**DOI:** 10.7251/SSH1702087P
**Paper review**

**UDC:** 615.849.11
**Pregledni rad**

# CONTEMPORARY PRINCIPLES OF MAGNETOTHERAPY APPLICATION IN PHYSICAL MEDICINE AND REHABILITATION

**TAMARA POPOVIĆ**
*Public Institution Medical College, Prijedor, Bosnia and Herzegovina*

***Correspondence:***
*Tamara Popović*
*Public Institution Medical College Prijedor*
*tamaralukac@yahoo.com*

**Abstract:** Magnetotherapy is one of the oldest methods of treatment and throughout the history of medicine it passed the path from alternative to official method. In the 21st century a large number of scientific researches broadened the indication areas based on magnetotherapy. The objective of the paper is to demonstrate: historical development, types of magnetotherapy, its biological effects, clinical application and mechanisms of effects. Available world reference from the fields of basic and clinical researches on magnetotherapy was used. Basic studies indicate that leucocytes, thrombocytes, osteoblasts, chondrocytes, fibrinogen, fibrin, cytokine, the factors of growth, collagen, elastin and free radicals show the alteration in its effects when exposed to magnetic field. Magnetic fields impact the proliferation of cells, epithelization, phagocytosis, vasodilation which certainly improves the physiological surrounding that contributes to the regeneration and healing. Therapeutic effects depend upon all characteristics of electromagnetic field and patient's condition. The widest application of PEMP has in stimulation of osteogenesis (badly coalesced fractures, pseudarthrosis, spinal fusions coalescence), osteoarthritis, osteoporosis and other painful conditions. Transcranial magnetic stimulation has an increasing application in neuro-rehabilitation. Precise mechanisms of electromagnetic therapy effects are not known yet which is certainly one of the reasons of various approach and sufficient and on evidence based clinical application of this physical modality. A precise dosimetry, well-defined laboratory conditions, designed clinical studies, defined treatment protocols contribute to clearer clinical application as well as actuality of magnetotherapy in the future.
**Key words**: magnetotherapy, clinical application, PEMF (pulsed electromagnetic field), TMS (transcranial magnetic stimulation)

## HISTORY

Data on biological effects of magnets date back from the time of magnetism discovery in an ancient Greece. Magnetotherapy is a physical therapy which has the lon-

# SAVREMENI PRINCIPI PRIMJENE MAGNETOTERAPIJE U FIZIKALNOJ MEDICINI I REHABILITACIJI

**TAMARA POPOVIĆ**
*JU Visoka medicinska škola, Prijedor, Bosna i Hercegovina*

***Korespondencija:***
*Tamara Popović*
*JU Visoka Medicinska škola Prijedor*
*tamaralukac@yahoo.com*

**Sažetak:** Magnetoterapija je jedna od najstarijih metoda liječenja i kroz istoriju medicine prolazi put od alternativne do zvanične metode. U XXI vijeku veliki broj naučnih istraživanja proširuje indikaciona područja zasnovana na magnetoterapiji. Cilj rada je da se prikažu: istorijski razvoj, vrste magnetoterapije, njihovi biološke efekti, klinička primjena i mehanizmi djelovanja. Korištena je dostupna svjetska literatura iz oblasti bazičnih i kliničkih istraživanja o magnetoterapiji. Bazične studije ukazuju da leukociti, trombociti, osteoblasti, hondrociti, fibrinogen, fibrin, citokini, faktori rasta, kolagen, elastin i slobodni radikali pokazuju alteraciju u svom djelovanju kad su izloženi magnetnom polju. Magnetna polja utiču na proliferaciju ćelija, epitelizaciju, fagocitozu, vazodilataciju što svakako poboljšava fiziološku sredinu koja doprinosi regeneraciji i izlječenju. Terapijski efekti zavise od svih karakteristika elektromagnetnog polja i od stanja pacijenta. Najširu primjenu pulsno elektromagnetno polje (PEMP) ima u stimulaciji osteogeneze (loše srasli prelomi, pseudoartroza, zarastanje spinalnih fuzija), osteoartritisa, osteoporoze i kod bolnih stanja. Transkranijalna magnetna stimulacija ima sve veću primjenu u neurorehabilitaciji. Precizni mehanizmi djelovanja elektromagnetne terapije još uvijek nisu poznati, što je svakako jedan od razloga različitih pristupa i nedovoljne i na dokazima utemeljene kliničke primjene ovog fizikalnog modaliteta. Precizna dozimetrija, dobro definisani laboratorijski uslovi, dizajnirane kliničke studije, definisani protokoli liječenja doprinose jasnijom kliničkoj primjeni, kao i aktuelnosti magnetoterapije i u budućnosti.
**Ključne riječi**: magnetoterapija, klinička primjena, pulsno elektromagnetno polje, transkranijalna magnetna stimulacija

