An excerpt from the scientific article

Knowledge from human relevant cell, tissue and mathematics-based methods as key tools for understanding COVID-19

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CHAPTER 8.7.

Diamagnetism as an alternative or integrating cellular therapy for COVID-19

Naturally occurring electric fields are not only important for cell-surface interactions but are also pivotal for the normal development of the organism and its physiological functions. Selective control of cell function by applying specifically configured, weak, time-varying magnetic fields has added a therapeutic dimension to biology and medicine, e.g., diamagnetic therapies. The word "diamagnetic" originated from diamagnetism, which refers to the magnetic property of some materials which, subjected to a sufficiently intense magnetic field, receive a repulsive and distancing force with respect to the magnetic source. One of the most common diamagnetic materials is body water, and most proteins and ions are diamagnetic. Using diamagnetic therapy, there is a powerful effect on cellular features including specific cell membrane mechanisms reducing edema and inflammatory processes and the damaged tissue is quickly repaired with an immediate analgesic effect. Field parameters for therapeutic, pulsed electromagnetic field (PEMFs) were designed to induce voltages similar to those normally produced during dynamic mechanical deformation of e.g., in human body connective tissues. As a result, a wide variety of challenging musculoskeletal disorders have been treated successfully over the decennia. Patients with delayed union or non-union fractures have benefitted, from this surgically non-invasive method. Many of the athermal bioresponses, at the cellular and subcellular levels, have been identified and found appropriate to correct or modify the pathologic processes for which PEMFs have been used supported by double-blind trials. As understanding of underlying molecular and cellular mechanisms expand, specific requirements for field energetics are being defined and the range of therapeutic

broadened. These include nerve regeneration, wound healing, graft behavior, diabetes, and myocardial and cerebral ischemia (heart attack and stroke), among other conditions. [219]

The biophysical stimulation induced by Low Frequency – High-Intensity Pulsed Electromagnetic Fields (LF- HI- PEMF) – Diamagnetotherapy, has recently been demonstrated to be effective in the treatment of lung fibrosis associated to autoimmune diseases as well as to fibrosis in post COVID-19 pneumonia.

In both conditions that share a dysregulation of the immune system, diamagnetotherapy, ameliorated the functionality of respiratory muscles in treated patients, improved dyspnoea, oxygen saturation, indicative of a better performance of the lung. In these cases, a double effect in lung parenchyma and in respiratory muscles has been evaluated, also considering that in post-intensive care syndrome, patients report muscle weakness, impaired mobility and balance, joint stiffness while the associated neuropathy and myopathy are a consequence of SARS-CoV-2 infection. These clinical conditions worsen the morbidity and the mortality in COVID-19 patients. Diamagnetoteraphy opens the possibility to treat symptoms in COVID-19 patients such as epilepsy, cognitive impairment, or motor imbalance, including the problems of the peripheral nervous system.

The rationale to employ diamagnetotherapy for medical problems is attributed to the intensity of the magnetic field that ensures the optimal and safe electric stimulation of the cell membranes. Moreover, the diamagnetic effect is also composed of a multi-variable spectrum of electromagnetic frequencies that selectively interact with the different electric state of the cell membrane in various situations. This phenomenon has been observed with electromyography fallowing the stimulation of the motor cortex in healthy individuals. [220] This opens the possibility to treat symptoms in COVID-19 patients such as epilepsy, cognitive impairment, or motor imbalance, including the problems of the peripheral nervous system.

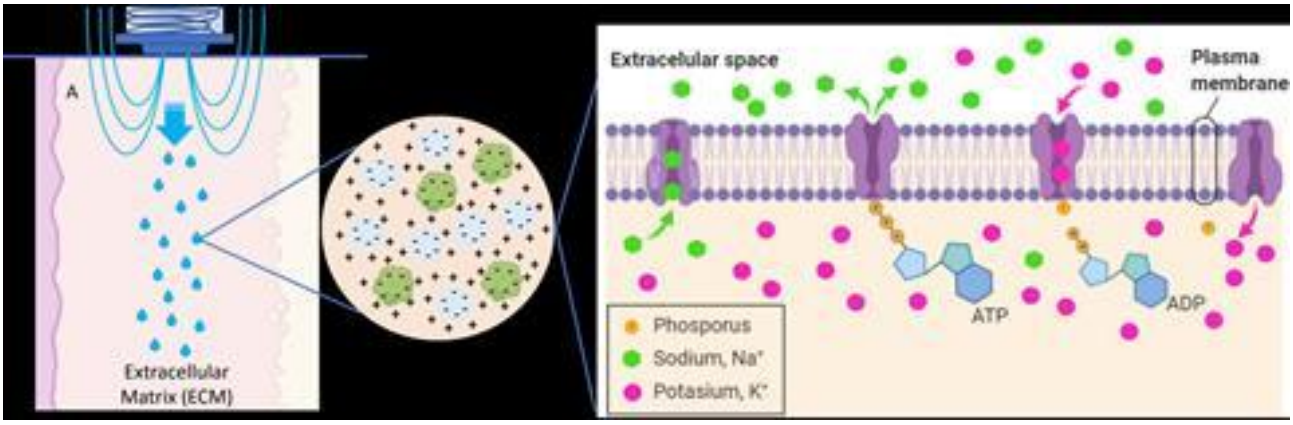
Diamagnetotherapy takes its name from a mechanical repulsive effect on diamagnetic substances e.g., water. 60% of the human adult body is water. Already in 1945 the % of water content in human body organs was described for an adult (Table 7) with an average weight of 70.5 kg. [221]

Table 7
Water content in human body organs/tissues.

