Review

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Review

Pulsed Electromagnetic Field Stimulation in Bone Healing and Joint Preservation: A Narrative Review of the Literature

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Abstract: *Background:* biophysical stimulation therapy, and in particular Pulsed Electromagnetic Fields (PEMFs) and capacitively coupled electric fields (CCEFs) has significantly increased in the last twenty years. For this, it is necessary to have clear information regarding the efficacy, the therapeutic indication and the expected objectives. *Methods*: we conducted a narrative review taking into consideration different types of studies with different areas of application. 19 studies present in literature and published in the last 15 years were considered to obtain a clear and broad opinion on this topic. *Results:* There is unanimous opinion regarding the usefulness of applying biophysical therapy on the bone compartment both in terms of the tissue healing process and the symptoms associated with this situation. Differently, but no less importantly, in the joint compartment positive opinions were observed mainly on the inflammatory and catabolic process, however, we did not report evidence regarding cartilaginous tissue regeneration. *Conclusion:* the effectiveness of PEMFs and CCEFs on the bone healing process in the Orthopedic and Traumatology fields is consolidated evidence in the literature. We have also found positive results on symptoms and patient compliance with rehabilitation therapies. Therefore, notable application can be envisaged in the fields of Prosthetic Surgery and Sports Medicine.

Keywords: pulsed electromagnetic fields; PEMFs; capacitively coupled electric fields; CCEFs; bone healing; joint preservation; traumatology; Sport Medicine; hip and knee replacement; reverse shoulder arthroplasty

1. Introduction

Clinical biophysics exploits the effect of electromagnetic fields (EFs) on biological systems to obtain benefits during different biological processes. The musculoskeletal system is highly sensitive to such stimuli.

Over the last twenty years, the approach to this discipline has changed considerably, leading to a clear improvement in the physical parameters relevant to these processes with consequent optimization of therapies and clinical effects.

Biophysical stimulation can reduce the potential risk by promoting osteogenic stimulus and reducing healing times. There are numerous publications in the literature in favor of the use of these physical therapies in risk conditions however it must be used following the correct administration criteria [1].

The possibility of delivering the therapy locally allows you to optimize the treatment while avoiding any dose-dependent side effects. This characteristic, which makes it potentially suitable for chronic therapies, excludes its use for systemic pathologies [1].

The use of biophysical therapy in bone tissue pathologies is now widespread and consequently we have the possibility of evaluating a large scientific production in this regard. However, the application for cartilaginous tissue and related joint pathologies is much more recent.

The objective of this review is to take into consideration several recent studies regarding the application of Pulsed Electromagnetic Fields (PEMFs) and capacitively coupled electric fields (CCEFs) for the improvement of bone and cartilage tissue condition. For this reason, heterogeneous studies present in the literature were included with the aim of obtaining detailed information that can be used in the clinical context.

The physical parameters are fundamental for the quality of the therapy provided and concern the amplitude, frequency and shape of the impulse generated by the devices. Optimizing these parameters translates into an improvement in the dose-response of the therapy and therefore in the effectiveness of the treatment. For this reason, the use of equipment supported by verified publications and data is essential.

The better understanding of the mechanisms of interaction of biophysical stimuli on the cellular component has given a strong boost to use in the clinical field with the application of PEMFs/CCEFs designed to obtain benefits in the process of repair and regeneration of bone and cartilage tissue. These changes are mediated by an increase in endogenous production of growth factors at the bone and cartilage level with a consequent increase in the activity of the stem component obtaining greater and more rapid tissue regeneration.

1.1. Modulation of membrane receptors for adenosin [2]

Adenosine and its receptors play a fundamental role in cellular homeostasis through the expression of the A_{2A} receptor it regulates the pathway Wnt/B-catenina which is fundamental in anabolic processes at the bone and cartilage level. Exposure to electromagnetic fields causes greater exposure of A_{2A} and A_{3R} membrane receptors on synoviocytes, chondrocytes and osteoblasts with a consequent increase in intracellular cAMP levels and decreased activation of NF-kβ, a key regulator of the expression of metalloproteases and others pro-inflammatory factors. All this translates into signals of attenuation of the inflammatory process and promotion of both the bone and cartilage regenerative process.

1.2. Activation of osteoinductive and angiogenesis pathways [3][4]

Stimulation by EFs causes an increase in the genes of the transforming growth factor beta (TGF-β), family, in particular bone morphogenetic proteins 2 and 4 (BMPs 2-4) and the protein mediators controlled by them [3]. Also, in this situation there is modulation of the Wnt/B-catenina pathway with consequent stimulation in both an osteogenic and chondrogenic sense. This is associated with an increase in the gene expression of fibroblast growth factor-2 and angipoietin-2 with improvement of the angiogenesis process [4].

