



Opinion Article

Are New Approaches Needed to Solidify Pulsed Electromagnetic Fields and Osteoarthritis Associations: A 50-year Retrospective Showing Promise but No Definitive Lab or Clinical Research Conclusions (1974-2024)

Ray Marks^{1*}

¹Department of Research, Osteoarthritis Research Center, Box 5B, Thornhill, ONT L3T 5H3, Canada

*Correspondence author: Ray Marks, Department of Research, OARC Clinical Research and Education Director, Ontario L3T 5H3, Canada;

Email: rm226@columbia.edu; RayMarks@osteoarthritisresearchcenter.com

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Abstract

Background: Osteoarthritis, a painful oftentimes disabling joint disorder affects many older adults and others globally. Involving progressive and distinctive biologic as well as structural alterations of the articular cartilage tissue lining freely moving joints such as the knee joint and often the underlying bone the condition is presently considered incurable.

Objective: In seeking to advance therapies for this condition, this report was designed to examine the rationale for and potential efficacy of, applying pulsed electromagnetic fields clinically for purposes of reducing osteoarthritis pain and other related symptoms disease features, especially through its impact on cartilage, the tissue most consistently implicated in this disease.

Methods: Available English language literature published largely on PUBMED between 1974 and 2024 were reviewed a) in general; b) to specifically examine whether favourable changes in pain as well as the disease itself might be expected from the application of pulsed electromagnetic fields in some form to an osteoarthritic joint and c) why this occurs, if observed. Key search terms used were: Pulsed Electromagnetic Fields, Cartilage, Chondrocyte, Disability and Osteoarthritis.

Results: The data search revealed a large body of basic and clinical research in this field has persisted over time with no definitive conclusion, but with tentative support for its possible potential use for mitigating pain and improving cartilage homeostasis and joint function via several biologic pathways.

Conclusion: Further basic and carefully controlled short and long term clinical research alongside comparable lab studies appear strongly indicated and may help to better validate and support the possible more mainstream and/or targeted clinical use of one or more forms of pulsed electromagnetic fields in facilitating function and possible joint reparative processes in adults with osteoarthritis, while reducing pain, inflammation, stiffness and the magnitude of joint derangement and dysfunction.

Keywords: Articular Cartilage; Disability; Pulsed Electromagnetic Fields; Osteoarthritis; Pain

Introduction

Osteoarthritis, the most common form of arthritis is usually accompanied by focal structural and functional alterations of the cartilage tissue lining one or more synovial or freely moving joints and that serves to attenuate excess loads, such as that at the knee joint. In addition, the condition may be accompanied by extensive remodeling of those bone surfaces that lie adjacent to cartilage, plus varying degrees of inflammation, muscle weakness and adverse reactive cognitive responses. Unfortunately, no well accepted method of detecting osteoarthritis early on in the disease process prevails and the disease, which is often progressive, only emerges clinically in its more advanced stages when pain is persistent and the joint space of the affected joint

appears deranged radiographically. Affecting high numbers of aging adults, the primary signs and symptoms of osteoarthritis other than pain that render this disease highly disabling include stiffness, muscle weakness, joint instability, joint inflammation, joint deformity and a decreased degree of mobility and range of joint motion. Commonly there is an accompanying general decrease in the affected adult's ability to function psychologically, as well as socially and economically.

Because there is no cure for osteoarthritis, individuals with this disease, particularly those who find little benefit from prescribed medications or cannot use these drugs without hazard are sent to physical therapists and other health providers for non-pharmacologic and non-surgical treatments to alleviate their symptoms and to restore optimal functional capacity [1]. Among those therapies commonly advocated for treating symptoms of osteoarthritis are a wide array of electrotherapeutic modalities with each showing some promise in improving one or more osteoarthritis signs and symptoms even though well-designed research in this field has been and remains limited and non-conclusive [2].

In this respect, one modality constituted by low-frequency/energy pulsed electromagnetic fields applied as a single or pulse burst quasi-rectangular or triangular waveform, has been found to have some promise in this respect in some cases especially in the case of early osteoarthritis or in its own right as a form of therapeutic support due to an observed ability to accelerate or reinitiate healing and to relieve pain [3-12]. Its multiple benefits when observed as an application for ameliorating osteoarthritis disability have also included the mitigation of joint inflammation and associated bone damage, plus the possible 'healing' or regeneration of articular cartilage and soft tissue lesions found to varying degrees in osteoarthritic joint disease [1].

