair and therefore clinical outcomes.

Future comparative studies using histological analysis would be useful to confirm the hypothesis that PEMFs can help bone marrow-derived cells in directing toward hyaline cartilage differentiation.

The same approach seems to be interesting if applied to fractures, and nonunion, were the role of PEMFs is already well established.

Apart from the above-mentioned sport-related injuries, PEMFs might be also used on other common athlete's pathological conditions, such as plantar fasciitis (PF) [52].

PF represent a common condition in athletes, resulting in approximately 8% of all running-related injuries. While PF treatment is mainly conservative, the period to resolution can be quite long, in some cases up to 2 years [52]. PEMFs may represent a valid tool in order to speed up the healing process.

Brook J et al. [52] conducted a multicenter, prospective, randomized, double-blind, and placebo- and positive-controlled trial to determine the effects of nightly use of a wearable Pulsed Radiofrequency Electromagnetic Field (PRFE) device (ActiPatch, Bioelectronics) on patients diagnosed with plantar fasciitis. Seventy subjects were enrolled and randomly assigned a placebo or active PRFE device.

The PRFE device was applied overnight, and pain was recorded using a 0- to 10-point VAS every morning, and evening. A significantly different pain reduction was registered between the two groups (p = 0.03). The study group (active PRFE device) showed progressive reduction in morning pain. After 7 days, pain was 40% lower than day 1. On the other hand, the control group showed a 7% pain reduction. Authors concluded that PRFE therapy represent a simple, drug-free, noninvasive therapy to reduce PF pain.

The data reported in this review article are the result of a solid scientific research, and highlight the role of PEMFs as a promising approach for different clinical applications.

Although there are many studies concerning preclinical trial [36,53–57], there are less clinical data, and even fewer regarding foot and ankle injuries management.

Moreover, in the literature, only few studies include exclusively sportsmen or athletes, who could most benefit from these treatments.

While on the one hand this can represent a limitation, on the other hand it is an incentive to continue research in this field, and to keep developing possible applications and treatments.

PEMFs for athletes will need to be evaluated in terms other possible beneficial effects: injury prevention; lactic acid flush from the cells, and soreness reduction; decrease in stiffness, cramping, and pain from physical exertion; and better blood oxygenation, cellular metabolism and hydration.

4. Future Perspectives

Future clinical indications are still at the stage of in vitro studies in particular regarding the dynamic behavior of cellular structures.

However, current evidence seems to suggest that these treatment approaches will become increasingly widespread in the clinical setting. These evolutions do not concern only BME, OCD, fractures, and nonunions, but many other conditions, such as tendons painful conditions.

PEMFs treatment on BME is known to promote osteogenic activity, and to prevent subchondral bone collapse. This treatment appears the more effective the earlier BME is diagnosed [7,13]. Future perspectives should focus not only on the BME cellular mechanisms in response to PEMFs, but also on exploring new clinical and imaging tools to make early diagnosis.

PEMFs seems to play a role in helping stem cells to differentiate into mature hyaline cartilage cells, in particular by decreasing pro-inflammatory cytokines releases [29,31]. These properties have been reported in vitro with bone marrow-derived mesenchymal stem cells [29,31], but in the future should be evaluated also in vivo, comparing different sources of stem cells: bone marrow, adipose tissue, synovial membrane, etc.

The role of PEMFs is well established in the treatment of fractures, and nonunion. However, future perspectives should focus on histological analysis to better to understand how the bone healing process works, both in physiological and pathological settings. Randomized controlled trials would be a worthwhile endeavor.

Tendons, as well as fasciae [52], may benefit from PEMFs therapy.

Tendons painful conditions in response to overuse are known as tendinopathies: in addition to degenerative aspects, inflammatory mediators have been found to be sometimes present [57,58].

Colombini et al. [58] studied the interaction between inflammation and matrix remodeling in human tendon cells (TCs) and demonstrated that the attempt of TCs to counteract the catabolic/inflammatory state induced by IL-1β is in part mediated by A2A, Rs and reinforced by PEMF treatment [58]. These findings demonstrated that A2A, Rs have a role in the promotion of the TC anabolic/reparative response to PEMFs and to IL-1β.