1.3. Alteration Alteration of the extracellular matrix [5]

The signals taken into consideration previously play a significant role in managing the structure of the extracellular matrix (ECM), improving skeletal tissue capabilities and facilitating the repair process.

The clinical implications of such interactions between biophysical stimuli and cellular responses are exploited in clinical practice to obtain tissue repair and regeneration processes in less time and with greater efficiency.

The main fields of use currently are [1]:

- Delayed union and Non-Union
- Fractures with associated risk factors (open fractures, severe soft tissue damage, patient-specific factors)
- Osseointegration of prosthetic components
- Stress fractures

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- Modulation of cartilage damage
- Reduction of inflammatory and catabolic processes at the joint

In the bone repair process an improvement in the timing of bone consolidation and fracture healing was observed [1][2][3]. For this reason, its use in recent fractures or surgical osteotomies has progressively increased in recent years.

As regards the problem of fracture non-union, an increase in bone healing of between 73% and 85% is reported in the literature [6][7]. Even the presence of infectious processes does not compromise the validity of these treatments. Furthermore, the cost-benefit ratio supports the choice of therapy with EFs.

Several reviews in the literature report a valid reaction of cartilage tissue to electromagnetic biophysical stimuli [1]. An increase in the production of proteoglycans is observed even in elderly cartilaginous tissues with restoration of a production value like that of younger tissues. However, in in vivo studies it emerged that real benefits in cartilage structural improvement occur in cases of early osteoarthritis (OA) and less so in forms where there is already greater damage to the structural matrix.

The modulation by PEMFs or CCEFs on the pathways mediated by TGF-β produces positive effects on the joint inflammatory process through an improvement in cytokine production in favor of anabolic processes and to the detriment of catabolic ones. In vivo it translates into a lower production of matrix-degrading enzymes and consequent preservation of tissue components. These benefits appear particularly valid in recent forms of arthritis [8]. For the reasons mentioned above, the application of PEMFs after joint surgery is becoming widespread, obtaining positive results both on the tissue healing process and on the aspect of pain control and the resumption of sporting activity [9].

The increase in fields of use and the greater propensity to use biophysical therapy has led to a clear increase in literature on the subject. The objective of this work is to take into consideration the main and most recent studies to analyze the data they present.

2. Materials and Methods

For this narrative review we have selected articles published in accredited scientific journals in the last fifteen years.

Different types of scientific studies have been included in order to have greater completeness of information in this regard. We decided to include both studies concerning applications on bone tissue and effects on cartilaginous tissues or, more generally, on the joint compartment.

Currently there aren't specific guidelines regarding the application of biophysical therapy, however clear therapeutic indications and protocols are expressed by the device suppliers.

The search was conducted in PubMed, ORCID, CINAHL, MEDLINE, Scopus, Google Scholar and ScienceDirect. Therefore 19 studies were selected, favoring the most recent publications. Studies regarding Traumatology, Orthopedics, Spinal Surgery and Sports Medicine were taken into consideration.

The studies examined are listed in Table 1 below:

Table 1. summary of the studies considered and their structure. These studies are reported in chronological order.

No.	Year	Authors	Title and Journal	Type of Paper	Area
1	2008	Benazzo F. et al. [9]	Effects of biophysical stimulation in patients undergoing arthroscopic reconstruction of anterior cruciate	Prospective cohort study	Joint preservation

			ligament: Prospective, randomized and double blind study. *Knee Surgery, Sports Traumatology, Arthroscopy*		
2	2009	Massari L. et al. [19]	Pulsed electromagnetic fields and low intensity pulsed ultrasound in bone tissue. *Clinical Cases in Mineral and Bone Metabolism*	Short Survey	Bone healing
3	2010	Faldini C. et al. [10]	Electromagnetic bone growth stimulation in patients with femoral neck fractures treated with screws: prospective randomized double-blind study. *Current Orthopaedic Practice*	Prospective randomized double-blind study.	Bone healing
4	2012	Assiotis A. et al. [11]	Pulsed electromagnetic fields for the treatment of tibial delayed unions and nonunions. A prospective clinical study and review of the literature *Journal of Orthopaedic Surgery and Research*	Prospective clinical study Review of the literature	Bone healing
5	2013	Shi H. et al. [13]	Early application of pulsed electromagnetic field in the treatment of postoperative delayed union of long-bone fractures: a prospective randomized controlled study. *BMC Musculoskeletal Disorders*	Prospective randomized controlled study	Bone healing
6	2014	Hannermann P F W et al. [17]	CT scan-evaluated outcome of pulsed electromagnetic fields in the treatment of acute scaphoid fractures. *Bone Joint J 2014*	Prospective cohort study	Bone healing