In particular we examine:

- The existing rationale underlying the application of pulsed electromagnetic fields for the treatment of painful osteoarthritic joints in general and from the viewpoint of its interaction with cartilage tissue as viewed in the laboratory
- Existing evidence of the extent of its clinical potential and possible underlying mechanisms of action as deduced from preclinical studies

Rationale

It is increasingly apparent that osteoarthritis treatments currently fail to produce results commensurate with the many research efforts conducted for more than a century in this regard. In terms of pain relief alone, the growing usage of narcotics and other medications to quell pain implies a failure to address this universal complaint and feature of osteoarthritis [13]. On the other hand, even if osteoarthritis is continuously viewed through a degenerative lens, various forms of bio physical stimulation such as low energy, low frequency electromagnetic fields have been shown to trigger a variety of biological cellular responses via specific membranous and intracellular biological pathways that can impact articular cartilage cells or chondrocytes, subchondral bone synovial membrane and connective tissue cells so as to foster its potential reparative capacity [7,14]. What has been shown is that due to their differential abilities to stimulate or trigger selected cell-based molecules and structural components, intermittent or low frequency externally applied electrophysiological applied fields may favorably influence multiple intrinsic joint structures and functional status implicated in osteoarthritis, such as cartilage cells, bone cells, possible muscle and tendon repair processes as required and others [11,15]. As such, their application alone or as a complementary modality may be especially helpful in efforts to improve the cartilage tissue integrity to a degree that fosters mobility as well as joint stability, while securing protection against future loading insults [16-22].

In addition, pulsed electromagnetic fields are non-invasive and practical to apply at low cost when weighing their safety and multiple possible functional benefits. Commonly applied with no unwanted heating effect these currents may help to improve joint status even in the absence of movement that is often hard to perform in the case of pain and may lessen rather than heighten joint swelling and inflammation. Even if not a perfect solution, their insightful use may well delay surgery or foster better post-surgery healing effects if this is needed [23,24].

Most importantly, their application may conceivably help to reduce the attendant disability often found to increase progressively in those diagnosed as having osteoarthritis and where cartilage matrix degradation often increases over time [25-27]. Moreover, as opposed to multiple areas of osteoarthritis intervention where the mechanism of action is poorly understood, these aforementioned observations do appear with a high consistency and are found to yield considerable biological support for why

osteoarthritis beneficial impacts may arise post stimulation, even if disputed by some or ignored by groups seeking osteoarthritis solutions [28,29].

These beneficial impacts when observed have been attributed to several explanations that include the potential of pulsed electromagnetic low intensity stimuli to:

- Favorably alter cartilage cell morphology, cartilage chondrocyte density, protein and cytoskeletal regulation, while reducing the extent of premature cartilage cell death [26,30-32]
- Improve cartilage cell physiology enhancing processes, including the production of favourable anabolic processes that build and maintain cartilage infrastructure, while reducing adverse cellular based production of destructive enzymes and m-RNA effects [22,26,33-35]
- Reduce the rate of chondrocyte stress-induced cell death via its impact DNA synthesis bone cell enhancement, inflammation resolution and muscle regeneration [16,24-26,36-38]
- Improve or stimulate the cyclotron resonance frequencies of critical ions and their motion through cartilage cell membrane and subsequent transduction effects [9]
- Foster a rise in cartilage collagen support tissue, as well as total protein synthesis in surrounding tissues if injured nerve regeneration if compromised, inflammation, pain, stiffness and function [5,39-43]

According to these theories and others, the unique or cumulative or supportive impacts of pulsed electromagnetic fields can conceivably be favourable if applied to stimulate cartilage and bone cell proliferation and tissue repair in damaged joints [44-47]. They can help reduce inflammatory processes, even if their overall efficacy in other spheres is deemed equal to other traditional non-surgical approaches [48,49].