De Girolamo et al. [59,60] studied the effect of PEMF treatment (1.5 mT, 75 Hz) on chronic tendinopathy, a degenerative process causing pain and disability [59,60]. PEMF's effect was assessed on primary TCs, harvested from semitendinosus and gracilis tendons of patients, under different experimental conditions. Authors found that PEMF, in a dose-dependent manner, enhance the proliferation, tendon-specific marker expression, and release of anti-inflammatory cytokines and angiogenic factor in a healthy human TCs culture model.

In tendon regeneration, the use of PEMFs together with mesenchymal stem cells (MSCs) is another intriguing option, but still investigational. Marmotti et al. [61] investigated the effect of PEMF on MSCs isolated from the human umbilical cord (UC-MSCs) and found that PEMF exposure generates a biophysical preconditioning effect on UC-MSCs, promoting the expression of tenogenic markers and anabolic cytokines involved in tendon regeneration [61].

These results have a clinical relevance, suggesting a possible large-scale clinical application of this approach as an adjuvant non-invasive therapy in the early postoperative period of tendon surgical repair.

In addition, a study conducted on culture of tendon derived cells from healthy donors, who underwent knee anterior cruciate ligament reconstruction with autologous hamstring, showed that PEMFs may represent a possible tool for enhancing and accelerating the physiological ligamentization process during the postoperative period of tendon reconstruction [62].

The role of PEMF in improving the tendon healing process was also evaluated in a rat model of collagenase-induced Achilles tendinopathy [63,64]. The PEMF group showed an improvement in the fibers organization, a decrease in cell density, vascularity, and fat deposition, and a restoration of the physiological cell morphology compared to untreated groups. The authors concluded that PEMFs exerted a positive role in the tendon healing process, thus representing a promising conservative treatment for tendinopathies.

As a consequence, hypothetical clinical application of PEMFs in further studies may regard the role of PEMFs as an adjunctive treatment for different tendon pathologies, which are particularly common in sportsmen or athletes.

5. Conclusions

Sport-related foot and ankle injuries are common. Extensive efforts have been made to speed up the athletes' return-to-sport and to prevent joint degeneration. Among the conservative treatment options, PEMFs represents a well-established therapeutic approach. This narrative review aimed to outline current applications of PEMFs in main foot and ankle sport-related injuries. Currently, BME, OCD, fractures, and nonunions represent the main application areas. PEMFs stimulation on BME has shown to promote osteogenic activity, thus preventing subchondral bone collapse. OCD repair with bone marrow-derived cells transplantation seems to benefit from PEMFs application, due to a reduction in pro-inflammatory cytokines release. PEMFs can also be helpful in the treatment of acute fractures and nonunions, in particular regarding time to radiological and clinical union. Further high-quality studies in terms of patients and methods are needed to draw stronger conclusions. However, PEMFs achieved promising results so far, with many possible fields of application, also in athlete patients with foot and ankle sport-related injuries.

Author Contributions: Conceptualization, A.M. and S.S.; methodology, L.L. and S.O.Z.; data curation, A.A.; writing—original draft preparation, E.A.; writing—review and editing, M.L. and E.M.S.; supervision, C.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare that they have no competing interests.