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7	2015	Massari L. et al. [21]	Biophysical stimulation and the periprosthetic bone: Is there a rationale in the use of pulsed electromagnetic fields after a hip or knee implant? *Journal of Biological Regulators and Homeostatic Agents*	Narrative review	Joint replacement
8	2016	Streit A et al. [14]	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 International®*	Double-Blind Randomized Study	Bone healing
9	2018	Massari L. et al. [12]	Can Clinical and Surgical Parameters Be Combined to Predict How Long It Will Take a Tibia Fracture to Heal? A Prospective Multicentre Observational Study: The FRACTING Study. *BioMed Research International*	Prospective Multicentre Observational Study	Bone healing
10	2019	Massari L. et al. [1]	Biophysical stimulation of bone and cartilage: state of the art and future perspectives. *International Orthopaedics*	Narrative review	Bone healing; Joint preservation; Joint replacemtent; Spinal Surgery
11	2019	La Verde L. et al [25]	Applicazione dei campi magnetici pulsati nei pazienti sottoposti a protesi inversa di spalla: valutazione clinica e funzionale. *GIOT*	Prospective randomized controlled study	Joint replacement

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12	2020	Lullini G. et al. [22]	Role of pulsed electromagnetic fields after joint replacements *World Journal of Orthopedics*	Narrative review	Joint replacement
13	2020	Massari L. et al. [18]	Does capacitively coupled electric fields stimulation improve clinical outcomes after instrumented spinal fusion? A multicentered randomized, prospective, double-blind, placebo-controlled trial. *International Journal of Spine Surgery*	Randomized controlled trial	Spinal Surgery
14	2020	Krzyz˙an´ska L. et al. [15]	Beneficial Effects of Pulsed Electromagnetic Field during Cast Immobilization in Patients with Distal Radius Fracture. *BioMed Research International Volume 2020*	Prospective randomized controlled study	Bone healing
15	2021	Moretti L. et al. [23]	Biophysical Stimulation in Athletes' Joint Degeneration: A Narrative Review. *Medicina*	Narrative Review	Joint preservation
16	2021	Jie Tong et al. [8]	The Efficacy of Pulsed Electromagnetic Fields on Pain, Stiffness, and Physical Function in Osteoarthritis: A Systematic Review and Meta-Analysis. *Pain Research and Management*	Systematic Review and Meta-Analysis	Joint preservation
17	2021	Liu W et al. [20]	Pulsed Electromagnetic Field Affects the Development of Postmenopausal Osteoporotic Women with Vertebral Fractures. *BioMed Research International*	Randomized controlled study	Bone healing

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18	2022	D'Ambrosi R. et al [24]	Pulsed electromagnetic fields improve pain management and clinical outcomes after medial unicompartmental knee arthroplasty: A prospective randomised controlled trial. *Journal of Isakos*	Randomized controlled study	Joint replacemtent
19	2023	Factor S. et al. [16]	The Effects of Novel Pulsed Electromagnetic Field Therapy Device on Acute Distal Radius Fractures: A Prospective, Double-Blind, Sham-Controlled, Randomized Pilot Study. *Journal of Clinical Medicine*	Prospective Randomizes Pilot Study	Bone healing

4. Discussion

The current literature presents a valid number of publications regarding the use of magnetic fields with standardized protocols. In the first years of applications of these therapies, unfortunately, it was difficult to distinguish devices supported by real scientific evidence from more generic and unvalidated "magnetotherapies". The improvement of the application protocols of these therapies, in addition to making them more effective, makes it possible to carry out an objective comparison between the different publications.

Initially we focused on the problem of bone healing, which is the first therapeutic rationale for which these therapies were applied. By broadening the focus, we were able to evaluate the results in the different Orthopedic and Traumatology disciplines.

4.1. Bone Healing

Several studies in the literature support the effectiveness of biophysical stimulation with electromagnetic fields to obtain better results following a traumatic event. The study conducted by Faldini C. et al. [10] in 2010 presented valid results in patients undergoing osteosynthesis surgery with canulated screws for fractures of the femoral neck Garden 1,2 or 3 type. The application of PEMFs is started 7 days after surgery to exploit a treatment protocol of 8 hours for 90 days. Radiographic healing was observed in 94% of treated cases vs. 69% of patients in the placebo group. Furthermore, in the placebo group, a higher percentage of osteonecrosis and higher scores in the VAS pain assessment were observed.