Tissue	Water (%)
Lung	83.74
Striated Muscle	79.52
Kidney	79.47
Digestive tract	79.07
Spleen	78.69
Brain, spinal cord, nerve trunks	73.69
Hearth	73.69
Pancreas	73.08
Liver	71.46
Skin	64.86
Adipose tissue	50.09
Skeleton	31.81
Teeth	5
Liquid Tissues	**93.33**
Remaining Solid Tissues	**70.40**

The diamagnetic phenomenon moves liquids and solutes of the extracellular matrix (ECM) and of the intracellular environment. This, positively stimulate the metabolic activities of the treated tissues, reduce fibrosis and ameliorate peripheric oedema in limbs and the possibility to treat lymphatic imbalance related to the prolonged COVID-19 related immobility is a possible scenario.

Although different in terms of variability and strength of the physical features, HI magnetic fields have therapeutic biological effects in comparison to the the more studied Low Intensity- PEMF with main regards to the anti-inflammatory, regenerative and trophic on the extracellular matrix (ECM). [222] The diversity consists in the interaction of HI-MF with a chain of diamagnetic nanoparticles of the cell membrane (ions, membrane receptor proteins, cholesterol, glycol, and phospholipids) and the intracellular cytosol. HI-MF modifies the hydrostatic pressure of the ECM and the transmembrane flux of ions reflecting on the electric potential of the cells. The phenomenon is enforced by the variability of the frequencies of the Electromagnetic Field (Figure 17).



Variable intensities of the magnetic field inhibit IL-6 and TNF-α expression at the gene level as well as IL-6, IL-1β and TNFα expression at protein level in injured tissues. [223] This modulatory effect is confirmed in other studies that reveal the increase of the anti-inflammatory IL-10, observed in tendon cell cultures [224], and is also known for a strict relationship with the immune system in various, including autoimmune, pathologies. [225] Reference to COVID-19 induced immune dysregulation is consequential. Finally, PEMF preserve ECM integrity of the cultured embryonic cartilage explants by modulating the metabolism of proteoglycans without affecting their gross structural nature.

These experiences show that diamagnetism-based therapeutic interventions should be further explored as an alternative or integrating cellular therapy for COVID-19 for e.g., brain, immune system muscles and parenchymal organs.

The chronobiology of the inflammatory process relates to the of IL-1, IL-6 and TNF. [226] This physiological self-control and cellular self-defense of inflammation is shown in the response time of IL-10, and TGF-Beta and increase in the genetic expression of the interleukins involved in the inflammatory process. [227]

However, we know that the rapid and exaggerated increase in IL-6 in patients with COVID-19 presents a response that can lead to a chronic increase in IL-6 leading to a chronic activation of IL-17. This leads to a response in the activity of specific antibodies to tissues, cells, cell membranes and/or intracellular organelles, which may have

autoimmune or degenerative sequelae. However, the physiological response to the elevation of interleukin IL-6 and the subsequent elevation of IL-10 and TGF-beta [228] should be taken into account . As a consequence, we have an overexpression of these last two molecules, and the return to normality of TGF-beta is slow and usually occurs between 3-6 weeks after the acute pro-inflammatory event. However, the continuous activation of TGF-beta can cause changes in ECM [229], making it less soluble and evoking an increase in secondary fibrosis caused in the inflamated human body tissue areas. In the case of the post-COVID-19 patients, these tissues are identified by ACE receptors and through the stimulation given by chemotaxis and necrotaxis, these tissues change the inflammatory adaptation response of metalloproteinases. [230]

The ECM takes within its sol-gel regulation a management of remodeling and plasticity of the matrix. [231] This dynamic remodeling acts as a control in homeostasis, and protection of cell proliferation, migration and differentiation. As such, the ECM has a molecular filter control crucial for cell survival. [232] The ECM filter function is regulated by the electromagnetic and sterilization processes, which is maintained through the control of reactive oxygen species (ROS) and pH, the changes on the heparan sulfate chains thus stimulating the activation of metalloproteinases, capable of achieving changes in the sol-gel turn. [232], [233] The sol phase within the ECM has a protease activity, to initiate a reshaping of the matrix through the hydrolysis of proteoglycans. The maximum pH in this phase is 7.35, with sympathicotonic activation. The gel phase within the ECM has an anti-protease activity, performing a reconstruction and deposit of the matrix by means of the synthesis of matrix proteins. The pH peak in this phase is 7.45 so it is an alkaline phase with vagotonic activation. [234]