References

1. Fong, D.T.P.; Hong, Y.; Chan, L.K.; Yung, P.S.H.; Chan, K.M. A Systematic Review on Ankle Injury and Ankle Sprain in Sports. *Sports Med.* **2007**, *37*, 73–94. [CrossRef] [PubMed]
2. Murray, I.R.; Benke, M.T.; Mandelbaum, B.R. Management of Knee Articular Cartilage Injuries in Athletes: Chondroprotection, Chondrofacilitation, and Resurfacing. *Knee Surg. Sports Traumatol. Arthrosc.* **2016**, *24*, 1617–1626. [CrossRef] [PubMed]
3. Herdea, A.; Struta, A.; Derihaci, R.; Ulici, A.; Costache, A.; Furtunescu, F.; Toma, A.; Charkaoui, A. Efficiency of Platelet-Rich Plasma Therapy for Healing Sports Injuries in Young Athletes. *Exp. Ther. Med.* **2022**, *23*, 215. [CrossRef] [PubMed]
4. Massari, L.; Benazzo, F.; Falez, F.; Perugia, D.; Pietrogrande, L.; Setti, S.; Osti, R.; Vaienti, E.; Ruosi, C.; Cadossi, R. Biophysical Stimulation of Bone and Cartilage: State of the Art and Future Perspectives. *Int. Orthop.* **2019**, *43*, 539–551. [CrossRef] [PubMed]
5. Moretti, L.; Bizzoca, D.; Giancaspro, G.A.; Cassano, G.D.; Moretti, F.; Setti, S.; Moretti, B. Biophysical Stimulation in Athletes' Joint Degeneration: A Narrative Review. *Medicina* **2021**, *57*, 1206. [CrossRef]
6. Aigner, N.; Petje, G.; Steinboeck, G.; Schneider, W.; Krasny, C.; Landsiedl, F. Treatment of Bone-Marrow Oedema of the Talus with the Prostacyclin Analogue Iloprost. An MRI-Controlled Investigation of a New Method. *J. Bone Jt. Surg. Br.* **2001**, *83*, 855–858. [CrossRef]
7. Martinelli, N.; Bianchi, A.; Sartorelli, E.; Dondi, A.; Bonifacini, C.; Malerba, F. Treatment of Bone Marrow Edema of the Talus with Pulsed Electromagnetic Fields: Outcomes in Six Patients. *J. Am. Podiatr. Med. Assoc.* **2015**, *105*, 27–32. [CrossRef]
8. Tonbul, M.; Guzelant, A.Y.; Gonen, A.; Baca, E.; Ozbaydar, M.U. Relationship between the Size of Bone Marrow Edema of the Talus and Ankle Pain. *J. Am. Podiatr. Med. Assoc.* **2011**, *101*, 430–436. [CrossRef]
9. Fini, M.; Giavaresi, G.; Carpi, A.; Nicolini, A.; Setti, S.; Giardino, R. Effects of Pulsed Electromagnetic Fields on Articular Hyaline Cartilage: Review of Experimental and Clinical Studies. *Biomed. Pharmacother.* **2005**, *59*, 388–394. [CrossRef]
10. Ongaro, A.; Pellati, A.; Masieri, F.F.; Caruso, A.; Setti, S.; Cadossi, R.; Biscione, R.; Massari, L.; Fini, M.; de Mattei, M. Chondroprotective Effects of Pulsed Electromagnetic Fields on Human Cartilage Explants. *Bioelectromagnetics* **2011**, *32*, 543–551. [CrossRef]
11. Yen-Patton, G.P.A.; Patton, W.F.; Beer, D.M.; Jacobson, B.S. Endothelial Cell Response to Pulsed Electromagnetic Fields: Stimulation of Growth Rate and Angiogenesis In Vitro. *J. Cell. Physiol.* **1988**, *134*, 37–46. [CrossRef] [PubMed]
12. Canè, V.; Botti, P.; Soana, S. Pulsed Magnetic Fields Improve Osteoblast Activity during the Repair of an Experimental Osseous Defect. *J. Orthop. Res.* **1993**, *11*, 664–670. [CrossRef]