A study conducted by Assiotis A. et al. [11] in 2012 on 44 fractures involving the diaphyseal portion of the tibia with delay or non-union without ongoing infectious phenomena. Patients were treated with PEMFs for 3 hours/day for a maximum of 36 weeks (average of 29,5 weeks). Although a positive correlation was observed between the duration of stimulation and recovery, statistically significant results could not be collected. The authors therefore conclude that success is not associated with specific fractures or patient-related variables and cannot clearly be considered a time-dependent phenomenon.

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To facilitate the choice regarding the application of biophysical stimulation, an algorithm called FRACTING SCORE to predict bone healing in a specific body area, i.e. the tibia, was published by Massari et al. [12]. This study involved the recruitment of patients from 41 Italian orthopedic traumatology centers. Final targets were identified to make the evaluation homogeneous, and a 12-month follow-up was identified. Within 12 months from trauma, the date at which the fracture healed was used to calculate days and months elapsed since treatment called "healing time". At the end of the selection process, 363 patients were selected and treated with different means of synthesis (external fixation, plate and screw and nail). The purpose of the study was to assess, immediately after the treatment of the fracture, the time needed to get to healing.

In this way the clinician can have objective information about the usefulness of applying the device, identifying and standardizing patients with higher risk factors and therefore potentially more suitable for these therapies.

Further confirmation of the effectiveness of stimulation with electromagnetic fields is reported in the study of Shi H F et al. [13] conducted on 64 patients with delayed union of fractures involving long bones. The treatment protocol involved the application of PEMFs for 8 hours a day for an average of approximately 4,5 months. The authors concluded that the early application of PEMFs for a period of 4,4-4,8 months promotes fracture healing and union rate with statistically significant results compared to the placebo group.

To obtain a more complete evaluation of effectiveness, studies involving the application of the devices on very limited bone portions were also taken into consideration.

The study conducted by Streit A et al. [14] on fractures of the 5th metatarsal bone took into consideration a small population of patients with delayed or failed bone union. On these patients, a bone biopsy was performed at time 0, after having performed the fixation with a cannulated screw, and a new biopsy after 3 months of stimulation with PEMFs. The authors conclude that in the group treated with biophysical stimulation, compared to placebo, there is a significant increase in placental growth factor (PIGF), brain-derived neurotrophic factor (BDNF) and bone morphogenetic protein (BMP) 7 and 5, all factors of angiogenic and osteogenic growth factors important for the formation of new bone tissue. This work presents a peculiar aspect because, unlike most studies, it does not focus exclusively on radiographic and clinical parameters but takes into consideration a more objective biomolecular variable.

In accordance with what was previously stated, we report the studies conducted in 2020 by Krzyz˙an´ska L. et al. [15] and in 2023 by Factor S. et al. [16] regarding fractures of the distal radius treated with a plaster cast. Both studies focus mainly on the clinical symptoms reported by patients and their adherence to physiotherapy programmed. In the study by Krzyz˙an´ska L. et al. [15] PEMFs are administered from the first day for 30 minutes per day for a duration of 10 days, subsequently 3 applications per week of 30 minutes for 6 weeks. The authors conclude that, compared to the control groups, better scores were observed on the DASH (disability of arm, shoulder, hand), SF12 (12-Item Short Form Survey) and PRWE (Patient Rated Wrist Evaluation) questionnaires. Only the study by Factor S. et al. [16] expresses positive conclusions regarding the radiographic evaluation of the healing process. The group treated with PEMFs for 24 hours a day had the possibility of removing the cast earlier (33 ± 5,9 days vs 39,8 ± 7,4 days), showed a better joint ROM at both 12 and 24 weeks after the trauma and had better scores on the clinical tests reported above.

In this regard, it is also interesting to report the study conducted by Hannermann P F W et al. [17] in 2014 relating to the evaluation of PEMFs on conservatively treated scaphoid fractures. This study disagrees with the predominant opinion in the literature. During the follow up of the study, conducted up to 52 weeks after the traumatic event, no statistically significant differences were highlighted between the treated group and the placebo group by performing a hand CT control, concluding that, in the acute management of fractures of scaphoid treated conservatively, no positive effects on the speed of the bone healing process were found.

