Medical Applications of Diamagnetism: A Narrative Review

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Abstract

Magnetism includes the tendency of the matter to react to an incoming Magnetic Field both in attractive and repulsive way. With regard to the latter phenomenon , Diamagnetism, the ultra-structure of the matter shows unpaired electrons with an antiparallel spin, the high polarity, and the absence of a proper magnetic moment. All this results in a repulsive effect which induces the movement of diamagnetic liquids and molecules, the water first, so realizing the so called diamagnetic effect . This effect involves both the extracellular and intracellular environment , with the possibility to move various diamagnetic molecules and the flux of ions across the cell membrane, acting on the metabolic processes of the biological matter.

The full realization of this phenomenon requires a high intensity of the magnetic field together with the possibility to modulate two key parameters such the Frequency and the Amplitude of the impulse.

This review analyses the real and possible applications of Diamagnetism in clinical practice.

Keywords: Diamagnetism, Repulsive Effect, High Intensity Magnetic Fields.

Introduction

From the origins of the universe, magnetic fields permeate matter at various levels, from subcellular to planetary, and galactic as a natural physical phenomenon [1]. In biology, the most known effects are related to the transport of ions and molecules throughout the interstitial spaces and the cell membrane, acting on their electrical potentials. This, directly and indirectly, modulates the metabolic events in living beings including the plant world [2].

Technologies based on pulsed electro-magnetic fields (PEMFs) have become in recent years a developing reality of the research aimed at understanding and implementing new non-invasive therapeutic techniques in medical applications, mainly regenerative [3]. All this comes from the first therapeutic attempts to use PEMFs to stimulate bone healing in delayed union and non-unions of fractures, whose rationale lies in mimicking the load-related piezo-electric osteal effect according to Wolff's law [4]. Over time, the knowledge of PEMFs has been applied to various medical conditions, and currently, their use is addressed to anti-inflammatory, regenerative, and pain relief effects [5]. Moreover, for several decades the same effects have been progressively highlighted for High Intensity-Low Frequency-Magnetic Fields (Diamagnetism), which increasingly proves to be an effective and innovative method to apply the bio-active potentialities of electromagnetic induction, opening new scenarios in the aim of creating personalized therapies in musculoskeletal disorders, in nervous system diseases, in parenchymal organs dysfunction, and tissue regeneration [6,7].

This narrative review analyses diamagnetism as a therapeutic tool, the physical principles, the data of literature, and future perspectives.

Physics and Principles of Diamagnetism

The atomic structure rules the magnetic properties of matter. These can vary from an attractive effect to a repulsive one. Diamagnetism is a part of this dualism and relates to the molecular repulsion of the diamagnetic matter resulting from the application of a High-Intensity Magnetic Field (HI-MF). Hence, diamagnetic, paramagnetic, and ferromagnetic materials have different aptitude to magnetize, named magnetic susceptivity (χ). In diamagnetic materials χ is negative, in paramagnetic χ is small positive, and in ferromagnetic materials, χ is largely positive. This low tendency of diamagnetic matter to magnetize is offset by HI-MF, whose effect is to move the matter from higher to lower energy levels (Diamagnetic effect) [8]. This occurs because diamagnetic substances have a "closed shell structure" in which the electrons are not unpaired, the spin alignment is anti-parallel, and the atomic magnetic moment is zero [9]. HI-MF changes this state by acting on the rotational speed of electrons around the nucleus, thus modifying the dipole magnetic moment in a direction opposite to that of the outer magnetic field [10]. Hence, electrons having an orbital magnetic moment aligned with the external magnetic field slow