13. Al-Jabri, T.; Yan, J.; Tan, Q.; Tong, G.Y.; Shenoy, R.; Kayani, B.; Parratt, T.; Khan, T. The Role of Electrical Stimulation in the Management of Avascular Necrosis of the Femoral Head in Adults: A Systematic Review. *BMC Musculoskelet. Disord.* **2017**, *18*, 319. [CrossRef] [PubMed]
14. Ficat, R.P. Idiopathic Bone Necrosis of the Femoral Head. Early Diagnosis and Treatment. *J. Bone Jt. Surg. Br.* **1985**, *67*, 3–9. [CrossRef] [PubMed]
15. Marcheggiani Muccioli, G.M.; Grassi, A.; Setti, S.; Filardo, G.; Zambelli, L.; Bonanzinga, T.; Rimondi, E.; Busacca, M.; Zaffagnini, S. Conservative Treatment of Spontaneous Osteonecrosis of the Knee in the Early Stage: Pulsed Electromagnetic Fields Therapy. *Eur. J. Radiol.* **2013**, *82*, 530–537. [CrossRef]
16. Cebrián, J.L.; Milano, G.L.; Francés, A.; Lopiz, Y.; Marco, F.; López-Durán, L. Role of Electromagnetic Stimulation in the Treatment of Osteonecrosis of the Femoral Head in Early Stages. *J. Biomed. Sci. Eng.* **2014**, *7*, 252–257. [CrossRef]
17. Massari, L.; Fini, M.; Cadossi, R.; Setti, S.; Traina, G.C. Biophysical Stimulation with Pulsed Electromagnetic Fields in Osteonecrosis of the Femoral Head. *J. Bone Jt. Surg. Am.* **2006**, *88* (Suppl. S3), 56–60. [CrossRef]
18. Windisch, C.; Kolb, W.; Röhner, E.; Wagner, M.; Roth, A.; Matziolis, G.; Wagner, A. Invasive Electromagnetic Field Treatment in Osteonecrosis of the Femoral Head: A Prospective Cohort Study. *Open Orthop. J.* **2014**, *8*, 125. [CrossRef]
19. Bassett, C.A.; Schink-Ascani, M.; Lewis, S.M. Effects of Pulsed Electromagnetic Fields on Steinberg Ratings of Femoral Head Osteonecrosis. *Clin. Orthop. Relat. Res.* **1989**, *246*, 172–185. [CrossRef]
20. Aaron, R.K.; Lennox, D.; Bunce, G.E.; Ebert, T. The Conservative Treatment of Osteonecrosis of the Femoral Head. A Comparison of Core Decompression and Pulsing Electromagnetic Fields. *Clin. Orthop. Relat. Res.* **1989**, *249*, 209–218. [CrossRef]
21. Zengerink, M.; Szerb, I.; Hangody, L.; Dopirak, R.M.; Ferkel, R.D.; van Dijk, C.N. Current Concepts: Treatment of Osteochondral Ankle Defects. *Foot Ankle Clin.* **2006**, *11*, 331–359. [CrossRef] [PubMed]
22. Mandelbaum, B.; Waddell, D. Etiology and Pathophysiology of Osteoarthritis. *Orthopedics* **2005**, *28*, S207–S214. [CrossRef] [PubMed]
23. Flanigan, D.C.; Harris, J.D.; Trinh, T.Q.; Siston, R.A.; Brophy, R.H. Prevalence of Chondral Defects in Athletes' Knees: A Systematic Review. *Med. Sci. Sport. Exerc.* **2010**, *42*, 1795–1801. [CrossRef] [PubMed]
24. Chuckpaiwong, B.; Berkson, E.M.; Theodore, G.H. Microfracture for Osteochondral Lesions of the Ankle: Outcome Analysis and Outcome Predictors of 105 Cases. *Arthroscopy* **2008**, *24*, 106–112. [CrossRef] [PubMed]
25. Varani, K.; Vincenzi, F.; Ravani, A.; Pasquini, S.; Merighi, S.; Gessi, S.; Setti, S.; Cadossi, M.; Borea, P.A.; Cadossi, R. Adenosine Receptors as a Biological Pathway for the Anti-Inflammatory and Beneficial Effects of Low Frequency Low Energy Pulsed Electromagnetic Fields. *Mediat. Inflamm.* **2017**, *2017*, 2740963. [CrossRef] [PubMed]