4.2. Spinal Surgery

The usefulness of biophysical stimulation has also been investigated in the field of Spinal Surgery to improve the outcome of patients after Lumbar Spinal Fusion surgeries. The study conducted by Massari L. et al. [18] in 2020 reports the results relating to clinical symptoms in this area following the use of capacitively coupled electric fields (CCEFs) for 90 days. In this study forty-two patients undergoing LSF were assessed and randomly allocated to either the active or to the placebo group. Follow-up visits were performed at 1, 3, 6, and 12 months after surgery. The treatment was started 7 days after the surgery and included the application of CCEFs for 9 hours a day. The device was able to stimulate the area between 2 intervertebral disk spaces. Comparison with a placebo group identified positive results both in the short and medium term with regard to symptoms reported by patients. The Visual Analogue Scale (VAS) for pain, the 36-item Short Form Health Survey (SF-36) and the Oswestry Disability Index (ODI) for functional results were used to assess efficacy. For this reason, the authors conclude by advocating the usefulness of these therapies to improve the quality of life.

In 2009 Massari L. et al. [19] they described the main fields of use of PEMFs and their rational Scientific considering several published studies. The work also produces a decision tree to guide the orthopedic surgeon in identifying whether the patient is suitable for biophysical stimulation and when and how to evaluate the results of stimulation. The authors have reported the usefulness of biophysical therapies in bone healing, emphasizing the importance of both the correct therapeutic indication by the clinician and the adherence by the patient. This last statement seems essential to obtain satisfactory results, so the achievement of the final goal requires correct information of the patient.

More recently, a study conducted by Liu W et al. [20] in 2021 on a population of 82 female patients surgically treated with percutaneous vertebroplasty for vertebral fractures due to osteoporosis. The patients selected were those aged 60-75. Statistically significant differences were observed already at 1 month of follow up regarding the Six Minutes Walking Test, while significant differences were only evident at 3 months for the VAS assessment of pain and for the radiographic appearance. The aim of the study was also to look for a correlation between clinical efficacy and post-stimulation change of bone structure, for this reason, in addition to analyzing the clinical effect, an assessment was carried out at hip bone level, radius and tibia effects on bone mass and microstructure. After 1 month and 3 months there was a marked improvement in the quality of life of the patients but there was no increase in bone density at the level of the examined portions. Differently it was used, after 3 months, are changes of the bone microstructure.

4.3. Joint Replacement

A further field of application for biophysical therapies concerns the application after joint replacement.

In 2015 Massari L. et al [21] conducted a narrative review regarding the application of PEMFs in the period following hip or knee prosthetic replacement. The data present in the literature at the time of the study demonstrated that the use of biophysical therapy could be useful to reduce bone edema, pain and to reduce excessive bone resorption around the femoral stems.

The same conclusions were reported after a more recent review of the literature also by Lullini G. et al. [22], underlining the improvement in the clinical parameters of the patients in the first post-operative period. The authors selected all available prospective studies or randomized controlled trials (RCTs) on the use of PEMFs in total joint replacement with the aim of investigating the effects of PEMFs in the postoperative period. Both reported studies highlighted the importance of these applications especially to make the patient more compliant with physiotherapy rehabilitation protocols, the authors in fact express themselves positively about the improvement of the symptomatology, about the edema and the inflammatory state of the interested portion.

The encouraging results observed in hip and knee prosthetic surgery are also reproducible for the upper limb. In 2019, the La Verde L. et al 25 study considered the use of PEMFs for 4 hours a day for 2 months following reverse shoulder arthroplasty surgery. The 50 patients considered in the study

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were divided into 2 groups (experimental group vs control group) to perform a prospective randomized study. During the 6-month follow-up, statistically significant results were observed for both 1 and 2 and 3 months for the VAS rating scale and for the Constant score for shoulder functionality. The authors therefore conclude that the application of magnetic fields in this field is safe and beneficial.

In 2022 D'Ambrosi R. et al [24] conducted a study regarding the application of PEMFs in patients treated with medial unicompartmental knee arthroplasty (UKA). The treatment protocol involved the application of PEMFs 4 hours a day, not necessarily consecutive, from day 3-7 post-surgery for 60 days. During this period the patient also underwent physiotherapy rehabilitation. The following scales were used: VAS for pain, Oxford Knee Score (OKS) and Short Form 36 (SF-36) for clinical evaluation. Furthermore, the degree of knee edema and the consumption of painkillers during follow-up were evaluated. The first statistically significant results for painful symptoms were observed at 3 months, while significant clinical results were collected with OKS and SF-36 from the first month. While as regards edema, the first significant differences were observed at 2 months. All these results remained significant at least until the 36-month follow-up. The authors therefore conclude that the use of PEMFs after UKA surgery leads to a clinical improvement, to a lower consumption of drugs, to a better state of the edema and therefore, more generally, to greater patient satisfaction.

