Effects of electrical physical stimuli on articular cartilage

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Effects of Electrical Physical Stimuli on Articular Cartilage

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Introduction

Articular cartilage is a hypocellular, avascular, alymphatic tissue with a dense collagen and proteoglycan matrix that provides a low-friction and highly durable wear-resistant surface to both shear and compressive stress.

Normal maintenance of articular cartilage results from the balance between anabolic and catabolic activity. Resident chondrocytes control the extracellular matrix turnover—collagen and proteoglycans synthesis and degradation—from the tidemark to the tangential zone of the cartilage. However, little is known about the physiological processes regulating cellular turnover and cartilage homeostasis, mainly because of the large number of factors involved (mechanical load, cell density, matrix composition, growth factors, cytokines, injury, and aging) and the complexity of their interactions.

Insufficient knowledge of the physiology and homeostasis of articular cartilage greatly impairs the ability to stop or slow disease progression. It is commonly accepted that articular cartilage is a tissue with little or no regenerative potential and thus undergoes degradation over time.

The notion that it is impossible to prevent or reverse degeneration of articular cartilage has been challenged recently by the growing body of evidence in the literature based on basic-research findings concerning the physiology and pathophysiology of articular cartilage, so that new strategies for its maintenance and repair are emerging. In two recent studies by Glasson et al. and Stanton et al., a knockout mouse model of osteoarthritis, a degenerative disease that eventually leads to destruction of articular cartilage, demonstrated how a single protein, ADAMTS 5, is the main aggrecanase responsible for cartilage degradation and the principal mediator of the catabolic effects of pro-inflammatory cytokines, such as interleukin-1 (IL-1). Their findings identify a rational target for therapeutic intervention to limit cartilage degradation in osteoarthritis and demonstrate that interference with a single pathway can dramatically alter the natural history of joint disease.

Chondral injury rapidly results in local chondrocyte apoptosis, which progresses with loss of the articular surface and leads to joint deterioration. Acute direct trauma as well as surgical procedures involving vascularized tissues, synovial tissues, and subchondral bone may elicit an inflammatory response; also, repetitive or prolonged overloading of lesser magnitude (shear load) may cause joint inflammation that initiates a series of events detrimental to cartilage integrity.

In the articular environment, the activity of inflammatory cells and pro-inflammatory cytokines can lead to degradation of the extracellular matrix and loss of proteoglycans, which compromises the mechanical competence of the cartilage. Once begun, cartilage loss accelerates through a combination of mechanical and biological events; therefore, it is of the utmost importance to prevent and limit the catabolic effect of inflammation of the articular cartilage (Fig. 1).

Efforts to develop chondroprotective treatments should be aimed toward limiting the damage of cartilage following injury (trauma or inflammation), augmenting the reparative response, and finally preventing degeneration. Therapy to prevent the negative effect of inflammation on articular cartilage can be both systemic, with use of anti-inflammatory steroidal or nonsteroidal drugs, and local (when the inflammation is limited to one or a few joints), with use of intra-articular injection or physical stimulation.

The use of physical stimuli has been the subject of several studies aimed at understanding the mechanism through which they are able to control inflammation and stimulate articular cartilage anabolic activities. Pulsed electromagnetic fields, which have been investigated for years by our group, can be easily applied to single joints without systemic effect. Their use is not indicated for the treatment of joint inflammation associated with systemic diseases such as rheumatoid arthritis.

In joints, especially the knee, pulsed electromagnetic fields, unlike drugs, have the ability to completely and homogeneously permeate the whole articular cartilage and the underlying subchondral bone. Their use is aimed at controlling inflammation, stimulating the anabolic activity of the chondrocytes, and preventing cartilage degeneration, ultimately re-
sulting in a chondroprotective activity. The treatment should lead to improvement in the overall articular function of the patient.

Present clinical use of pulsed electromagnetic fields as a chondroprotector is based on preclinical and clinical research studies conducted by the CRES (Cartilage Repair and Electrical Stimulation) study group over the past seven years.