## ISTORIJAT

Podaci o biološkim efektima magneta datiraju još iz vremena otkrića magnetizma u staroj Grčkoj. Magnetoterapija je fizikalna terapija koja se najduže primijenjuje gest application in the history of medicine. Old Greeks before Homer discovered magnetite in Magnesia, a province in Asia Minor where the term magnet is originally from. It was then considered for magnet to have a medical value and there are data they have used it for treatment of various diseases. In Egypt, in 3600 BC they used the magnets in treatment of head injuries and sunstroke. In India in Ayurveda mantras in some chapters was described the use of magnet. Greek physician Galen used the magnet as a purgative agent in 200 BC, and Avicenna, Arab physician for liver treatment in 1000 BC. During Renaissance in the 15th century a Swiss physician Paracelsus used the magnets for treating toothache and inflammation (Basford, 2001). The first scientific depiction about the use of magnet in treatment is found in the book "De magnete", which was written in 1600 by William Gilbert, Physician to the Queen Elizabeth I (Gilbert, 1991). This brilliant physician and philosopher recommended magnets to treat various diseases. He pointed that planet Earth is a large magnet and that geomagnetic field of Earth as part of biosphere significantly impacts the formation and survival of all living systems. In the 18th century, the Austrian psychiatrist Mesmer explained that disturbing magnetic forces in the body cause disease so that he used magnets to treat different diseases. In time of Empress Maria Theresa he was expelled to France. French Academy of Sciences discredited Mesmer a fraud after four years and banned his work and his learning about magnets was called "mesmerism" (Lažetić, 2004). In history of magnetic therapy Mesmer compromised this method for a long time. In the beginning of the 19th century there came to the increase of number of researchers in the field of magnetism and electricity that saw the relationship between electric and magnetic appearances. Physicists Oersted, Arago and Ampere contributed to define electrical magnetic fields. In 1831 Faradey discovered an electromagnetic induction, and in the end of the 19th century a research of Nikola Tesla completed a scientific depiction about electromagnetic appearances. In the second half of the 20th century there began a more intensive production of magnetotherapy devices with artificial sources of EMP of various characteristics. A discovery of piezoelectricity in bone (Fukada & Yasuda, 1957) of Japanese scientists Yasuda and Fukada in 1957 marked the beginning of modern and scientific era of magnetotherapy. In 1966 Brighton described the bioelectric potential of osteocytes which appear in bones in absence of load (Friedenberg, 1966). Bioelectric potentials are solely negative and they appear in the fields of active growth and bone repair. During the seventies, a team led by American orthopaedist Bassed applied a pulsed electromagnetic field for stimulation of osteogenesis in treatment of slow fracture healing

u istoriji medicine. Stari Grci prije Homera su otkrili magnetit u Magneziji, provinciji u Maloj Aziji, odakle potiče i naziv magnet. Još tada se smatralo da magnet ima medicinsku vrijednost i postoje podaci da su ih koristili za liječenje različitih oboljenja. U Egiptu su 3600 godina p.n.e koristili magnete u liječenju povreda glave i sunčanice. U Indiji u Ajurvedskim mantrama u nekim poglavljima je opisana upotreba magneta. Grčki ljekar Galen je 200. godine p.n.e. koristio magnet kao purgativno sredstvo, 1000. godine arapski ljekar Avicena za liječenje jetre. U renesansnom periodu u XVI vijeku švajcarski ljekar Paracelzus je koristio magnete za liječenje zubobolje i upalnih stanja (Basford, 2001). Prvi naučni prikaz o upotrebi magneta u liječenju nalazi se u knjizi „De magnete", koju je 1600. godine napisao Wiliam Gilbert, lični ljekar engleske kraljice Elizabete I (Gilbert, 1991). Ovaj briljantni ljekar i filozof je preporučivao magnete za liječenje različitih oboljenja. Ukazao je na to da je planeta Zemlja veliki magnet i da geomagnetno polje Zemlje kao dio biosfere značajno utiče na formiranje i opstanak svih živih sistema. U XVIII vijeku austrijski psihijatar Mesmer objašnjava da remećenje magnetnih sila u organizmu izaziva bolest, tako da je koristio magnete u liječenju različitih oboljenja. U doba kraljice Marije Terezije je protjeran u Francusku. Francuska akademija nauka je nakon četiri godine Mesmera proglasila varalicom i zabranila rad, a njegovo učenje o magnetima je nazvano „mesmerizam" (Lažetić, 2004). U istoriji magnetoterapije Mesmer je za duži vremenski period iskompromitovao ovu metodu. Početkom XIX vijeka je značajno porastao broj istraživača u oblasti magnetizma i elektriciteta i veliki broj naučnika je uočio povezanost električnih i magnetnih pojava. Fizičari Oersted, Arago i Ampere su dali doprinos u definisanju elektromagnetnih polja. Faradey je 1831. godine otkrio elektromagnetnu indukciju, a krajem XlX vijeka istraživanja Nikole Tesle su upotpunila naučnu sliku o elektromagnetnim pojavama. U drugoj polovini XX vijeka se počelo intenzivno sa proizvodnjom aparata za magnetoterapiju sa vještačkim izvorima elektromagnetnih polja (EMP) različitih karakteristika. Otkrićem piezoelektriciteta kosti (Fukada i Yasuda, 1957) japanskih naučnika Yasude i Fukade 1957. godine počinje moderna i naučna era magnetoterapije. Brighton je 1966. godine opisao bioelektrični potencijal osteocita koji se u kostima javljaju u odsustvu opterećenja (Friedenberg, 1966). Biolelektrični potencijali su isključivo negativni, a javljaju se u oblastima aktivnog rasta i reparacije kosti. Tokom 70-tih godina, tim na čijem je čelu bio američki ortoped Bassett je primjenjivao pulsno elektromagnetno polje za stimulaciju osteogeneze u liječenju

(Bassett, Pawluk & Pilla, 1974). The clinical application was based on results of numerous animal and human studies, based on which Food and Drugs Agency (FDA) in the USA in 1979 recommended the stimulation of osteogenesis with EMP biphasic low frequency field in bad coalescences of bone fractures, pseudarthrosis and postponed coalescence of spinal fusions (Linovitz et al., 2002). Magnetotherapy has an analgesic effect in patients with rheumatoid arthritis and it contributes to improvement of functionality of these patients (Leśniewicz, Pieszyński, Zboralski et al., 2014). Pulsed electric field has a large clinical use after arthroplasty of the hip joint (Kocić, Lazarević, Kojović et al., 2006). Pulsed electromagnetic field and transcranial magnetic stimulation have a neromodulatory effect and they have a wide clinical use in Parkinson's disease (Vadala, Vallelunga et al., 2015), rehabilitation after stroke (Hsu, Cheng, Liao et al., 2012) and multiple sclerosis (Vijaysheree, Bever, Bowen et al., 2014).

In the 21st century an interest in applying the magnetic and electromagnetic fields in clinical practice has increased so that this physical modality passes the transition from alternative to official method. Over the last six decades of development of contemporary magnetotherapy, a successful treatment of a wide spectrum of musculoskeletal diseases, pain and neurological diseases has become possible.

### Types of electromagnetic fields applied in clinical practice

Magnetotherapy is just one segment of magneto biology, a large interdisciplinary field which is nowadays intensively developed and researched. Undoubtedly, specialists in physical medicine and rehabilitation play an important role in development of magnetotherapy being those who use most this physical modality in their clinical practice.