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down, and those aligned in the opposite direction speed up (repulsive effect) [11].
Historically, the roots of these concepts lie in the Faraday studies on electromagnetic induction (1821), given by the electromotive force generated in an Electric Circuit by a variable external magnetic field. Later, Lenz's law (1834) states that this electromotive force is opposing the incoming magnetic field. This would be the first description of diamagnetism although numerous academics of the time claimed this finding. Thus, the real paternity of diamagnetism remains undefined [12].
Diamagnetism is a weak phenomenon that, to be effective, requires a HI-MF. It is quite amazing that most of the biological substances playing primary roles in the metabolism of the cells are structurally diamagnetic: Water, ions, molecules, and the greater part of proteins [13]. Hence, over time new routes of research in pulsed magnetic fields, no longer confined to the electrochemical interactions with the cellular membrane, have opened to sophisticated models of cell-to-cell communication.
Significant biological effects arise by modulating selected parameters of the HI-MF such as the rise time, the amplitude, and the electromagnetic frequency bands conveyed by the magnetic field [14]. The exposure to a homogeneous magnetic field (B) modifies the magnetic moment (M) of the target leading to the superposition of a uniform precession of angular frequencies in the direction of the applied MF (Larmor precession) according to the gyromagnetic ratio of the target [15, 16]. Then, for each variation of the external magnetic field, proper frequencies are emitted by the target (Larmor Frequency), the resonance phenomenon takes place, and the absorption of the external energy occurs.
Variable Frequency, Wavelength, and Magnetic Field gradients, characterize the safety profile of Diamagnetism in medical applications: Extremely Low-Frequency (<50 Hz) High wavelength (>6 Km), Magnetic Field Gradient <400 MT/m/sec [17].

Biological Effects of Diamagnetism

The first consequence of diamagnetism is the movement of diamagnetic substances and, consequently, this mechanical force promotes the flow of biologically active molecules, both in the extracellular and intracellular environment. This phenomenon regulates many functions of the cells: changes in membrane electric potential controlled by the Na+/K+ pump, changes in cell motility, cell division, intracellular interactions, enzymatic and mitochondrial reactions, and cell signaling [18]; in summary the activation of specific metabolic pathways.
The magnetic field features significantly affect the cells functioning. Large High Magnetic Field Gradients have been employed to simulate microgravity by producing greater magnetic forces such as to induce the extreme diamagnetic phenomenon of magnetic levitation (Magnetic field intensity ranging from 10 T to 16 T-Gradient of 1300 T2/m). In such conditions, negative changes in the physiological mechanotransduction occur. Osteoblast-like cells showed changes in the endoplasmic reticulum and mitochondria, microvilli, and actin filaments aggregates. Furthermore, osteocyte viability, ALP secretion, and the disruption of Col I structure [19, 20]. Hence, an optimal ratio between the intensity and the MF gradient is mandatory. The combination of lower intensity of the MF (1T) and large gradient, (1 GT/m) observes positively changes the membrane potential of the cell and thus has a significant impact not only on the properties and biological functionality of cells but also on cell fate. Considering that the great part of cells and tissue are diamagnetic with susceptibility very close to that of water, the differences in the diamagnetic susceptibilities of cellular components are low and lead to tiny effects [21,22].
Regenerative effects of diamagnetism have been recently supported in vivo, in a Zebrafish model of fracture of the fin. The diamagnetic treatment results in different lengths of regenerated fin's rays 5 days after amputation, with a statistically significant dimensional increase, compared with untreated fishes ($P < 0.01$). Furthermore, the whole growth curve, calculated until the end of the regeneration process (10 days), indicated a stimulatory effect of HI LF-PEMFs in respect of untreated controls, with a peak of regeneration achieved before and faster in the treated group compared to the control group, 8 days versus 10 days [23]. In addition, this study demonstrated that the diamagnetic stimulation on bone tissue at 2.9 mT in the target, with an exposure time of 64 min/2 times each day, reached significative biological effect compared to 9 h of continuous stimulation as observed in studies that applied low-intensity magnetic fields at 1.5 mT [24]. As in this case, the high intensity of the magnetic field at the origin (2T) gives the possibility to deliver a better level of stimulation respect to lower Intensities in force of the attenuation of the magnetic flow with the distance, according to the Biot-Savart equation for a given type of solenoid. This means that the structure of the electromagnetic coil, MF intensity, and the MG gradient are pivotal elements of effective treatments.