As per Funk these research derived theories are not spurious and indeed can be predicted because biological data reveal there are endogenous mechanisms in cartilage that can be duly activated differentially if exposed to various pulsed electromagnetic field stimulation [28]. Applied in an insightful manner, these reactions can be mobilized to foster cartilage and joint based cellular protective processes while lowering degrading inflammatory signals.

However, the degree of influence may depend upon the nature of the substrate plus what is measured and how and when. As well, application placements and extent of any underlying genetic based predispositions towards cartilage cellular repair responses may determine its efficacy and impact. Also, of import when trying to assimilate multiple study results are the widespread differences across these studies of the dosage schedule of the applied pulsed electromagnetic fields in question, including its amplitude, duration and frequency. The deterministic role of the density and status of the cells and tissues under exposure is also difficult to discern without further study. Moreover, even if known in the laboratory to be effective, the duration, timing and frequency of such applications in the clinical realm may not be comparable and rather than a static environment, the joint may yet be exposed to variations in external static and dynamic mechanical force factors falling on the joint post stimulation, thus raising the potential for engendering differing or unpredictable stimulation outcomes, including null outcomes [50].

Method and Procedures

To examine some of these aforementioned ideas and thoughts, this report of public data that required no ethics review was designed to examine relevant data covering the time periods 2004-2024, including observations from a former analysis conducted on 1985-2003 data and published topical reviews. PUBMED was largely employed for the search due to its immense coverage of peer reviewed and accepted as reliable medical literature. Key words focused on: Articular Cartilage, Osteoarthritis; and Pulsed Electromagnetic Fields [PEMF]. All forms of study were accepted, but no systematic analysis or synthesis of either the laboratory or the clinical literature was attempted-given their diversity and limited numbers of recent studies. A focus was placed on selecting and reviewing preclinical data and their findings rather than clinical studies, with the exception of studies detailing the influence of pulsed electromagnetic fields on stem cells at are widely undergoing examination to assess cartilage and bone repair strategies and applications in the clinic as well as post-surgical situations. Extracted data focusing on the most important cited works to date were analyzed carefully and a narrative summary of more recent data covered in the last five years is provided alongside commentary derived from some key findings made over the past 50 years as follows below. Readers interested in clinical and past analyses and observations may want to examine references [50-52]. The data were extracted initially by an

independent reviewer and key observations were critically evaluated in prior preclinical and clinical spheres systematic reviews valid animal model and clinical trials [53-55]. Protocols for future study, sports injury associated studies, conference proceedings and non-English or incomplete studies were excluded as were many early citations covered in the reference section of references 51 and 52. It was assumed most studies were acceptable to peer experts in the field and those published may not include all negative findings. However, it was assumed a general picture of the state of the art would be attained with relative confidence when assessed very carefully and across multiple perspectives and substrates.

Results

Since the early 1970s when several researchers began to examine pulsed electromagnetic fields and their interactions with cartilage and bone cells, this topic has continued to be of interest and very informative in the context of its basic potential to mitigate osteoarthritis. Most, albeit not all continue to largely lend support to using or studying this mode of physical energy as a form of osteoarthritis therapy in the future, regardless of methods of inquiry that includes but is not limited to an array of cell culture assays, animal models of osteoarthritis, animals with naturally occurring or age associated osteoarthritis, stem cell substrates and cartilage and bone explants.

Among those that have emerged recently, that by Yang, et al., examined a mouse model of osteoarthritis induced by destabilization processes found pulsed electromagnetic field application were able to attenuate the degree of ensuing osteoarthritis and its progression [56]. It was shown that was due to the ability of the applied biophysical stimulation to the injury site to inhibit inflammatory signaling processes. In particular, the stimulation attenuated the structural and functional progression of osteoarthritis commonly found to emerge in this model. The pulsed fields were hence deemed protective and appeared to attenuate the magnitude of verifiable cartilage chondrocyte death processes.