Magnetotherapy involves seven groups of electromagnetic fields, developed and used in various countries of the world over the last 50 years (Markov, 2015):

Static/permanent magnetic fields created by different permanent magnets as well as the passage of direct current through the coil

Low-frequency sine wave electromagnetic fields mostly use 60 Hz (in the USA and Canada) and 50 Hz in Europe and Asia frequency in power distribution networks

Pulsed electromagnetic field (PEMP)(5-300Hz) are low-frequency fields with different shapes and amplitudes

Pulsed radio frequency electromagnetic fields (PRF) uses the selected frequencies in range of radio frequency: 13.56, 27.12, and 40.68 MHz.

usporenog zarastanja preloma (Bassett, Pawluk i Pilla, 1974). Klinička primjena zasnovana je na rezultatima brojnih animalnih i humanih studija, na osnovu kojih je 1979.godine Agencija za hranu i lijekove u SAD (FDA) preporučila stimulaciju osteogeneze EMP-om dvofaznim poljem niske frekvencije kod loše sraslih preloma kosti, pseudoartroza i odloženih srastanja spinalnih fuzija (Linovitz i sar., 2002). Magnetoterapija ima analgetski efekat kod pacijenata sa reumatoidnim artritisom i doprinosi poboljšanju funkcionalnosti oboljelih (Leśniewicz, Pieszyński, Zboralski i sar., 2014). Pulsno elektromagnetno polje ima veliku kliničku upotrebu nakon artroplastike zgloba kuka (Kocić, Lazarević, Kojović i sar., 2006). Pulsno elektromagnetno polje i transkranijalna magnetna stimulacija imaju neuromodulatorni efekat i našli su široku kliničku upotrebu kod Parkinsonove bolesti (Vadala, Vallelunga i sar., 2015), rehabilitaciji nakon moždanog udara (Hsu, Cheng, Liao i sar., 2012) i multiple skleroze (Vijaysheree, Bever, Bowen i sar., 2014).

U XXI vijeku je povećan interes za aplikaciju magnetnih i elektromagnetnih polja u kliničkoj praksi, tako da ovaj fizikalni modalitet prolazi tranziciju od alternativne do zvanične metode. Tokom zadnjih šest decenija razvoja savremene magnetoterapije, omogućeno je uspješno liječenje širokog dijapazona muskuloskeletnih oboljenja, bolnih stanja i neuroloških oboljenja.

### Vrste elektromagnetnih polja koja se primijenjuju u kliničkoj praksi

Magnetoterapija je samo jedan segment magnetobiologije, velikog interdisciplinarnog područja koje se danas intenzivno razvija i istražuje. Svakako da važnu ulogu u razvoju magnetoterapije imaju specijalisti fizikalne medicine i rehabilitacije koji ovaj fizikalni modalitet najviše primijenjuju u svojoj kliničkoj praksi.

Magnetoterapija uključuje sedam grupa elektromagnetnih polja, razvijenih i korišćenih u različitim zemljama svijeta tokom proteklih 50 godina (Markov, 2015):

Statična/permanentna magnetna polja koja stvaraju razni permanentni magneti kao i prolazak jednosmjerne struje kroz kalem.

Niskofrekventna sine talas elektromagnetna polja većinom koriste 60 Hz (u SAD i Kanadi) i 50 Hz u Evropi i Aziji frekvencija u elektrodistributivnim mrežama

Pulsno elektromagnetno polje (PEMP)(5-300Hz) su niskofrekventna polja sa različitim oblicima i amplitudama

Pulsna radio frekvencijska elektromagnetna polja (PRF) koristi izabrane frekvencije u rasponu radio frekvencije: 13.56, 27.12, i 40.68 MHz.

Transcranial magnetic/electric stimulation (1-200Hz) is a treatment method of selected brain areas with short but intensive magnetic pulses.

Millimeter waves have a very high frequency 30–100 GHz. Over the last 10 years this modality has been tested and used for treatment of large number of diseases;

Ultra-short pulses have been developed and researched in the last decade.

Permanent magnets are made of special ferrous alloys (so-called hard ferromagnetic materials) and they permanently retain magnetic properties. They are put directly on to the body as a magnetofore or fitted in jewelry ( bracelets, necklaces, ring) as well as in chairs and mattresses.

Pulsed electromagnetic field has found a very wide clinical application.

It is a specific electromagnetic field which contains of impulse train of low-frequency impulses or "packages" of high-frequency impulses. The basic frequency is divided into packages of impulses (burst/sec), which last for 60 microseconds (μs), with a changeable pause 1 000-10 000 μs, which repeats 5-640 times. From a therapeutic point of view, PEMP combines useful effects of low-frequency and high-frequency EMP. Low-frequency components create transmembrane potentials which normalize the changed membrane potential of the cell. High-frequency component enable more effective entry of electromagnetic energy into the organism and quicker movement of the particles.

PRF field of pulsed radio frequency was originally suggested by Ginsburg in 1934 and later FDA permitted the treatment of pain and edema in surface soft tissue (Diapulse) to use 27.12 MHz . In that manner, a short 65 ms burst and 1600 ms pause between the pulsed bursts do not create the heat during a 30-minute-long use.

Transcranial magnetic stimulation (TMS*)* (1-200Hz) is a method of treatment of selected brain areas with short but intensive, low-frequency or high-frequency magnetic pulses. It is applied via calvarium because a magnetic wave penetrates well through bone tissue. In clinical practice we have a repetitive transcranial magnetic stimulation (rTMS). TMS is a safe and non-invasive method of electric stimulation of neurons in brain tissue modifying the neuron activity locally and in remote areas. TMS is also useful to research various aspects of human neurophysiology in healthy and patients with neurological diseases.

There are three types of devices for magnetotherapy: (a) solenoid, (b) two coils and (c) flat mattresses. Each of these devices has its advantages and faults connected to the benefit of use, standardization of param-

Transkranijalna magnetna/električna stimulacija (1-200Hz) je metod liječenja izabranih područja mozga sa kratkim ali intenzivnim magnetnim pulsevima.