26. De Mattei, M.; Pellati, A.; Pasello, M.; Ongaro, A.; Setti, S.; Massari, L.; Gemmati, D.; Caruso, A. Effects of Physical Stimulation with Electromagnetic Field and Insulin Growth Factor-I Treatment on Proteoglycan Synthesis of Bovine Articular Cartilage. *Osteoarthr. Cartil.* **2004**, *12*, 793–800. [CrossRef] [PubMed]
27. De Mattei, M.; Caruso, A.; Pezzetti, F.; Pellati, A.; Stabellini, G.; Sollazzo, V.; Traina, G.C. Effects of Pulsed Electromagnetic Fields on Human Articular Chondrocyte Proliferation. *Connect. Tissue Res.* **2001**, *42*, 269–279. [CrossRef]
28. Amin, H.D.; Brady, M.A.; St-Pierre, J.P.; Stevens, M.M.; Overby, D.R.; Ethier, C.R. Stimulation of Chondrogenic Differentiation of Adult Human Bone Marrow-Derived Stromal Cells by a Moderate-Strength Static Magnetic Field. *Tissue Eng. Part A* **2014**, *20*, 1612–1620. [CrossRef]
29. Cadossi, M.; Buda, R.E.; Ramponi, L.; Sambri, A.; Natali, S.; Giannini, S. Bone Marrow-Derived Cells and Biophysical Stimulation for Talar Osteochondral Lesions: A Randomized Controlled Study. *Foot Ankle Int.* **2015**, *35*, 981–987. [CrossRef]
30. Reilingh, M.L.; Van Bergen, C.J.A.; Gerards, R.M.; Van Eekeren, I.C.; De Haan, R.J.; Sierevelt, I.N.; Kerkhoffs, G.M.M.J.; Krips, R.; Meuffels, D.E.; Van Dijk, C.N.; et al. Effects of Pulsed Electromagnetic Fields on Return to Sports after Arthroscopic Debridement and Microfracture of Osteochondral Talar Defects: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. *Am. J. Sport. Med.* **2016**, *44*, 1292–1300. [CrossRef]
31. Cadossi, M.; Sambri, A.; Sandro, G.; Massari, L. Effects of Pulsed Electromagnetic Fields after Debridement and Microfracture of Osteochondral Talar Defects: Letter to the Editor. *Am. J. Sport. Med.* **2016**, *44*, NP60–NP61. [CrossRef] [PubMed]
32. Benazzo, F.; Zanon, G.; Pederzini, L.; Modonesi, F.; Cardile, C.; Falez, F.; Ciolli, L.; La Cava, F.; Giannini, S.; Buda, R.; et al. Effects of Biophysical Stimulation in Patients Undergoing Arthroscopic Reconstruction of Anterior Cruciate Ligament: Prospective, Randomized and Double Blind Study. *Knee Surg. Sport. Traumatol. Arthrosc.* **2008**, *16*, 595–601. [CrossRef] [PubMed]
33. Osti, L.; del Buono, A.; Maffulli, N. Application of Pulsed Electromagnetic Fields after Microfractures to the Knee: A Mid-Term Study. *Int. Orthop.* **2015**, *39*, 1289–1294. [CrossRef] [PubMed]
34. Zorzi, C.; Dall'Oca, C.; Cadossi, R.; Setti, S. Effects of Pulsed Electromagnetic Fields on Patients' Recovery after Arthroscopic Surgery: Prospective, Randomized and Double-Blind Study. *Knee Surg. Sport. Traumatol. Arthrosc.* **2007**, *15*, 830–834. [CrossRef]
35. Schmidt-Rohlfing, B.; Silny, J.; Woodruff, S.; Gavenis, K. Effects of Pulsed and Sinusoid Electromagnetic Fields on Human Chondrocytes Cultivated in a Collagen Matrix. *Rheumatol. Int.* **2008**, *28*, 971–977. [CrossRef]
36. De Mattei, M.; Fini, M.; Setti, S.; Ongaro, A.; Gemmati, D.; Stabellini, G.; Pellati, A.; Caruso, A. Proteoglycan Synthesis in Bovine Articular Cartilage Explants Exposed to Different Low-Frequency Low-Energy Pulsed Electromagnetic Fields. *Osteoarthr. Cartil.* **2007**, *15*, 163–168. [CrossRef]