**Preclinical Data**

**In Vitro**

Pulsed Electromagnetic Fields Have an Adenosine A2A Receptor Agonist Activity

Recent investigations into inflammation have revealed the physiological role that adenosine receptors play in the control of inflammatory events. Adenosine interacts with four cell-surface adenosine receptor subtypes (A1, A2A, A2B, and A3), which are coupled to different G-proteins and finally reduce nitric oxide production and down-regulate the expression of pro-inflammatory cytokines. The A2A receptor has the highest anti-inflammatory activity. Adenosine levels are tightly regulated in cartilage since depletion leads to increased glycosaminoglycan release and to production of matrix metalloproteinase (MMP)-3, MMP-13, prostaglandins, and nitric oxide. Drugs with A2A adenosine receptor agonist activity have been shown to protect articular cartilage in animal models of induced osteoarthritis (Fig. 2).

In 2002, Varani et al. observed a significant increase in binding of adenosine to the adenosine receptor subtype A2A in human neutrophils exposed to pulsed electromagnetic fields (p < 0.05). Dose-response studies demonstrated that the effect was detectable after thirty minutes of exposure and saturation of the receptors was achieved with a magnetic field of 1.5 mT (Fig. 3). The effect of pulsed electromagnetic fields on adenosine binding with the A2A adenosine receptor was later confirmed in cultures of isolated fibroblast-like bovine synoviocytes and chondrocytes by the same group (Fig. 4). Together, these findings show that pulsed electromagnetic fields have an A2A adenosine receptor agonist activity, thereby identifying the A2A adenosine receptor as the pharmacological molecular target of therapeutic intervention with pulsed electromagnetic fields in patients with inflammatory joint diseases.

**Pulsed Electromagnetic Fields Favor Chondrocyte Proliferation**

In another study, human chondrocytes were isolated from articular cartilage of donors and cultured. Exposure to pulsed electromagnetic fields increased chondrocyte proliferation, as measured by H3-thymidine incorporation. The effect was observed when cultures were exposed to pulsed electro-
magnetic fields for more than six hours; furthermore, proliferation was significantly increased when 10% fetal calf serum was present in the culture medium \( (p = 0.0392) \), and it was also increased in low-density cultures compared with high-density cultures \(^{12,13} \).

**Ex Vivo**

**Pulsed Electromagnetic Fields Show Anabolic Activity in Full-Thickness Cartilage Explants in a Dose-Response Manner**

To test the sensitivity of chondrocytes in a microenvironment that more closely mimics the in vivo conditions, full-thickness bovine articular cartilage explants were exposed to pulsed electromagnetic fields in culture. Under these experimental conditions, it is possible to challenge the explants in the presence of both catabolic and anabolic stimuli \(^{14} \). Dose-response curves for proteoglycan synthesis in explants subjected to pulsed electromagnetic fields were prepared. Figure 5 shows the effect of the duration of the exposure, the magnetic field peak value, and the pulse frequency \(^{15} \). On the basis of these findings, we selected 75 Hz and 1.5 mT as the magnetic field parameters to be used in subsequent studies.

The effect of pulsed electromagnetic fields on cartilage explants was then challenged against catabolic or anabolic stimuli. When the cartilage explants were exposed to pulsed electromagnetic fields, proteoglycan synthesis increased. When a pro-inflammatory cytokine (IL-1\( \beta \)) was added to the culture medium, proteoglycan synthesis increased significantly compared with control basal values; however, when the cultures were exposed to pulsed electromagnetic fields, proteoglycan synthesis returned to basal values. These data demonstrate that pulsed electromagnetic fields can reverse the catabolic effect of IL-1\( \beta \) on the cartilage matrix \(^{16} \) (Fig. 6). Another study showed that pulsed electromagnetic fields had a synergistic-summatory effect when an anabolic cytokine, insulin growth factor-1 (IGF-1), was added to the culture medium at high concentrations \(^{17} \) (Fig. 7).

Overall, the ex vivo data demonstrate that pulsed electromagnetic fields stimulate anabolic activities in full-thickness cartilage explants and counteract the catabolic effect of the pro-inflammatory cytokine IL-1\( \beta \). These results are consistent with the described \( A_\lambda \) adenosine receptor agonist activity of pulsed electromagnetic fields.

**In Vivo**

**Effective Chondroprotection by Pulsed Electromagnetic Fields in an Osteoarthritis Model**

Because osteoarthritis with strict morphological, biochemical, and immunohistochemical similarities to human osteoarthritis spontaneously develops in the Dunkin Hartley guinea pig, this animal model is frequently employed to study osteoarthritis and the activity of disease-progression-modifying drugs. The capability of pulsed electromagnetic fields to modify osteoarthritis progression was first reported by Ciombor et al. \(^{18} \). They demonstrated that pulsed electromagnetic fields could prevent cartilage degeneration as measured with the Mankin histologic
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score, and their immunohistochemical analysis showed that the expression of IL-1β was down-regulated while the expression of transforming growth factor-1 beta (TGF-1β) was up-regulated, in animals treated with pulsed electromagnetic fields (Fig. 8). These results indicate a chondroprotective effect of pulsed electromagnetic fields on articular cartilage in vivo.