Millimetarski talasi imaju veoma visoku frekvenciju 30–100 GHz. U posljednjih 10 godina ovaj modalitet se ispituje i koristi za liječenja velikog broja bolesti;

Ultra kratki pulsevi su razvijeni i istražuju se u posljednjoj deceniji

Stalni ili permanentni magneti izrađuju se od posebnih željeznih legura (tzv. tvrdih feromagnetskih materijala) i trajno zadržavaju magnetska svojstva. Oni su kao magnetofore stavljaju direktno na tijelo ili se ugrađuju u nakit (narukvice, ogrlice, prsten), kao i u stolice i madrace.Pulsno elektromagnetno polje je našlo vrlo široku kliničku primjenu. To je specifično elektromagnetno polje, koje se sastoji od povorki niskofrekventnih impulsa ili "paketa" visokofrekventnih impulsa. Osnovna frekvencija je podijeljena u pakete impulsa (burst/s), koji traju 60 mikrosekundi (μs), sa promjenljivom pauzom 1 000-10 000 μs, što se ponavlja 5-640 puta. Sa terapijskog stanovišta, PEMP objedinjuje korisne efekte niskofrekventnog i visokofrekventnog EMP. Niskofrekventne komponente stvaraju transmembranske potencijale, koji normalizuju izmijenjen membranski potencijal ćelije. Visokofrekventne komponente omogućavaju efikasnije unošenje elektromagnetne energije u organizam i življe kretanje čestica.

PRF polje pulsne radiofrekvencije je prvobitno predložio Ginsburg 1934. a kasnije Agencija za lijekove i hranu dozvolila za liječenja bola i edema u površinskim mekim tkivima (Diapulse) koristi 27.12 MHz u pulsnom hodu. Na taj način, kratki 65 ms prasak i 1600 ms pauza između pulsnih prasaka, ne stvara toplotu tokom 30 minuta korišćenja.

Transkranijalna magnetna stimulacija (TMS) (1-200Hz) je metod liječenja izabranih područja mozga sa kratkim ali intenzivnim, niskofrekventnim ili visokofrekventnih magnetnim pulsevima. Aplikuje se preko kalvarije jer kroz koštano tkivo dobro penetrira magnetni talas. U kliničkoj praksi imamo i repetitivnu transkranijalnu magnetnu stimulaciju (rTMS). TMS je bezbjedan i neinvazivan metod električnog stimulisanja neurona u moždanom tkivu, modifikujući neuronsku aktivnost lokalno i na udaljenim mjestima. TMS je takođe korisna za istraživanje različitih aspekata humane neurofiziologije kod zdravih i pacijenata sa neurološkim oboljenjima.

Postoje tri vrste uređaja za magnetoterapiju:(a) solenoid, (b) dva kalema i (c) ravni dušek. Svaki od ovih aparata ima prednosti i nedostatke povezane sa pogodnošću korišćenja, standardizacijom parametara i kontrolom uslova eters and control of condition use. Magnetotherapy is a non-invasive, a cost-effective way and comfortable for application.

In clinical use the devices for magnetotherapy do not provide complete data on physical and biophysical dosimetry. Producers and distributors of magnetotherapy devices usually do not provide enough information on devices properties. In most cases it happens due to the lack of knowledge in sense what information is necessary to physicians to make an adequate choice of devices and treatment protocol.

Parameters characterizing the electromagnetic field are frequency, intensity, a shape of impulse and duration of exposure. Frequencies are divided into extremely low frequencies from 3 Hz to 3 KHz, very low frequencies from 3 Hz to 30 KHz and ultra-low frequencies below 3 Hz. Intensity of EMP was prescribed by the World Health Organization in tutorial where a certain intensity does not harm tissues and is from 5-50 mT (WHO, 1989). Time of exposure duration is from 20 minutes to 8-10 hours a day which varies from pathological state and biotropic characteristics of the fields. Both the shape and the form are important. We have a sinusoidal and non-sinusoidal form of the field.

With his research team Markov gave recommendations for conducting correctly designed studies and clinical researches. Parameters needed for characterization of devices are (Markov, 2015): the type of field, frequency, a shape of pulse, intensity or induction, gradient (dB/dt), vector (dB/dx), component (electric or magnetic), the depth of penetration, localization and time of exposure (duration of session). Biotropic characteristics of electromagnetic field are just one component impacting the regular dosimetry. The other components are the cells, tissues, living systems, i.e. characteristics of the patient. The following characteristics are important for clinical studies: age of patient, sex, general condition, stage of disease, types of pathological process on a tissue, organ, disease duration and/or injuries and hypersensitivity to magnetotherapy.

### Biological effects and mechanisms of EMP activity on living systems

Electromagnetic field as part of biosphere is a natural and constant surrounding not only for the humans but for all living systems. There can be stressed the assumption that in living organisms representing the complex hierarchy of cells, tissues, organs and systems there are endogenous magnetic fields and electromagnetic homeostasis. A principle of magnetotherapy is to impact with activity of exterior EMP on pathological process and put interior sur-

korišćenja. Magnetoterapija je neinvazivna, ekonomična i komforna za primjenu.

U kliničkoj upotrebi su aparati za magnetoterapiju koji ne daju kompletne podatke o fizičkoj i biofizičkoj dozimetriji. Proizvođači i distributeri magnetoterapijskih uređaja u pravilu ne pružaju dovoljno informaciju o karakteristikama uređaja. U većini slučajeva se to dešava zbog nedostatka znanja u smislu koja informacija je potrebna kliničarima da bi napravili odgovarajući izbor uređaja i protokola za liječenje.

Parametri koji karakterišu elektromagnetno polje su frekvencija, intenzitet, oblik impulsa i trajanje ekspozicije. Frekvencije su podijeljene u ekstremno niske frekvencije od 3 Hz do 3KHz, veoma niske frekvencije od 3Hz do 30 KHz i ultra niske frekvencije ispod 3Hz. Intenzitet EMP-a je propisala Svjetska zdravstvena organizacija u vodiču gdje je određen intenzitet koji ne šteti tkivima i iznosi od 5-50 mT (WHO, 1989). Vrijeme trajanja ekspozicije je od 20 minuta do 8-10 sati dnevno što varira od patološkog stanja i biotropnih karakteristika polja. Bitni su i oblik i forma signala. Postoji sinusoidalni i nesinusoidni oblik polja.