37. Tepper, O.M.; Callaghan, M.J.; Chang, E.I.; Galiano, R.D.; Bhatt, K.A.; Baharestani, S.; Gan, J.; Simon, B.; Hopper, R.A.; Levine, J.P.; et al. Electromagnetic Fields Increase In Vitro and In Vivo Angiogenesis through Endothelial Release of FGF-2. *FASEB J.* **2004**, *18*, 1231–1233. [CrossRef]
38. Aleem, I.S.; Aleem, I.; Evaniew, N.; Busse, J.W.; Yaszemski, M.; Agarwal, A.; Einhorn, T.; Bhandari, M. Efficacy of Electrical Stimulators for Bone Healing: A Meta-Analysis of Randomized Sham-Controlled Trials. *Sci. Rep.* **2016**, *6*, 31724. [CrossRef]
39. Peng, L.; Fu, C.; Xiong, F.; Zhang, Q.; Liang, Z.; Chen, L.; He, C.; Wei, Q. Effectiveness of Pulsed Electromagnetic Fields on Bone Healing: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Bioelectromagnetics* **2020**, *41*, 323–337. [CrossRef]
40. Breccia, M.; Rossi, B.; Farneti, A.; Setti, S.; Ferranti, S. Orthopedic & Muscular System: Current Research the Effect of Pulsed Electromagnetic Fields Stimulation in Percutaneous Surgery for Hallux Valgus and Metatarsalgia. *Orthop. Muscular Syst.* **2019**, *8*, 270.
41. Hannemann, P.F.W.; Mommers, E.H.H.; Schots, J.P.M.; Brink, P.R.G.; Poeze, M. The Effects of Low-Intensity Pulsed Ultrasound and Pulsed Electromagnetic Fields Bone Growth Stimulation in Acute Fractures: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Arch. Orthop. Trauma Surg.* **2014**, *134*, 1093–1106. [CrossRef] [PubMed]
42. Cunningham, B.P.; Brazina, S.; Morshed, S.; Miclau, T. Fracture Healing: A Review of Clinical, Imaging and Laboratory Diagnostic Options. *Injury* **2017**, *48* (Suppl. S1), S69–S75. [CrossRef] [PubMed]
43. Gupta, A.K.; Srivastava, K.P.; Avasthi, S. Pulsed Electromagnetic Stimulation in Nonunion of Tibial Diaphyseal Fractures. *Indian J. Orthop.* **2009**, *43*, 156. [CrossRef] [PubMed]
44. Adie, S.; Harris, I.A.; Naylor, J.M.; Rae, H.; Dao, A.; Yong, S.; Ying, V. Pulsed Electromagnetic Field Stimulation for Acute Tibial Shaft Fractures: A Multicenter, Double-Blind, Randomized Trial. *J. Bone Jt. Surg. Am.* **2011**, *93*, 1569–1576. [CrossRef] [PubMed]
45. Lehman, R.C.; Torg, J.S.; Pavlov, H.; Delee, J.C. Fractures of the Base of the Fifth Metatarsal Distal to the Tuberosity: A Review. *Foot Ankle* **1987**, *7*, 245–252. [CrossRef]
46. Holmes, G.B. Treatment of Delayed Unions and Nonunions of the Proximal Fifth Metatarsal with Pulsed Electromagnetic Fields. *Foot Ankle Int.* **1994**, *15*, 552–556. [CrossRef]
47. Zelko, R.R.; Torg, J.S.; Rachun, A. Proximal Diaphyseal Fractures of the Fifth Metatarsal—Treatment of the Fractures and Their Complications in Athletes. *Am. J. Sport. Med.* **1979**, *7*, 95–101. [CrossRef]
48. Delee, J.C.; Evans, J.P.; Julian, J. Stress Fracture of the Fifth Metatarsal. *Am. J. Sport. Med.* **1983**, *11*, 349–353. [CrossRef]
49. The Jones Fracture Revisited: JBJS. Available online: https://journals.lww.com/jbjsjournal/Abstract/1978/60060/The_Jones_fracture_revisited_.8.aspx (accessed on 31 December 2022).