Wang, et al., agree that pulsed electromagnetic stimuli can foster a state of chondrocyte proliferation, while exerting a protective effect on cartilage cell catabolic actions and their impact on the cellular environment [17]. Furthermore, this form of stimulation may foster cartilage healing plus beneficial bone micro architecture effects that may have a key protective impact on loading induced progressive osteoarthritis pathology [24,33,35]. In addition, the degree of pain relief that can be duly modulated, may improve the overall ability of the affected adult to function physically [57]. Although not discussed here, it also appears pulsed electromagnetic stimuli applied at a low intensity have great promise as far as stimulating desirable results in engineered cartilage growth and repair procedures [58], post traumatic osteoarthritis and inflammation [60]. Also likely to be impacted favorably are meniscus tears and tendon lesions [59-61].

Liu, et al., who explored the protective efficacy of pulsed electromagnetic fields on the progression of osteoporotic osteoarthritis using a rat model showed the treated group presented with a retarded form of cartilage degeneration and bone loss, while preventing excess cartilage cell death [62]. Another group who studied a mouse model with surgically induced unilateral knee osteoarthritis showed an analogous pulsed electromagnetic field stimulation outcome that promoted the expressions of cartilage matrix proteins or aggrecans and inhibited the expression of destructive enzymes [63]. In support of this idea Xu, et al., found that pulsed electromagnetic stimulation of adipose tissue stem cell units yielded a favorable anti-inflammatory and a slower or attenuated extracellular chondrocyte matrix catabolic effect [65]. Moreover, inflammation alone may be attenuated even in the case of knee osteoarthritis in an aged animal model of cartilage destruction in response to specifically selected parameters of stimulation [65-67].

Similarly, despite a lack of agreement as a whole in this realm of possible osteoarthritis remediation, Yang, et al., who examined the efficacy of pre-emptive, early and delayed pulsed electromagnetic field treatment on cartilage and the adjacent bone tissues in a rat model of knee osteoarthritis found the treatment preserved the bone's structure and prevented its loss [68]. Indeed, it appeared to increase bone as well as cartilage formation according to this group.

Cadossi, et al., propose that these aforementioned results and others are not unexpected if one considers that cell membrane receptors at the stimulation site appear to induce signals that have dose-like response effects as far as the synthesis of structural and signaling extracellular matrix components of cartilage is concerned [35]. Through these actions, the structural integrity of bone and cartilage can undergo enhanced repair and can alter the homeostatic balance of cytokines, producing anti-inflammatory

effects with a pro anabolic effect on the bone and cartilage matrix, as well as an anti-catabolic effect [69].

Iwasa, et al., further describe a role for pulsed electromagnetic fields in the treatment of non-union bone fractures that may yet be of benefit in osteoarthritis cases in terms of fostering overall joint function [70]. This was also observed to some degree by Ma, et al., and Cadossi, et al., and implies bone-based stimulation alone may prove helpful as an early intervention approach for averting osteoarthritis of one or more joints in the clinical realm [6,35].

In sum, although not all published preclinical studies examined in this overview are in favour of any form of pulsed electromagnetic field stimulation as far as having beneficial cartilage cell and pain impacts more positive than negative or null conclusions prevail [71]. However, as in many current realms of inquiry, these affirmative and promising data must be extrapolated with some caution to the bedside. The fact that transcriptional, cellular and sub-cellular molecular effects within damaged cartilage and bony tissues have however been quite well documented and replicated must surely keep the door open for those interested in undertaking and unravelling possible clinical applications to mitigate osteoarthritis or even arrest or reverse this disease. In this regard, at the very least, the fact that osteoarthritis derived cartilage cells do respond to biophysical stimuli is promising and warrants future study [14]. In addition, secondary bone and adjacent tissue repair may have the potential to foster cartilage viability and possible repair [61,62,71-73].

Experimental factors however, including a lack of careful consideration of the nature of the measurement properties applied factors could slow or interfere with healing, as can a failure to control for competing interventions, disease stage and extent and all are paramount potential confounders to eliminate. Moreover, even if assessed in some way, the failure to employ advanced technologies that can detect cartilage cell transformations at the nano molecular level as well as functional mechanics may weaken the chances for valid insights of high veracity to emerge. As well, the study of homogeneous osteoarthritis groups may yield rather than contaminate the attainment of meaningful and insightful results to supplement those already observed [74,75]. Carefully considered integrated therapy efforts that proceed in the face of optimal exposure and stimulus dosage also hold great promise even if disputed [12,22,76-84].