Markov sa svojim istraživačkim timom je dao preporuke za izvođenje korektno dizajniranih studija i kliničkih istraživanja. Parametari koji su potrebni za karakterizaciju uređaja su (Markov, 2015): tip polja, frekvencija, oblik pulsa, intenzitet ili indukcija, gradijent (dB/dt), vektor (dB/dx), komponenta (električna ili magnetna), dubina prodiranja, lokalizacija i vrijeme izlaganja (trajanje sesije). Biotropne karakteristike elektromagnetnog polja su samo jedna komponenta koja utiče na pravilnu dozimetriju. Druga komponenta su ćelije, tkiva, živi sistemi, odnosno karakteristike bolesnika. Za kliničke studije su bitne sljedeće karakteristike: starost pacijenta, pol, opšte stanje, stadijum bolesti, vrste patološkog procesa na tkivu/organu, dužina trajanja bolesti i/ili povrede i preosjetljivost na magnetoterapiju.

### Biološki efekti i mehanizmi djelovanja EMP-a na žive sisteme

Elektromagnetno polje je kao dio biosfere prirodno i stalno okruženje ne samo čovjeka već svih živih sistema. Može se istaći pretpostavka da u živim organizmima koji predstavljaju složenu hijerarhiju ćelija, tkiva, organa i sistema postoje endogena magnetna polja i elektromagnetna homeostaza. Princip magnetoterapije je da djelovanjem spoljnjih EMP-a utičemo na patološki proces i vraćamo unutrašnju sredinu organizma u ekvilibrijum (Lažetić, 2004). Većina istraživača koja ispituje interakrounding of the organism into equilibrium (Lažetić, 2004). Most of researchers exploring the interaction of EMP and living systems accept that cellular membrane and transmembrane proteins are the primary place of interaction with EMP (Adey, 2004). This finding is important because intramembrane proteins play the role of ionic channels, enzymes or receptors so that the change of functional status of one or several of these proteins would undoubtedly cause consequences for intracellular processes. Oscillations caused by impulsed magnetic field lead to movement of cell membrane, hyperpolarization on the north pole and hypopolarization on the southern pole which leads to periodic increase of permeability of membrane with no energy consumption for ions of sodium, potassium and other molecules (Kirilov, Uhov, Lastučkin et al., 1995).

Under influence of PEMP there comes to the increase of the partial pressure of oxygen in tissues and usage of adenosine triphosphate (ATP) in mitochondria of the cells (Barnothy, 1969). Magnetic field acts on biochemical processes as well as physical-chemical characteristic of water (surface voltage, viscosity, electrical conductivity and dielectric permeability (Markov, Todorov & Ratcheva, 1975). An important factor of EMP and the cell are the type of cell, cellular cycle, a shape of cell, existence of specific growth/mitosis, cellular density as well as temperature during exposure (Liburdy, 1995).

Calcium is nowadays accepted as the main cation with the role of mediator between the activity of EMP and effects creating on biological systems (Pilla, 2015). In vitro researches showed that under the influence of EMP there comes to significant increase of intracellular concentration of calcium ions after a 30-minute long exposure and this increase is completely dependent on influx of these ions from an extracellular medium (Cho, Thatte, Silvia & Golan, 1999), whilst the liberation of calcium's ions from intracellular depots is inhibited (Ikehara, Park, Yamaguchi et al., 2002). In a series of studies calcium calmodulin a depending myosin of phosphorylation (24) it has showed that special magnetic fields as well as 27.12 MHz PRF can modulate the binding of calcium with CAM and increase its kinetic.

A biomagnetic researching group has developed a few methods of biophysical dosimetry including the miosine phosphorylation (Markov, 2004) which is able to predict what electromagnetic fields may be bio-effective and it monitors this efficiency. Therefore, theoretic models and biophysical dosimetry could be effective in selecting appropriate signals and in applying new electromagnetic therapeutic devices in engineering and clinical application. Magnetic fields impact the vasodilation, decrease the vis-

cije EMP-a i živih sistema prihvata da je ćelijska membrana i transmembranski proteini primarno mjesto interakcije sa EMP-om (Adey, 2004). Ovaj nalaz je značajan jer intramembranski proteini imaju ulogu jonskih kanala, enzima ili receptora, tako da bi promjena funkcionalnog statusa jednog ili više ovih proteina nesumljivo imala posljedice po intraćelijske procese. Oscilacije izazvane impulsnim magnetnim poljem dovode do kretanja ćelijske membrane, hiperpolarizacija na sjevernom polu i hipopolarizacija na južnom polu što dovodi do periodičnog povećanja propustljivosti membrane bez utroška energije za jone natrijuma, kalijuma i druge molekule (Kirilov, Uhov, Lastučkin i sar., 1995).

Pod uticajem PEMP-a povećava se parcijalni pritisak kiseonika u tkivima i iskorišćavanje adenozintrifosfata (ATP) u mitohondrijama ćelija (Barnothy, 1969). Magnetno polje djeluje na biohemijske procese kao i fizičko-hemijska svojstva vode (površinski napon, viskoznost, električnu provodljivost i dielektričnu propustljivost) (Markov, Todorov i Ratcheva, 1975). Važan faktor interakcije EMP-a i ćelije su tip ćelije, ćelijski ciklus, aktivacija ćelije, oblik ćelije, postojanje specifičnih rast/mitoza faktora, ćelijska gustina kao i temperatura u toku ekspozicije (Liburdy, 1995).