This regulation turn of the ECM is given by the activity of metalloproteinases (MMPs) that are 22 human proteolytic enzymes regulated by Th1 lymphocytes and therefore carry out degradation effects of the ECM. The regulation of these MMPs are made by the inhibitory tissue of metalloproteinases (TIMPs), which are 4 inhibitory proteins of MMP. These are regulated by Th2 lymphocytes and therefore carry out protein deposition in the ECM, this inhibition is carried out 1:1 from TIMPs to MMPs. [235], [236]

Therefore, inflammation as well as the increase in free radicals, increase the expression and secretion of the interleukins IL-1, IL-6 and TNF-alpha. This control in the degradation of matrix proteins is by means of the IL-4, IL-10 and TGF-beta1. This increases the deposit of glycoproteins and provides a control in physiological anti-inflammatory homeostasis. [237] Oxidative stress processes control cell aging. It is known that low levels of free radicals do not achieve the protection of cell survival that is needed and the high increase in oxidative stress causes a loss of oxidation reduction causing cell death and having low-grade chronic inflammation. [238]

ROS overexpression and pH reduction create pathological inflammation starting with an acute phase of inflammation like the one seen in COVID-19 in the acute and semi-acute phases, which enters into the sol phase as a degradative and inflammatory phase. At the same time, after the acute phase, a low-grade inflammation due to the increase in the expression and secretion of IL-6, causes as a regulatory control an increase in the secretion and expression of TGF-beta1, creating ECM rigidity due to an increase in the deposits of the proteoglycans giving the fibrotic phenotype. [239]

However, chronic alteration not only causes a rigidity of the ECM, it also creates an alteration of the intercellular junctions. In the case of inflammation caused by COVID-19, the mucosa represents alterations in the intercellular junctions of lung and receptors of the respiratory and oropharyngeal mucosa. In the processes of traditional inflammatory control, IL-10 activates the STAT3 receptors that decrease the expression of Claudin-2 and increase the expression of Claudin-4. TGF-beta activating the ERK and SMAD2 receptors, increasing the expression of Claudin-1, has been observed in autoimmune control processes in intestinal mucosa caused by Crohn's disease and treated with low interleukin dose and sequential kinetic activation. [240], [241], [242], [243]

An integrative treatment option with diamagnetic therapy is the implementation, penetration or implantation of therapeutic agents directly on the tissues under treatment. Due to the effect of diamagnetic repulsion movement, it is possible to introduce a product up to 8-10 cm deep (Figure 18).

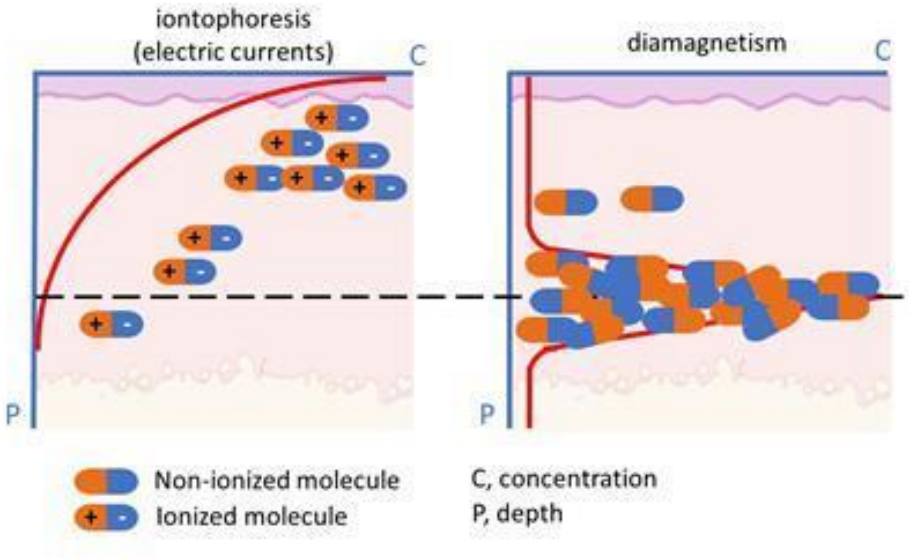


Figure 18

Distribution curve of pharmacological substances (physical model) expressed as concentration-depth ratio (PC) induced respectively by electric currents or High Intensity-PEMF Iontophoresis (electric currents). The delivery of the therapeutic agent decreases with the distance and depends on the ionization of the molecules. B) Homogeneous and deeper distribution of hydro-soluble (diamagnetic) therapeutic agent as a result of the impulse originating from the High Intensity of Magnetic Field. The ionization of the molecule is not necessary.

Therapeutic agents with the greatest possibility of transport are interleukins, hormones, neuropeptides or growth factors at low dose , which have already shown adequate control of the processes of low-grade chronic inflammation which causes COVID-19 inflammatory, autoimmune or degenerative sequelae, that is observed in patients between 2-3 weeks after the acute phase and up to 3-4 months. [244]

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