4.4. Joint preservation

The use of PEMFs also has a role in preserving the joint compartment. A meta-analysis regarding the application of low and high frequency electromagnetic fields in the presence of inflammatory degenerative joint diseases was recently conducted by Tong J. et al. [8]. This review states that there is evidence for low frequency PEMFs for these pathologies at the knee and hand level, obtaining an improvement in clinical symptoms and range of motion.

The positive results on the improvement of joint inflammation and cartilage damage are also reported in the study conducted by Benazzo F. et al. [9] in patients undergoing arthroscopic knee surgery for ACL reconstruction. 60 patients were identified, divided into 31 treated with biophysical stimulation and 29 in the placebo group. All patients underwent ACL reconstruction with use of quadruple hamstrings semitendinosus and gracilis technique. At baseline there were no differences in the International Knee Documentation Committee (IKDC) scores between the two groups. Based on interesting pre-clinical efficacy studies, a treatment protocol was developed which involved the use of the stimulator for 4 hours a day, not necessarily consecutively, for 60 days. Treatment started within 7 days from the surgery. The authors observed a lower consumption of painkillers and an improvement in the SF-36 Health Survey score at 2 and 6 months. However, it is more complex to analyze the results of IKDC score where, as reported by the authors, there are some confounding factors. The conclusion of the work is expressed favorably regarding the reduction of the inflammatory process and the improvement of the joint catabolic processes, with benefit of both the articular cartilage and the subchondral bone. For this reason, a rationale for use after arthroscopic surgery is suggested, particularly in those subjects who need a rapid return to physical activity.

In accordance with what has been stated, we also report the review conducted by Moretti L. et al. [23] considering works on athletes with high functional demands treated with PEMF and extracorporeal shock wave therapy (ESWT). Even in this situation, biophysical stimulation reduced the inflammatory process, improving adherence to the physiotherapy program and the return to sporting activity in non-advanced forms of osteoarthritis (OA). The authors conclude that, although there are extremely interesting findings, it is essential to develop high-quality studies in athletes to draw stronger conclusions.

The results observed and reported in this review agree with what was stated by Massari L. et al. [1] in the narrative review conducted in 2019. This publication examined the results in various specialist fields, concluding positively regarding the application of biophysical therapies. The study examines the different fields of use to draw indications from the literature. Improvements in the bone healing process have been observed in subjects at risk of malunion, improvements in the symptoms reported in patients undergoing spinal surgery, better rates of osseointegration in the femoral components of cementless hip prostheses, effective results of core decompression and grafts of trabecular bone in the treatment of osteonecrosis of the femoral head and improvements in inflammatory processes in the articular compartment. None of the authors of these studies suggests a generalized use of biophysical stimulation but the importance of a reasoned therapeutic prescription is highlighted.

In the current literature we have not found opinions regarding the cartilage regenerative process after stimulation with PEMFs. In fact, although there are pre-clinical studies with encouraging results, it is not yet possible to provide clear recommendations for clinical practice.

5. Conclusions

The analysis of recent literature determines a level of evidence regarding the improvement of the bone healing process in patients treated with PEMF. The effectiveness of these therapies is now consolidated with cure rates that largely support the cost-benefit ratio. In the literature review we conducted no validated scientific studies were identified that reported side effects of these therapies. All the works considered reiterate the fundamental importance regarding the correct diagnosis of use, methods and times of application and above all compliance with the treatment by the patient. The dominant opinion that emerges is in favor of the use of stimulation with electromagnetic fields in the sectors taken into consideration. The studies in which there was no evidence of statistically significant results presented, as declared by the authors, bias with potential impact on the interpretation of the result.

As observed in the studies examined during the discussion, the major problem lies precisely in the different therapeutic protocols applied by the Authors. This makes it more difficult to compare the results obtained.

Otherwise, there is more discussion about applications in the field of chondroprotection. In this application, the choice of the moment of application of the stimulation plays a fundamental role; better results have in fact been reported in recent forms of OA with a predominance of the inflammatory component, while the results are less evident in advanced and structured forms of cartilage damage. The effectiveness on the joint inflammatory phase makes the application interesting after joint replacement and in the field of arthroscopic surgery due to the promising preliminary results regarding the improvement of catabolic processes. We also found positive results on clinical symptoms and patient compliance with rehabilitation therapies. For this reason, notable applications can be expected in the fields of Prosthetic Surgery and Sports Medicine. In the coming years we will observe a strong increase in applications in these areas. In fact, the valid results on joint inflammatory pathology demonstrate a strong indication for use both in the field of Joint replacement and Joint preservation. In this last sector, and even more so in Sports Medicine, it will be extremely interesting to evaluate the results emerging from preclinical studies on devices dedicated to the regeneration of cartilage tissue. In fact, unlike bone tissue, there is currently no dominant opinion on the regeneration of cartilage tissue, however the preliminary results mentioned above suggest an optimistic attitude in this field of application.