Kalcijum je danas prihvaćen kao glavni katjon sa ulogom medijatora između djelovanja EMP-a i efekata koje ostvaruje na biološke sisteme (Pilla, 2015). In vitro istraživanja su pokazala da pod uticajem EMP-a dolazi do značajnog povećanja intracelularne koncentracije jona kalcijuma već nakon 30 minuta izlaganja i da je ovo povećanje u potpunosti zavisno od influksa ovih jona iz ekstracelularnog medijuma (Cho, Thatte, Silvia i Golan, 1999), dok je oslobađanje jona kalcijuma iz intracelularnih depoa inhibirano (Ikehara, Park, Yamaguchi i sar., 2002). U seriji studija kalcijum-kalmodulin zavisni miozin fosforilizacije je pokazano da posebna magnetna polja i PEMP kao i 27.12 MHz PRF mogu modulirati vezivanje kalcijuma sa CAM i povećavaju njegovu kinetiku. Bioelektromagnetna istraživačka grupa je razvila nekoliko metoda biofizičke dozimetrije uključujući analizu miozin-fosforilizacije (Markov, 2004) koja je u stanju da predvidi koja bi elektromagnetna polja mogla biti bio-efektivna i nadgleda ovu efikasnost. Zato bi teoretski modeli i biofizička dozimetrija mogli da budu djelotvorni u izboru odgovarajućih signala i u inženjeringu i kliničkoj primjeni novih elektromagnetnih terapijskih uređaja. Magnetna polja utiču na vazodilataciju, smanjenje viskoznosti krvi, stimulaciju osteogeneze, proliferaciju ćelija, formiranje mreže ćelija, epitelizaciju, na imunitet, a imaju i sedacijski, biostimulativni i analgetski efekat. EMP-e cosity of blood, stimulate the osteogenesis, the proliferation of cells, form the networks of cells, epithelization, the immunity and have a sedation, biostimulative and analgesic effect. EMP can have a various efficiency depending upon target tissues and medical problem to be treated. A term of "biological window" (Berg, 1995) has been actual for a while. "Biological windows" are preferable combinations of amplitude and frequencies of exogenous EMP which can be recognized by the cell and respond to it. A research in that direction requires the estimation of replies in a range of amplitudes and frequencies. A question of "dosage" of electromagnetic field is much more complicated than dosing the pharmacological substances. Therapeutic dosage of EMP has been designed to induce in treated tissues the potentials similar to those physiologically being created. By bringing the exogenous EMP to the place of a fracture is possible by applying energy from exterior surrounding to change the polarization of cellular membrane and by effecting the fibroblasts, chondroblasts and osteoblasts to stimulate osteogenesis. Numerous in vitro, in vivo studies on animals as well as clinical experience suggest that initial conditions of sensible way of electromagnetic field determine whether physiological bio-effects can be achieved. Gap junction connections directly impact the electric conductibility which comes from the exogenous stimulus of EMP inside the cellular membrane (Sreedharan & Yhang, 2003). Researchers show that increasing the proliferation stimulated by PEMP is independent from gap junction communication, whilst the increasing of the enzyme activity (alkaline phosphatase) is depending on electrical communication being accomplished through gap junction (Vander, Donahue, Rubin & McLeod , 2000). PEMP stimulation of osteogenesis is an impetus to the general biological laws, it does not speed up osteoporosis but it optimizes its physiological course, supplements and strengthens their effect (Zečević-Luković et al., 2007). For instance, when the broken bone is treated with electromagnetic field, a surrounding tissue receives the same dosage as the fractured one, but physiologically important response happens only in an injured tissue of the bone while the changes in the soft tissue have not been detected. This is crucially important effect indicating that magnetic fields are more effective when the tissue is out of balance. Certainly, basic researches confirm that healthy tissues do not have the same sensitivity to EMP effect. The most sensitive is the neuroendocrine system (Lukač, Matavulj A., Matavulj M. et al., 2006), whilst the bone tissue is the least sensitive to EMP stimulation. Also, healthy tissues have the capability of better compensation and adaptation to EMP effect (Lažetić, 2004).

može imati različitu efikasnost u zavisnosti od target tkiva i medicinskog problema koji treba tretirati. Već dugo je aktuelan koncept "biološkog prozora" (Berg, 1995). "Biološki prozori" su poželjne kombinacije amplitude i frekvencije egzogenih EMP-a koje ćelija može prepoznati i na njih odreagovati. Istraživanje u ovom pravcu zahtijeva procjenu odgovora u rasponu amplituda i frekvencija. Pitanje "doze" elektromagnetnog polja je mnogo komplikovanije nego doziranje farmakoloških supstanci. Terapijske doze EMP-a dizajnirane su tako da indukuju u tretiranim tkivima potencijale slične onima koji se fiziološki stvaraju. Dovođenjem egzogenog EMP-a na mjesto preloma moguće je primjenom energije iz spoljašnje sredine mijenjati polarizaciju ćelijske membrane, a dejstvom na fibroblaste, hondroblaste i osteoblaste stimulisati osteogenezu. Brojne in vitro, in vivo studije na životinjama kao i klinička iskustva sugerišu da inicijalni uslovi senzitivnog puta elektromagnetnog polja određuju da li fiziološki značajni bioefekti mogu da se postignu. Gap junction veze direktno utiču na električnu provodljivost koja dolazi od egzogenog stimulusa EMP-a unutar ćelijske membrane (Sreedharan i Yhang, 2003). Istraživanja pokazuju da je povećanje proliferacije stimulisano PEMP-om nezavisno od gap junction komunikacije, dok je povećanje enzimske aktivnosti (alkalna fosfataza) zavisno od električne komunikacije koja se ostvaruje kroz gap junction (Vander, Donahue, Rubin i McLeod, 2000). Stimulacija PEMP-om osteogeneze je poticaj opštim biološkim zakonima, ne ubrzava osteogenezu, već optimizira njen fiziološki tok, dopunjava i pojačava njihov efekat (Zečević-Luković i sar., 2007). Na primjer, kad se na slomljenoj kosti uradi tretman elektromagnetnim poljem, okolno meko tkivo prima istu dozu kao i prelomljeno, ali fiziološki važan odgovor događa se samo u povrijeđenom tkivu kosti, dok promjene u mekom tkivu nisu primjećene. Ovo je suštinski važno dejstvo, ukazujući da su magnetna polja djelotvornija kad je tkivo van ravnoteže. Svakako da bazična istraživanja potvrđuju da zdrava tkiva nemaju istu senzitivnost na djelovanje EMP-a. Najsenzitivniji je neuroendokrini sistem (Lukač, Matavulj A., Matavulj M. i sar., 2006), dok je koštano tkivo najmanje osjetljivo na stimulaciju EMP-om. Isto tako zdrava tkiva posjeduju mogućnost bolje kompenzacije i adaptacije na djelovanje EMP-a (Lažetić, 2004).