We investigated the effect of pulsed electromagnetic fields in Dunkin Hartley guinea pigs. Animals of twelve or fifteen months of age were exposed to pulsed electromagnetic fields for three or six months, respectively, to determine if the effect of pulsed electromagnetic fields could be observed in cartilage lesions of increasing severity. We evaluated the effect of pulsed electromagnetic fields on both femoral and tibial cartilage joint surfaces. The whole joint was sectioned, and the six most central slices (300 µm thick) were microradiographed and then reduced to 5 µm for histologic evaluation. The effect of pulsed electromagnetic fields was evident on all joint surfaces and was greater in the medial tibial plateau, where the degeneration begins. We observed higher Mankin scores, decreased cartilage thickness, and increased fibrillation in control animals than in animals treated with pulsed electromagnetic fields (Fig. 9). These data confirmed the results reported by Ciombor et al.18.

Microradiographic investigation of these animals demonstrated that the treatment prevented the subchondral bone from thickening (Fig. 10). This effect was particularly evident in the older animals, in which the thickness of the tibial medial plateau averaged 263 ± 18 µm after treatment with pulsed electromagnetic fields compared with 329 ± 82 µm in controls (p < 0.05). This effect was also observed in the subchondral bone of the femur 20. These findings were confirmed by bone density studies. Subchondral bone thickening as arthritis progressed was explained by considering that cartilage degeneration observed in control animals reduces its mechanical competence to absorb the load applied to the joint, which is instead transferred to the bone.

Overall, the results of these studies demonstrate that stimulation with pulsed electromagnetic fields significantly slowed the progression of osteoarthritic lesions in knee cartilage. Even in the presence of severe osteoarthritic lesions, pulsed electromagnetic fields maintained a significant capacity to reduce lesion progression in both the cartilage and the subchondral bone.

Pulsed Electromagnetic Fields and Cartilage Healing: Autologous Osteochondral Grafts in Sheep

The above-described experiments did not address the hypothesis that pulsed electromagnetic fields might reverse already...
established severe lesions with associated exposure of subchondral bone. We have no rationale for hypothesizing that pulsed electromagnetic fields can by themselves result in healing of a cartilage defect. On the other hand, it is recognized that factors in the microenvironment as well as in the joint space environment may play a role in the success of techniques used for the repair of full-thickness cartilage defects.

Use of autologous osteochondral grafts is a well-established technique for the treatment of cartilage lesions; nevertheless, there are several conditions that may jeopardize the success of the graft. Osteochondral grafts may undergo central necrosis, subchondral cyst formation, or insufficient integra-

![Image](image1.png)

**Fig. 7**


![Image](image2.png)

Immunohistochemical analysis of cytokines in cartilage from the lateral plateaus of Dunkin Hartley guinea pigs (×10). A reduction in the number of cells immunoreactive to IL-1 and an increase in the number of cells immunoreactive to TGF-β were observed in the cartilage treated with pulsed electromagnetic fields. **A:** Untreated control in IL-1 analysis. **B:** Cartilage treated with pulsed electromagnetic fields in IL-1 analysis. **C:** Untreated control in TGF-β analysis. **D:** Cartilage treated with pulsed electromagnetic fields in TGF-β analysis. (Reproduced, with modification, from: Ciombor DM, Aaron RK, Wang S, Simon B. Modification of osteoarthritis by pulsed electromagnetic field—a morphological study. Osteoarthritis Cartilage. 2003;11:460. Reprinted with permission of Elsevier.)
tion with subchondral bone, which together cause mechanical instability of the graft and poor cartilage nutrition, and ultimately may result in graft failure. Furthermore, a strong local inflammatory response following graft insertion may lead to an excessive local increase in pro-inflammatory cytokines that can severely damage the cartilage. Thus, early graft integration and stabilization, inhibition of osteoclast activity, and local control of inflammation are biological targets of paramount importance for the success of an osteochondral graft.