50. Streit, A.; Watson, B.C.; Granata, J.D.; Philbin, T.M.; Lin, H.N.; O'Connor, J.P.; Lin, S. Effect on Clinical Outcome and Growth Factor Synthesis with Adjunctive Use of Pulsed Electromagnetic Fields for Fifth Metatarsal Nonunion Fracture: A Double-Blind Randomized Study. *Foot Ankle Int.* **2016**, *37*, 919–923. [CrossRef]
51. Martinelli, N.; Cancilleri, F.; Marineo, G.; Marinozzi, A.; Longo, U.G.; Denaro, V. Pseudarthrosis after Percutaneous Distal Osteotomy in Hallux Valgus Surgery: A Case Report. *J. Am. Podiatr. Med. Assoc.* **2012**, *102*, 78–82. [CrossRef]
52. Brook, J.; Dauphinee, D.M.; Korpinen, J.; Rawe, I.M. Pulsed Radiofrequency Electromagnetic Field Therapy: A Potential Novel Treatment of Plantar Fasciitis. *J. Foot Ankle Surg.* **2012**, *51*, 312–316. [CrossRef] [PubMed]
53. Petecchia, L.; Sbrana, F.; Utzeri, R.; Vercellino, M.; Usai, C.; Visai, L.; Vassalli, M.; Gavazzo, P. Electro-Magnetic Field Promotes Osteogenic Differentiation of BM-HMSCs through a Selective Action on Ca(2+)-Related Mechanisms. *Sci. Rep.* **2015**, *5*, 13856. [CrossRef] [PubMed]
54. Ross, C.L.; Siriwardane, M.; Almeida-Porada, G.; Porada, C.D.; Brink, P.; Christ, G.J.; Harrison, B.S. The Effect of Low-Frequency Electromagnetic Field on Human Bone Marrow Stem/Progenitor Cell Differentiation. *Stem Cell Res.* **2015**, *15*, 96–108. [CrossRef] [PubMed]
55. Tesch, A.M.; MacDonald, M.H.; Kollias-Baker, C.; Benton, H.P. Effects of an Adenosine Kinase Inhibitor and an Adenosine Deaminase Inhibitor on Accumulation of Extracellular Adenosine by Equine Articular Chondrocytes. *Am. J. Vet. Res.* **2002**, *63*, 1512–1519. [CrossRef]
56. Yuan, J.; Xin, F.; Jiang, W. Underlying Signaling Pathways and Therapeutic Applications of Pulsed Electromagnetic Fields in Bone Repair. *Cell. Physiol. Biochem.* **2018**, *46*, 1581–1594. [CrossRef]
57. Barnaba, S.; Papalia, R.; Ruzzini, L.; Sgambato, A.; Maffulli, N.; Denaro, V. Effect of Pulsed Electromagnetic Fields on Human Osteoblast Cultures. *Physiother. Res. Int.* **2013**, *18*, 109–114. [CrossRef]
58. Colombini, A.; Orfei, C.P.; Vincenzi, F.; de Luca, P.; Ragni, E.; Viganò, M.; Setti, S.; Varani, K.; de Girolamo, L. A2A Adenosine Receptors Are Involved in the Reparative Response of Tendon Cells to Pulsed Electromagnetic Fields. *PLoS ONE* **2020**, *15*, e0239807. [CrossRef]
59. De Girolamo, L.; Stanco, D.; Galliera, E.; Viganò, M.; Colombini, A.; Setti, S.; Vianello, E.; Corsi Romanelli, M.M.; Sansone, V. Low Frequency Pulsed Electromagnetic Field Affects Proliferation, Tissue-Specific Gene Expression, and Cytokines Release of Human Tendon Cells. *Cell Biochem. Biophys.* **2013**, *66*, 697–708. [CrossRef]
60. De Girolamo, L.; Viganò, M.; Galliera, E.; Stanco, D.; Setti, S.; Marazzi, M.G.; Thiebat, G.; Corsi Romanelli, M.M.; Sansone, V. In Vitro Functional Response of Human Tendon Cells to Different Dosages of Low-Frequency Pulsed Electromagnetic Field. *Knee Surg. Sport. Traumatol. Arthrosc.* **2015**, *23*, 3443–3453. [CrossRef]
61. Marmotti, A.; Peretti, G.M.; Mattia, S.; Mangiavini, L.; De Girolamo, L.; Viganò, M.; Setti, S.; Bonasia, D.E.; Blonna, D.; Bellato, E.; et al. Pulsed Electromagnetic Fields Improve Tenogenic Commitment of Umbilical Cord-Derived Mesenchymal Stem Cells: A Potential Strategy for Tendon Repair—An In Vitro Study. *Stem Cells Int.* **2018**, *2018*, 9048237. [CrossRef]
62. Stephenson, M.C.; Krishna, L.; Pannir Selvan, R.M.; Tai, Y.K.; Kit Wong, C.J.; Yin, J.N.; Toh, S.J.; Torta, F.; Triebl, A.; Fröhlich, J.; et al. Magnetic Field Therapy Enhances Muscle Mitochondrial Bioenergetics and Attenuates Systemic Ceramide Levels Following ACL Reconstruction: Southeast Asian Randomized-Controlled Pilot Trial. *J. Orthop. Transl.* **2022**, *35*, 99–112. [CrossRef] [PubMed]
63. Perucca Orfei, C.; Lovati, A.B.; Lugano, G.; Viganò, M.; Bottagisio, M.; D'Arrigo, D.; Sansone, V.; Setti, S.; de Girolamo, L. Pulsed Electromagnetic Fields Improve the Healing Process of Achilles Tendinopathy: A Pilot Study in a Rat Model. *Bone Jt. Res.* **2020**, *9*, 613–622. [CrossRef] [PubMed]
64. Orfei, C.P.; Lovati, A.B.; Viganò, M.; Stanco, D.; Bottagisio, M.; Di Giancamillo, A.; Setti, S.; De Girolamo, L. Dose-Related and Time-Dependent Development of Collagenase-Induced Tendinopathy in Rats. *PLoS ONE* **2016**, *11*, e0161590. [CrossRef]