Clinical Evidence in Diamagnetism

A series of clinical studies report on therapeutic applications of diamagnetism. They refer to an original device, CTU Mega 20 (Periso SA, Switzerland), also known as the "diamagnetic pump." The name derives from the main effect of the HI-MF, the movement of water and other diamagnetic substances. The machine produces a non–ionizing low frequency (<50 Hz) HI-PEMF (up to 2.2 Tesla), able to generate a diamagnetic effect in the treated body area. The magnetic impulses last 5 ms with a period of 1000 ms, and the waveform can be modulated to produce a selective stimulation of the tissue target of the treatment.
A first controlled clinical trial refers to the treatment of chronic lymphoedema compared with a 2nd class compression stocking. The diamagnetic force creates a mechanical repulsion able to resolve the liquid's imbalance in the extracellular space, more precisely both the "low output failure" and "high output failure" of the lymphatic system, similarly to other experimental studies [25]. Furthermore, chronic inflammation occurs due to the triggering of the monocyte-macrophage system and the fibroblast, with consequential growth of the interstitial matrix. In this study, the diamagnetic pump supplies a double therapeutic effect: Reabsorption of interstitial edema given by diamagnetic stimulation (displacement of liquids), and the reactivation of the lymphatic flow also due to the thermal effects of diathermia, (provided by the machine), and a micro-hyperemia that overcomes the artery-arteriolar deficit and increases the flow speed

in capillaries. The combination of diamagnetic treatment and limb compression showed the reduction of limb circumferences and meaningful changes concerning limb compression only. Ultrasound evaluation gave the possibility to objectify a lower tissue consistency, from hard edema to soft edema in derma and hypodermal structure, with more homogeneous and thinner connective tissue, and the reduction of the synechiae between derma and hypoderm and between hypoderm and superficial muscular fascia, as a possible effect on fibrosis [26].

A randomized double-blind sham-controlled crossover trial shows the effects of diamagnetism to modulate long-term corticospinal excitability in healthy subjects. A 15-min single shot of sham and real treatment, both addressed to the primary motor area, was employed to evaluate the corticospinal excitability (index of Long-Term Potentiation-Like Cortical Plasticity) recording the Motor Evoked Potentials from the contralateral first dorsal interosseous muscle at 15 and 30 min after treatment. Comparing the measurements pre-and post, the cortical excitability increased by more than 60% in real subjects, lasting for 30 min after the stimulation, maintaining a significant difference versus the sham group ($P < 0.005$) [14] The proof-of-concept supports the potentiality of the diamagnetic stimulation as a new approach to brain neuromodulation, given the larger stimulation volume, up to 27 cm3 compared to 1–2 cm3 for conventional Transcranial Magnetic Stimulation, the achievable modulation of an extended portion of the cortical surface, an easy and a ready to use machine thanks to predefined programs of selected stimulation of the nervous system, not requiring specialized staff.

This programmable system can be optimized for different types of neurological diseases, as shown in a case series study including various settings to treat Rare and Orphan diseases [6], a group of multiorgan disabilities that limit the life quality in young and adult patients, affecting the socio-economic burden for the families and the community. Thirteen variously aged patients suffering from 2 Limb-girdle muscular dystrophies, 1 neuroaxonal dystrophy, 4 spastic cerebral palsies, 1 hemorrhagic stroke, 1 dystonia, 1 glass syndrome, 1 dysgenesis of the corpus callosum, 1 hypoplasia of the cerebellar bridge, and 1 dysgenesis of the dorsum - lumbar spine were treated with individualized diamagnetic stimulation (average 10 sessions), in addition to the standard care. The set-up of the Diamagnetic Pump included: Pain Control mode, fast and slow Nerve Fibers stimulation, Liquids Movement, Cell membrane stimulation, and Muscle stimulation. The machine provides the possibility to deliver selected multi-band electromagnetic frequencies able to match the specific resonance frequencies of the tissues according to the Larmor precession Model (see Physics and Principles of Diamagnetism section). Given the complexity and diversity of these pathologies, only a qualitative analysis of the clinical progression was done in terms of the absence/presence of improvement compared to the starting conditions: Motor and relationship difficulties. Two patients reported a decrease in upper limb strength: Limb-girdle muscular dystrophy and dysgenesis of the anterior dorsum-lumbar spine. A muscular improvement is described for the other clinical conditions: The significant reduction in the number of falls and better ability to maintain bipedalism standing in another case of Limb-Girdle Muscular Dystrophy, general improvement in spontaneous motor activities concerned three cases of Spastic Cerebral Palsy, including better reactivity in hand movements, the maintenance of cephalic control, the disappearance of primary reflexes, and better cognitive skills. A better reactivity to external stimuli and the ongoing activity of the hand is reported as Neuro Axonal Dystrophy, while the improvement of spontaneous gesture involved a case of Corpus Callosum Dysgenesis. In Glass Syndrome, the motor improvement was sufficient to allow the integrated treatment with the rehabilitative program. This study points to how, given certain diseases, limited improvements can change the quality of life in patients and their families.