We hypothesized that the use of pulsed electromagnetic fields immediately after insertion of an osteochondral graft could favor healing of subchondral bone, control the local joint environment, and prevent the negative effects of pro-inflammatory cytokines released in the synovial fluid following the surgical procedure, all favoring cartilage healing.

Line-to-line osteochondral grafting was performed in the knees of sheep. This technique has the advantage of limiting the trauma required for graft insertion when a press-fit technique is used; however, immediate graft stability is not guaranteed, and the graft may be exposed to the detrimental effect of the synovial fluid.

In a short-term study, six animals were killed at the end of one month of treatment with pulsed electromagnetic fields for six hours a day. In a medium-term study, fourteen animals...
were treated for two months and then allowed to roam free in the pasture for another four months before they were killed. An external coil was positioned on the operatively treated knee of each animal, but it was not energized in the control group. Histologic examination and microradiographic analysis were performed on the osteochondral grafts and the subchondral bone.

In the short-term study, the microradiographs demonstrated that more bone had formed at the interface between the graft and the host tissue in the animals treated with the pulsed electromagnetic fields; furthermore, areas of bone resorption were present at the interface in the control animals. Histologic examination demonstrated a fibrous tissue surrounding the grafts, and, occasionally, histochemical analysis showed intense tartrate-resistant acid phosphatase (TRAP), a marker of osteoclast activity, in the control animals (Fig. 11). The transplanted cartilage appeared healthy in both groups of animals.

The results in the medium-term study (at six months) showed complete resorption of four grafts in the control group, while resorption was not observed in the animals treated with the pulsed electromagnetic fields. Also, cyst-like resorption areas were more frequent in the untreated grafts (Fig. 12).

Histologic analysis of the cartilage grafts did not show any difference between the two groups, although more fibrous tissue was present in the control grafts. We did not observe integration between the transplanted and the adjacent native cartilage. When the animals were killed, we recovered the synovial fluid from knees and tested the cytokine concentration. The concentrations of pro-inflammatory cytokines were lower (a 47% decrease in the IL-1β concentration and a 24% decrease in the TNF-α concentration) and the TGF-β1 concentration was higher (a 64% increase) in the knees treated with the pulsed electromagnetic fields than they were in the knees of the control animals.

These results show that treatment of osteochondral grafts with pulsed electromagnetic fields favors, in the short term, osteogenetic activity and early graft integration; in the medium term, this effect is associated with a lower frequency of resorption areas, which may be the weak points where graft failure begins. We have not observed an effect of pulsed electromagnetic fields on integration of grafted cartilage with the surrounding bone. Cartilage integration is, of course, a major
issue, not yet solved, which requires a more sophisticated approach, including the local control of chondrocyte activity and its progression to matrix synthesis and integration. Nevertheless, it is important to stress that the cytokine profile in the synovial fluid of animals treated with pulsed electromagnetic fields was more favorable for graft and cartilage survival than was the profile in the controls.

The experimental results discussed above support the hypothesis that exposure of articular cartilage to pulsed electromagnetic fields results in chondroprotection: pulsed electromagnetic fields stimulate chondrocyte anabolic activity, limit inflammation, and prevent cartilage degeneration.

Clinical Experience

Pulsed electromagnetic fields have been used to treat united fractures for more than thirty years; nevertheless, to our knowledge, until now they never have been applied to the joints of patients immediately after an arthroscopic procedure.

The results of the preclinical studies reported above provide a rational basis for the clinical use of pulsed electromagnetic fields to control inflammation and its catabolic effect on articular cartilage. Thus, we hypothesized that pulsed electromagnetic fields could be used in patients after minimally invasive surgery, such as arthroscopy, to control the inflammatory response, to enhance functional recovery, and ultimately to protect cartilage.

On the basis of our research, we selected pulsed-electromagnetic-field parameters with chondroprotective activity and developed a pulse generator (I-ONE; Igea, Carpi, Modena, Italy) to be used in clinical studies (Fig. 13).