Discussion

The question of whether an older adult suffering from painful incurable progressive disabling osteoarthritis of one or more joints might be helped therapeutically and safely using non-invasive nontoxic passive methods is a well-studied topic of high clinical and public health relevance. In this current overview that spanned a 50-year time period that has focused on one possible application derived from pulsed electromagnetic sources is one that has shown consistent promise of exposing damaged joints to various forms of this form of biophysical energy. Unfortunately, while some very well designed and transacted innovative laboratory studies have emerged that can currently pinpoint and verify focal molecular impacts of note and others, this research remains hard to translate into clinical comparable benefits in many cases. That is, even though preclinical work is largely supportive of a favorable role for low frequency pulsed electromagnetic field applications to offer a bridge to cartilage repair and pain relief in osteoarthritis cases, not all studies support this idea.

One reason for this may be that even when many carefully controlled studies have been conducted, these did not always account for varying forms of contamination, such as uncontrolled joint usage, co interventions, medication regimens, health status, numbers of affected joints and others. Synthesis is also impeded by the small number of studies, small sample sizes and short term rather than long term study durations. Dissimilar or non-comparable protocols or usage approaches such as similar energy sources and modes of delivery, scheduling, outcomes assessed are highly evident in the literature, as is the clinical definition of osteoarthritis and study of limited joint types. Unsurprisingly, even after more than 50 years of study, non-conclusive, negative, or confusing results prevail in terms of pain reduction and other disease correlates [71,82,85].

Consequently, even if several notable plausible evidence-based mechanisms appear to support the impact of pulsed electromagnetic fields in explaining its varied outcomes, magnetic fields applied in the laboratory to isolated cartilage cells and others may only yield results that translate readily if the application is carefully designed in all respects to closely replicate that examined in the laboratory as well as the osteoarthritis associated presentation [50-52]. As well, applying pulsed electromagnetic field results observed on extrinsically induced osteoarthritis or osteoarthritis cells placed in an artificial medium may not be

comparable to the influences on joint status in the human condition and bearing in mind aging impacts on joint physiology thus more creative study approaches are strongly recommended [86]. Alternately, even if the pulsed electromagnetic stimuli are carefully chosen and insightfully delivered, the measures that predominate in the clinic to discern baseline or outcome status must avoid the possibility of inadvertently relying largely on subjective responses and possible lack of validity and questionable reliability.

In sum and in light of the positive as well as the null clinical and on occasion laboratory results currently posted in early 2024 on the most well-known data source of PUBMED, it appears that until more definitive research is forthcoming caution is advised in not overestimating or underestimating the efficacy of pulsed electromagnetic fields for osteoarthritis mitigation.

Indeed, even if there are other articles in either respect that have been overlooked, most current reports including meta analytic reports are not only highly diverse, but may omit some studies and not others, apply few objective measures of pathology and/or joint viability indicators in favor of diverse subjective survey responses on a limited array of variables and that are based on the assumption of the respondent having optimal memory, language proficiencies, health literacy and hearing and vision. Most commonly, many focus almost exclusively on baseline and outcomes of pain often derived from non-uniform surveys or single items, with almost none focused on actual key osteoarthritis physical, social, or mental health correlates. At the same time, often unaddressed are uncontrolled factors in the environment as well as health behaviors and intrinsic factors that may play a role in skewing the data or undermining the actual stimulation impacts. In addition, limited sample sizes, selection criteria that may exclude some who may benefit as well as some who may react unfavorably, plus studies conducted on differing cases suffering from variable disease stages, numbers of affected joints and the role of unknown concurrent treatments prevent any overall consensus.

Additional general problems with related clinical studies employing pulsed electromagnetic fields that have been examined over time are: a) the lack of functional outcome measures, b) the predominance of subjective patient reported functional experience estimates rather than radiographic and/or biomechanical assays, c) dropouts that are not routinely followed and d) potential control group exposure to the effects of other physical therapy analogues. The mode of stimulation applied that may be crucial is often not well defined or chosen based on clear rules, thus even if proven beneficial in a study, how this benefit can be applied successfully to a potentially unique subject group and for how long and at what frequency surely prevents any readily replicable treatment approach as well as uniform conclusions and expectations even after 50 years of study.