We therefore conclude by stating that biophysical therapy can provide a valuable aid in clinical practice if the correct indications and methods of administration are respected.

6. Future Directions

The use of biophysical stimulation in the field of bone healing is now a consolidated reality; however, the need to have well-defined guidelines emerges to optimize the indications and identify the expected results. Furthermore, standardizing therapeutic protocols would be essential to be able to generate scientific results that are more comparable to each other, reducing the risk of misinterpreting data from populations treated incorrectly.

Objective assessments, such as the *FRACTING SCORE* [12], capable of predicting the risk of malunions, would be precious tools in the hands of the clinician, therefore we hope that further ones will be developed.

The evidence collected will lead to a greater use of these therapies also to improve the patient's adherence to the rehabilitation process both in the traumatology and elective surgery fields.

In the literature there are no side effects reported following the therapeutic protocols applied. For this reason, it would be interesting to develop therapeutic strategies for the chronic patient. In fact, the possibility to perform the administration locally, makes this stimulation particularly suitable for these situations. In this way the full potential of PEMFs and CCEFs in positively modulating harmful processes could be explored. This approach could also further justify the initial cost to patients in some situations.

Another area where data is scarce is the application on tissues involved by infectious processes. Preclinical results show a potential role both in improving tissue condition and as a direct bactericidal effect. That is why we hope that there will be further work in this area to have data that can be accessed in a short space of time.

Further stimuli come from the results observed in the field of cartilage tissue regeneration. We will probably see a remarkable development of literature in this regard due to very promising in vitro results. It will certainly be necessary to carry out a careful selection of the target population to avoid wrong interpretations of the results, however in subjects with still valid regenerative potential, a valid rational use could be configured.

For this reason, only continuing with a critical approach, in the various fields of use, and with a scrupulous collection of clinical data will it be possible to completely understand the potential of these therapies.

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References

1. Massari L, Benazzo F, Falez F. Biophysical stimulation of bone and cartilage: state of the art and future perspectives. *Int. Orthop* **2019**, 43:539–551. DOI 10.1007/s00264-018-4274-3.
2. Varani K, Gessi S, Merighi S. Effect of low frequency electromagnetic fields on A2A adenosine receptors in human neutrophils. *Br J Pharmacol* **2002**;*136:57-66.* DOI: 10.1038/sj.bjp.0704695.
3. Ongaro A, Pellati A, Bagheri L. Pulsed electromagnetic fields stimulate osteogenic differentiation in human bone marrow and adipose tissue derived mesenchymal stem cells. *Bioelectromagnetics* **2014** Sep;35. DOI: 10.1002/bem.21862.
4. Sollazzo V, Scapoli L, Palmieri A. Early effects of pulsed electromagnetic fields on human osteoblasts and mesenchymal stem cells. *Euro J Of Inflam* **2011**;1,1(S):95-100. DOI: 10.1007/s11999-010-1341-5.
5. Clark CC, Wang W, Brighton CT. Up-regulation of expression of selected genes in human bone cells with specific capacitively coupled electric fields: electrical stimulation of human osteoblasts. *J Orthop Res* **2014**; 32:894–903. DOI: 10.1002/jor.22595.
6. Hinsenkamp M, Tuerlinckx B, Rooze M. Effect of elf fields on bone growth and fracture repair. *Biol. Effects abd Dosimetry Of Static and ELF Electromagnetic Fields* **1985**; Springer, pp 441-476.
7. Murray HB, Pethica BA. A follow-up study of the in-practice results of pulsed electromagnetic field therapy in the management of non-union fractures. *Orthop Res Rev* **2016**; 8:67-72. DOI: 10.2147/ORR.S113756.
8. Tong J, Chen Z, Sun G. The Efficacy of Pulsed Electromagnetic Fields on Pain, Stiffness, and Physical Function in Osteoarthritis: A Systematic Review and Meta-Analysis. *Pain Res Manag* **2022.** DOI: 10.1155/2022/9939891**.**

9. Benazzo F, Zanon G, Pederzini L. Effects of biophysical stimulation in patients undergoing arthroscopic reconstruction of anterior cruciate ligament: Prospective, randomized and double-blind study. *Knee Surg Sports Traumatol Arthrosc* **2008**. DOI 10.1007/s00167-008-0519-9.
10. Faldini C, Cadossi M, Deianira L. Electromagnetic bone growth stimulation in patients with femoral neck fractures treated with screws: prospective randomized double-blind study. *Current Orth. Pract* **2010**.