Use of I-ONE After Arthroscopic Surgery

Microfractures

A prospective, randomized, double-blind study of thirty-four patients undergoing arthroscopic chondroabrasion or microfracture treatment of chondral lesions was conducted to assess tolerance to treatment with the I-ONE and the effect of the I-ONE on functional recovery7. Patients were instructed to use the stimulator for six hours per day for ninety days. The patients’ acceptance of the treatment was high, and no negative side effects were associated with the therapy. After the procedure, the percentage of patients using nonsteroidal anti-inflammatory medications was lower in the I-ONE-treatment group than in a control group (26% compared with 75%, p < 0.05). The patients treated with the I-ONE had faster functional recovery, and the average Knee Injury and Osteoarthritis Outcome Scores (KOOS) before and forty-five and ninety days after arthroscopic microfracture treatment in a group subsequently treated with pulsed electromagnetic fields (active) and in a control group. (Reproduced, with modification, from: 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 Sports Traumatol Arthrosc. 2007 Feb 28; [Epub ahead of print]. Reprinted with permission.)
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The tis Outcome Score (KOOS) for the I-ONE-treated patients at forty-one days was the same as that observed for the controls at ninety days (Fig. 14).

Anterior Cruciate Ligament Reconstruction

A multicenter, prospective, randomized, double-blind study was conducted to evaluate the effect of I-ONE treatment in sixty patients who had undergone arthroscopic reconstruction of the anterior cruciate ligament with use of a double-looped semitendinosus and gracilis tendon graft. After the tendons had been prepared with use of the classic technique, they were introduced in the previously prepared tibial and half femoral tunnels. The graft was fixed with the femur at 90° of flexion and in the tibia with an interference screw at 30° of tibial flexion (Fig. 15). Patients were evaluated at one, two, and six months after reconstruction. In the initial thirty days after the reconstruction, the I-ONE-treatment group used less nonsteroidal anti-inflammatory drugs compared with the control group (p < 0.05). After both two and six months of follow-up, the patients in the I-ONE-treatment group had higher International Knee Documentation Committee (IKDC) scores than the controls (p < 0.01). Furthermore, objective evaluation by an orthopaedic surgeon showed a faster resolution of joint swelling and an earlier recovery of a complete range of motion in the I-ONE-treatment group than in the controls (p < 0.05). Figure 16 shows that, in a subgroup of patients who underwent reconstruction of the anterior cruciate ligament and meniscectomy at the same time, the recovery of Short Form-36 scores was significantly faster among the I-ONE-treated patients (p < 0.05).

The two clinical studies reviewed here show that I-ONE treatment can be effective after knee surgery. Although we could not measure the cytokine levels in the synovial fluid of our patients, we hypothesize that an anti-inflammatory effect was indirectly demonstrated by the decrease in the use of nonsteroidal anti-inflammatory drugs, by the lower prevalence of joint swelling, and by the better range of motion of the treated patients compared with the controls.

Finally, the long-term results of the first study showed that patients in the treatment group were still doing better clinically at three years, thus supporting the hypothesis that pulsed electromagnetic fields may preserve the functional competence of cartilage.

Conclusions

Inflammation in a joint following surgery represents a potentially harmful event for the articular cartilage, which ultimately may jeopardize the positive effects expected from the surgery.

Our working hypothesis has been that the anti-inflammatory and anabolic effects of pulsed electromagnetic fields demonstrated in preclinical studies could be translated into useful treatment for patients who have undergone arthroscopic surgery, allowing early effective control of inflammation, protecting the articular cartilage from degeneration, and providing an earlier return to daily activity.

The CRES study group has thus provided the scientific background and has demonstrated the therapeutic value of pulsed electromagnetic fields for the control of inflammatory processes and ultimately for cartilage protection. The effect is limited to the area where the magnetic field is present, but the entire knee joint can be treated.

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Fig. 15
Magnetic resonance image of a reconstructed anterior cruciate ligament two months after surgery.

Fig. 16
Changes in SF-36 scores over time after anterior cruciate ligament and meniscectomy, with (blue line) and without (pink line) treatment with the I-ONE.
The rationale for the use of I-ONE therapy lies in the following observations: cartilage slowly degenerates during life and, every time that articular cartilage is exposed to an injury, catabolic consequences are triggered that may impair cartilage competence and integrity with different levels of severity. Unlike bone function, cartilage function does not return to its antecedent initial competence once the damaging event has resolved. Cartilage will continue to degenerate. Thus, all means to limit the duration and intensity of events that can damage the cartilage are of paramount importance. The work that has been done in the last seven years has provided the scientific background and allowed us to develop a rational basis for the use of I-ONE therapy to protect articular cartilage; it has also demonstrated that the treatment can be effective, is well accepted by the patients, and is without side effects. ■

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