However, in contrast to other physical therapy modalities which may invoke tissue heating and subsequent destructive enzyme activity and swelling if excessive, pulsed electromagnetic field applications can be applied with no heating effect to mimic those mechanical stimuli known to favour the production of molecules that can foster extracellular cartilage matrix production, joint mobility and stability [16]. In addition, it is possible that its insightful application using thermal doses may yet relieve pain and muscle spasm that accompanies the disease. Third, its application could help with repair of bone damage, which may be causing or perpetuating the disease to some extent.

In addition, collective evidence implies articular cartilage cells are indeed highly responsive to electrical, mechanical as well as chemical stimuli and can be manipulated accordingly by selected pulsed electromagnetic field effects, as can bone and supportive tissue structures that may enhance bone remodeling, while mitigating harmful joint stresses [51-52]. Careful applications may further obviate the need to resort to narcotic usage that may prove addictive. Its anti-inflammatory, effusion and pain reducing properties, may prove equally valuable in helping the affected individual to exercise, especially important in early as well as late life osteoarthritis [20].

However, to validate these assumptions, further studies might consider using more advanced state of the art diagnostic tools and technologies, alongside efforts to examine intrinsic cartilage and bone health status, with attention to design rigor and fidelity and comparable disease indicators across carefully selected groups using sensitive and reliable approaches [14,35,37]. Based on multiple successful preclinical studies, specific intracellular mechanisms of action that may yet be effective in clinical efforts should be sought as well even in damaged joints [87,88]. If not, it may be possible to find errors either in the context of these basically passive laboratory experiments or in those conducted in the clinical setting or both.

Implications

Although many older adults suffer with osteoarthritis without much relief and despite favorable preclinical related observations of possible relief and even disease regression or repair post electromagnetic stimulation, the shortcomings of clinical studies and especially those relying largely on aggregated data to guide clinical decisions in this sphere is clearly limited. This is not only due to an inconsistent array of studies that are inclusive of clinically meaningful well designed research reports, but reports where widely applied definitions of the form of magnetism, as well as osteoarthritis prevail. Moreover, the widespread reliance on subjective reports and their possible lack of sensitivity may well mask unique treatment effects. Other issues that may account for discordant meta-analytic clinical findings are the limited number of studies, joints and sample sizes of included studies, the application of competing or concurrent therapies in the placebo control group, a failure to control for activity levels, medications, degree of disability and numbers of affected joints and the diverse forms of magnetism employed. The meta-analytic conclusions are also confusing because when viewed individually the data base of some, include quite positive reports.

As such and after studying this topic for many years, it is still worthwhile in our view to pursue in light of the increasing rates of worldwide suffering among the older population from potentially treatable osteoarthritis pain. Here, we advocate with reasonable confidence that clinicians should consider that the benefits of applying pulsed electromagnetic field treatments to quell osteoarthritis pain safely and to foster function earlier rather than later and are encouraged to keep records of such progress or lack thereof in this regard and thereby for more 'practice based' evidence rather than sole reliance on evidence bases alone to emerge.

Conclusion

While this broad-based overview may not have included all available studies and the quality of those identified cannot be readily established or readily and rigorously validated in many cases, it appears safe to offer four key conclusions as follows:

- Low frequency pulsed electromagnetic fields may provide a widespread available form of biophysical energy that can be harnessed and titrated to safely promote intrinsic tissue healing, cartilage viability, joint pain and inflammation found in osteoarthritis
- Individuals with osteoarthritis may have a good chance of benefiting from the application of pulsed electromagnetic fields to their affected joints, especially if applied at the outset of the disease
- To validate and clarify the potential of pulsed electromagnetic fields as it may offer a cost-effective means of reducing considerable suffering, careful research and more widespread collaborations between biologists, biochemists, pathologists, rheumatologists and other health personnel to lay the groundwork for a unified approach of applying pulsed electromagnetic fields clinically to evoke favourable chondrocyte gene and repair based molecular responses and others
- Extending research efforts to embody the features of the whole joint and their interactions if impaired with various forms of pulsed field applications alone or as complementary intervention are also likely to prove highly promising

Conflicts of Interests

The author declares that there is no conflict of interest for this paper.

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