Jedno od osnovih pitanja interakcije NF-EMP-a i bioloških sistema je mehanizam kojim ova polja ostvaruju zapažene efekte. Za razliku od drugih vrsta nejonizirajućih zračenja (mikrotalasa i raditalasa) koji ostvaruju termalne efekte odnosno generisanje unutrašnjeg temperaturnog gradijenta EMP-a ne ostvaruju ovo djelovanje

One of the essential questions of interaction of NF-EMP and biological system is the mechanism by which these fields accomplish remarkable results. Unlike other types of non-ionizing radiation (a microwave and radio wave) which achieve the thermal effects, i.e. generating the interior temperature gradient of EMP not achieving this effect (Glaser, 1992). A group of scientists produced the overview of as-yet assumed mechanisms of EMP interaction and biological systems (Markov, 2015):

The first mechanism includes the transmission of energy by accelerating the ions and electrified proteins that modify the cellular membrane and protein receptors; however, this mechanism is not accepted because the energy carried by EMP is far smaller than energy characteristic for bio-molecules in the cell.

The second mechanism refers that electrical fields induced in the body act by force to the electrified particles and electrical moment; but these forces are far weaker than biological forces.

The third mechanism includes the magnetic moments of ferromagnetic particles and molecules of free radicals which interact with magnetic fields, but so far the existence of sensitive cells to the magnetic moment in the humans has not been established, whilst the modification of speed of radical re-combinations by EMP in the biological systems has been very problematic.

The fourth mechanism relates to the resonant interactions which involve by the EMP caused vibrations or orbital pass in complexes ion-biomolecule, however, this mechanism is not acceptable too because it is opposed to the knowledge of as-yet physics and numerous experimental tests having been conducted have not confirmed these assumptions.

To clarify the mechanisms of EMP effect it is crucial to have a multidisciplinary approach and a team work of experts from physics, engineering, biological sciences and clinical medicine (Markov, 2015).

## Animal studies on magnetotherapy effect

The most basic studies have been conducted in vitro on cultures of various cells and in vivo on animal models. Human lymphoide cells exposed to EMP (in 50 Hz, 2mT, 72h) modify the cytoskeletal organization, with increase of activity of protein kinase, without the cellular proliferation (Santono, Lisi, Pozzi et al., 1997). Selvam and associates showed that rats with induced arthritis exposed to the field of 5Hz, 4μT, 90 minutes during 52 days there comes to the anti-inflammatory effect through a change of activity of lymphocyte calcium ATP (Selvam et al., 2007). Reported was the decrease of level of inflammatory mediator

(Glaser, 1992). Grupa naučnika je dala pregled do sada pretpostavljenih mehanizama interakcije EMP-a i bioloških sistema (Markov, 2015):

Prvi mehanizam uključuje prenos energije akceleracijom jona i naelektrisanih proteina koji modifikuju ćelijsku membranu i proteinske receptore, međutim ovaj mehanizam nije prihvatljiv jer energija koju nosi EMP-e je daleko manje od energije svojstvene biomolekulima u ćeliji.

Drugi mehanizam upućuje da električna polja indukovana u tijelu djeluju silom na naelektrisane čestice i električni momenat; ali ove sile su znatno slabije u odnosu na biološke sile.

Trećim mehanizmom obuhvaćeni su magnetni momenti feromagnetnih čestica i molekula slobodnih radikala koji stupaju u interakciju sa magnetnim poljima, ali do sada nije ustanovljeno postojanje senzitivnih ćelija na magnetni momenat u ljudi, dok je modifikacija brzine radikalskih rekombinacija od strane EMP-a u biološkim sistemima veoma problematično.

Četvrti mehanizam odnosi se na rezonatne interakcije koje uključuju EMP-em izazvane vibracije ili orbitalne prelaze u kompleksima jon-biomolekul, međutim ovaj mehanizam takođe nije prihvatljiv jer je u suprotnosti sa saznanjima današnje fizike i brojni eksperimentalni testovi koji su sprovedeni nisu potvrdili ove pretpostavke.

Za razjašnjavanje mehanizama djelovanja EMP-a je bitan multidisciplinarni pristup i timski rad stručnjaka iz fizike, inženjeringa, bioloških nauka i kliničke medicine (Markov, 2015).

## Animalne studije o efektima magnetoterapije

Najviše bazičnih studija je izvedeno in vitro na kulturama različitih ćelija i in vivo na animalnim modelima. Humane limfoidne ćelije izložene EMP-u ( 50 Hz, 2mT, 72h) modifikuju citoskeletnu organizaciju, sa povećanjem aktivnosti protein kinaze, bez ćelijske proliferacije (Santono, Lisi, Pozzi i sar., 1997). Selvam i saradnici su prikazali da u pacova sa indukovanim artritisom koji su izloženi polju od 5Hz, 4μT, 90 minuta tokom 52 dana dolazi do antiinflamatornog efekta kroz promjenu aktivnosti limfocitne kalcijum ATP-ase (Selvam i sar., 2007). Saopšteno je i smanjenje nivoa upalnog medijatora $PGE_2$ i antioksidativni efekat. U grupi zdravih pacova koji su izlagani PEMP-u nemamo statistički značajne promjene ovih parametara.

U studiji iz 2016. godine (Anbarasan, Baraneedharan, Paul i sar., 2016) grupa istraživača je ustanovila da kratkotrajno (60 min / dan ), frekvencije 0,1 Hz, intenzite-

$PGE_2$ and anti-oxidative effect. In the group of healthy rats exposed to PEMP we do not have statistically important changes of these parameters.