Two clinical experiences deal with diamagnetism treatment in pulmonary fibrosis. The first paper is the case report of a woman with interstitial lung fibrosis due to Anti-Synthetase Syndrome associated with Sjogren's Syndrome, lasting from 19 years. This extremely rare combination with different etiopathogenetic factors (overlapping syndromes) causes, respectively, respiratory insufficiency due to the weakness of the respiratory muscles and Interstitial Lung Disease leading to pulmonary fibrosis. The protocol consisted of eight sessions (not regular rate) of Diamagnetic treatment focused on the thorax, shoulders, and the upper part of the abdomen (intercostal muscles, serratus anterior muscle, and the diaphragm). The authors reported the improvement in the oximetry values with reduced oxygen addiction, and better critical parameters, as reported in the MMRC questionnaire [27]. The peculiarity of this successful treatment underlines, in the beginning, the need for continuous O2 therapy with peripheral oxygen saturation values at 90% to 4 Lt/min and dyspnea at rest. At the end of the treatments, the request for oxygen was only at night, with peripheral O2 saturation at 98% and only residual exertional dyspnea 4 months after the start of the treatments. The second paper reports a case series of ten patients with lung interstitial disease in post-COVID-19 pneumonia. All subjects were treated in the posterior and posterolateral thoracic region, 3 times a week for 2 weeks. Despite no significant changes in the CT scan lung imaging at the hospital discharge all patients reported less dyspnea and fatigue with better functional skills at the 6 Minutes Walking Test, Tinetti Test, and Barthel Score) [28]. The improvement in the short term is remarkable and prefigures the possibility of standardized employment of Diamagnetic Therapy in the rehabilitative programs post-COVID Pneumonia as well as in Long COVID disease. Anyway, the lack of a controlled study and the low number of subjects significantly limits the value of these results.

In a series of 12 patients suffering from Low Back Pain (LBP) of various origins, with a duration >3 months, diamagnetic treatment shows antalgic and functional effects at the subjective and functional scores. 3 sessions/week of diamagnetic treatments, for 3 weeks (each treatment lasted 30 min with the handpiece placed at the lower back level) are reported. Pain (Numerical Rating Scale [NRS]) and physical function (Oswestry disability index) were assessed before therapy, after the first session, 1 week, and 4 weeks once completing the therapy. Both outcomes improved significantly ($P < 0.05$), and no patient reported discomfort or adverse events [29]. In this case, this inclusive technology acts, at the same time, on liquids movement (edema), vehiculation of drugs and molecules (FANS-Myorelaxant), stimulation of muscle, joint, and nerve fibers plus pain control mode, which could give positive effects in pathologies of difficult of categorization, due to various intrinsic and extrinsic factors, as for LBP. Control studies would give a greater significance to this articulated treatment.

Experiences in complex clinical cases are also described. In a 94-year-old poly-arthritic patient with a severe ulcer of the foot, dated from 1 year and unchanged over time, the diamagnetic treatment has been possible thanks to the unnecessary direct contact with the skin, also giving the possibility to continue the necessary debridement of the ulcer and hydrocolloid covering. The magnetic field flow reaches up to 7 cm deep, and the technology is effective without contact as in the case of patients wearing plasters or braces. After 6 sessions, one a week, the patient experienced a significant reduction in pain from 8 points on the Visual Analogical Scale to 2 points ($P < 0.01$), and the dimension of the lesion reduced from 6 × 4 cm at the start of the treatment to 2 × 2 cm at the end ($P < 0.01$), with progressive complete healing in a short time [7]. Contemporarily, an improvement in autonomy and quality of life has been observed in the SF36 questionnaire. The remarkable aspect of this report is the faster recovery after the starting of the treatments.