DOI: 10.1097/BCO.0b013e3181d4880f.

11. Assiotis A, Sachinis NP, Chalidis BE. Pulsed electromagnetic fields for the treatment of tibial delayed unions and nonunions. A prospective clinical study and review of the literature. J Orthop Surg Res **2012**. DOI: 10.1186/1749-799X-7-24.
12. Massari L, Benazzo F, Falez F. Can Clinical and Surgical Parameters Be Combined to Predict How Long It Will Take a Tibia Fracture to Heal? A Prospective Multicentre Observational Study: The FRACTING Study. *BioMed Res Int* **2018**. DOI: 10.1155/2018/1809091
13. Shi H, Xiong J, Chen Y. Early application of pulsed electromagnetic field in the treatment of postoperative delayed union of long-bone fractures: a prospective randomized controlled study**.** *BMC Musculoskelet Disord* **2013**. DOI: 10.1186/1471-2474-14-35.
14. Streit A, Watson BC, Granata JD. 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. DOI: 10.1177/1071100716652621.
15. Krzyżańska L, Straburzyńska-Lupa A, Rąglewska P. Beneficial Effects of Pulsed Electromagnetic Field during Cast Immobilization in Patients with Distal Radius Fracture. *Biomed Res Int* **2020**. DOI: 0.1155/2020/6849352.
16. Factor S, Druckmann I, Atlan F. The Effects of Novel Pulsed Electromagnetic Field Therapy Device on Acute Distal Radius Fractures: A Prospective, Double-Blind, Sham-Controlled, Randomized Pilot Study. *J Clin Med* **2023**. DOI: 10.3390/jcm12051866.
17. Hannemann PFW, Van Wezenbeek MR, Kolkman KA. CT scan-evaluated outcome of pulsed electromagnetic fields in the treatment of acute scaphoid fractures: a randomised, multicentre, double-blind, placebo-controlled trial. *Bone Joint J* **2014**. DOI: 10.1302/0301-620X.96B8.33767.
18. Massari L, Barbanti Brodano G, Setti S. Does Capacitively Coupled Electric Fields Stimulation Improve Clinical Outcomes After Instrumented Spinal Fusion? A Multicentered Randomized, Prospective, Double-Blind, Placebo-Controlled Trial. *Int J Spine Surg* **2020** Vol. 14, No. 6 pp. 936–943. DOI: 10.14444/7142.
19. Massari L, Caruso G, Sollazzo V. Pulsed electromagnetic fields and low intensity pulsed ultrasound in bone tissue. *Clin Cases Miner Bone Metab* **2009**, 6(2) pp 149-154.
20. Liu W, Jin X, Guan Z. Pulsed Electromagnetic Field Affects the Development of Postmenopausal Osteoporotic Women with Vertebral Fractures. *Biomed Res Int* **2021**. DOI: 10.1155/2021/4650057.
21. Massari L, Osti L, Lorusso V. Biophysical stimulation and the periprosthetic bone: is there a rationale in the use of Pulsed Electromagnetic Fields after a hip or knee implant? *J Bio Regul Homeost Agents*, **2015**, 29(49):1013-1015.
22. Lullini G, Cammisa E, Setti S. Role of pulsed electromagnetic fields after joint replacements. *World J Orthop* **2020**, 8;11(6), pp 285-293. DOI: 10.5312/wjo.v11.i6.285.
23. Moretti L, Bizzoca D, Giancaspro GA. Biophysical Stimulation in Athletes' Joint Degeneration: A Narrative Review. *Medicina* **2021**, 57 (11): 1206. DOI: 10.3390/medicina57111206
24. D'Ambrosi R, Ursino C, Setti S. Pulsed electromagnetic fields improve pain management and clinical outcomes after medial unicompartmental knee arthroplasty: A prospective randomised controlled trial. *J. ISAKOS*, **2022**, Oct;7(5):105-112. DOI: 10.1016/j.jisako.2022.05.002.
25. La Verde L, Franceschetti E, Palumbo A. Applicazione dei campi magnetici pulsati nei pazienti sottoposti a protesi inversa di spalla: valutazione clinica e funzionale. *GIOT* . **2019**; 45 pp 37–46.