The second report relates to a 69-year-old patient suffering from Complex Regional Pain Syndrome Type I (CRPS- I) at the right ankle for two years, with a Multiple Drug Intolerance condition. The level of pain was at the maximum 10/10 (NRS) and significantly reduced quality of life (Short Form-36 questionnaire). Local diamagnetic treatment consisted of 10 weekly sessions of CTU Mega 20 applications, with no pharmacological therapy associated. At the end of the treatment, a significant reduction in pain (NRS 2/10), edema, and improvements in quality of life, with no adverse events reported. The non-invasiveness strategy adopted with the use of the machine was demonstrated to be helpful in a difficult scenario given by patients who cannot benefit from pharmacological therapy due to intolerance, as in this case, or ineffectiveness. Particularly, when it the impossibility to start a new pharmacological therapy or the patient refuses invasive treatments, sympathetic nerve blocks for example [30]. On the other hand, is well known that PEMFs reduce the level of pro-inflammatory cytokines, including those involved in the rapid bone turnover and osteoporotic changes which occur during the chronic phase of the disease [31]. This clinical study confirms this peculiarity and remarks on the fast-healing time concerning the clinical history.

Most of the magnetic fields' accomplishments have been ascribed to regenerative and anti-inflammatory synergic effects [3]. In injured tissues, variable intensities of the magnetic field inhibit the expression of IL-6, IL-1β, and TNFα expression [32] and modulate the expression of the anti-inflammatory IL-10 in tendon cells cultures [33]. In addition, an anti-phlogistic effect involves the expression of A2A and A3 adenosine [34]. Differently from Low-Intensity Magnetic Fields, High-Intensity Diamagnetic pulse exerts biological regenerative, anti-inflammatory, and trophic effects on the extracellular matrix (ECM) too. Besides, the interaction with diamagnetic nanoparticles of the cell membrane [13] ions, membrane receptor proteins, cholesterol, glycol, phospholipids, and the intracellular cytosol, ECM changes in hydrostatic pressure derive from the HI-MF mechanical diamagnetic effect, mainly in chronic inflammation (low-grade inflammation) secondary to the persistent activity of Il-6 that triggers a regulatory control mediated by TGF-β1. In case of long-term expression of TGFβ1 stiffness in ECM occurs, by increased storage of the proteoglycans and leading to a fibrotic phenotype, as observed in COVID-19 where the dysregulation of the physiological chronobiology of inflammation happens [35]. Several clinical reports already prefigure this possible effect of diamagnetic therapy in fibrosis of various origins [26, 27, 28]. In addition, Diamagnetic Therapy may provide the vehiculation of therapeutic agents directly on the tissues under treatment exploiting the repulsive (diamagnetic) movement to transport inside the body therapeutic agents such as interleukins, hormones, neuropeptides, or growth factors at low doses sequential kinetic activation, which has already shown adequate control on low-grade chronic inflammation.

Conclusion

The magnetic repulsive phenomenon of diamagnetism offers new therapeutic chances for the treatment of muscle-skeletal disorders and more. The therapeutic effects derive from the mechanotransduction of the diamagnetic pulse, by moving liquids and solutes at both extracellular and intracellular levels; furthermore, the biochemical transduction at the cellular level, of the electromagnetic signal in biological responses, is similar to low-intensity magnetic fields. Although belonging to the family of low-frequency magnetic fields, diamagnetic stimulation diverges thanks to a multiplicity of effects that make it an interesting therapeutic novelty in the field of biophysical stimulation (diamagnetic therapy).

Data from the literature don't provide enough RCTs to allow a statistical validation of the Diamagnetic Therapy, mainly consisting of case reports but with appreciable results in common musculoskeletal conditions, and interesting perspectives on the treatment of the nervous system as shown in rare and orphan diseases or in a different type of lung and peripheral fibrosis. These reports also refer to the fast therapeutic response compared to low-intensity-MF reports.

Technical and practical features express diamagnetism as an original and unique therapeutic tool where it is possible to identify interesting peculiarities in the High-Intensity (Rise Time, Magnetic Field Gradient) amplitude, and the bandwidth frequencies of the variable pulse offering more therapeutical possibilities concerning conventional low-frequency magnetic field. Furthermore, practical advantages derive from Static and dynamic treatments, larger stimulation volume, ready-to-use technology, selected stimulation of the tissues for tailored therapies, and shorter duration of each treatment, as shown by the data from the literature. Very attractive is the possibility to move liquids in the treatment of edema, as well as the possibility to selectively modulate the transmission of painful signals both in nociceptive and neuropathic pain and to stimulate fast and slow nerve fibers.

Further studies are necessary to better understand the mechanism and the effectiveness of the technology in the consolidated application, as well as further therapeutic promising possibilities including basic research, addressed to the inner biological effects of the technology.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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