In a study from 2016 (Anbarasan, Baraneedharan, Paul et al., 2016) a group of researchers established that short-term (60 min / day), frequencies 0,1 Hz, intensity 1.95 mT PEMP has a positive effect on chondrocytes, production of extracellular matrix, its differentiation and cytoskeleton. A recommendation from this study is that a short-term exposure of patients with osteoarthritis to EMP in duration of 3 days can produce a beneficial clinical effect. Results of research must be confirmed with methodology involving the estimation of quality and quantity of chondrocytes exposed to PEMP. In most of the researches on animal models it was showed that PEMP effects the re-modelling the bones. In our research on a rat estrogen-deficient osteoporotic model showed that PEMP 40 Hz,10 mT, 45 minutes, a five-day long exposure in the course of five weeks statistically significantly improved the quality of bones. A statistically significant decrease of alkaline phosphatase and osteocalcin have correlated with improvement of bone quality and improvement of bone quality was proved in biomechanical measurements (Popović, 2007).

PEMP has a stimulative effect on an osteoblast proliferation and differentiation. In a study Yuan- Li and his associates stimulated with PEMP of 0,6 mT, 50 Hz the proliferation and osteogen differentiation of osteoblast of rats'calvarium. They showed that primary cilia of osteoblast are the sensors for electromagnetic field and important for osteogene effect of PEMP(Juan-Li, Jian at al., 2015). The effect of PEMP of 7,5 Hz on cultures of osteoblast impact its growth, stimulation of TGF-β and increase of activity of alkaline phosphatase (Li, Lin, Liu & Chang, 2007). In 2004 Chang and associates have tested on the culture of cells of bone marrow of ovariectomised rats the effects of 7,5 Hz EMP, exposure of 60 minutes a day during nine days on the process of osteoclastogenesis via effects on cytokine such as factor of tumor necrosis TNF-α, interleukin 1β (IL-1 β) and IL-6. It has been showed in their results that exposure to PEMP stimulation can inhibit the liberation of TNF-α, IL-1β and IL-6 and forming the osteoclast (Chang K, Chang WH, Yu, & Shih, 2004).

### CLINICAL STUDIES ON THE EFFECT OF PULSED ELECTROMAGNETIC FIELD

Bassett's group, after positive effects of PEMP on osteogenesis on animal model, confirmed it in a clinical study (Bassett, Mitchell, Norton et al., 1979). A study was conducted on patients who had tibia pseudarthrosis and who had been unsuccessfully

ta 1.95 mT PEMP-e ima pozitivno dejstvo na hondrocite, proizvodnju ekstracelularnog matriksa, njihovu diferencijaciju i citoskelet. Iz ove studije su preporučili da kratkotrajna izloženost pacijenata sa osteoartritisom EMP-u u trajanju od 3 dana može da proizvede povoljan klinički efekat. Rezultati istraživanja moraju biti potvrđeni sa metodologijom koja uključuje procjenu kvaliteta i kvantiteta hondrocita izloženih PEMP-u. U većini istraživanja na animalnim modelima pokazano je da PEMP djeluje na remodeliranje kosti. U našem istraživanju na pacovskom estrogen-deficijentnom osteoporotskom modelu je prikazano da PEMP 40 Hz,10 mT, 45 minuta, petodnevne ekspozicije u toku pet sedmica statistički značajno poboljšala kvalitet kosti. Statistički značajno sniženje alkalna fosfataze i osteokalcina su korelirali sa poboljšanjem kvaliteta kosti, a poboljšanje kvaliteta kosti je dokazano i biomehaničkim mjerenjima (Popović, 2007).

PEMP djeluje stimulativno na osteoblastnu proliferaciju i diferencijaciju. U studiji Juan-Li i saradnici su sa PEMP-om od 0,6 mT, 50 Hz stimulisali i proliferaciju i osteogenu diferencijaciju osteoblasta kalvarije pacova. Pokazali su da su primarne cilije osteoblasta senzori za elektromagnetno polje i značajni za osteogeni efekat PEMP-a (Juan-Li, Jian i sar., 2015). Djelovanje PEMP-a od 7,5 Hz na kulture osteoblasta utiče na njihov rast, stimulaciju TGF-β i povećanje aktivnosti alkalne fosfataze (Li, Lin, Liu i Chang, 2007).). Chang i saradnici 2004. godine su na kulturi ćelija koštane srži ovarijektomiranih pacova ispitivali efekte 7,5 Hz EMP-a, ekspozicije 6o minuta dnevno u toku devet dana na proces osteoklastogeneze preko efekata na citokine kao što su faktor tumorske nekroze TNF-α, interleukin 1β (IL-1 β) i IL-6. U njihovim rezultatima je pokazano da izloženost PEMP stimulaciji može inhibirati oslobađanje TNF-α, IL-1β i IL-6 i formiranje osteoklasta (Chang K, Chang WH, Yu i Shih, 2004).).

### KLINIČKE STUDIJE O DEJSTVU PULSNOG ELEKTROMAGNETNOG POLJA

Bassettova grupa je nakon pozitivnih efekata PEMP-a na osteogenezu na animalnom modelu to potvrdila i u kliničkoj studiji (Bassett, Mitchell, Norton i sar., 1979). Studija je provedena na bolesnicima koji su imali pseudoartrozu tibije i koji su bezuspješno hirurški liječeni. Izlagani su PEMP-u ugrađenom u gips sa frekvencijom od 75Hz i gustinom struje od 10μA. Postignuto je poboljšanje zarastanja kod 87% pacijenata, što je sličan rezultat kao kod hirurški liječenih pacijenata. Bassettov tim je zaključio da je povećana vaskularizacija i da ima treated. They were exposed to PEMP fitted in a cast with frequency of 75 Hz and density of electricity of 10μA. Improvement of healing in 87% of patients was reported which is a similar result to surgically treated patients. Bassett's team concluded that vascularization was increased with a synergic effect on osteogenesis. In a review study of clinical researches from 2013 (Seo,Yun, Kwang & Hyungsun, 2013) it was shown that even PEMP was not as efficient as placebo in treating the pain in osteoarthritis of the knee, but it was efficient in improving the function of the knee 8 weeks after the beginning of the therapy. However, results of this research used the methodology of high quality, give a proof supporting the efficiency of PEMP in reducing the pain. In conclusion there is a need for well-controlled randomized studies with adequate methodology to estimate at last the efficiency of PEMP in treating osteoarthritis. In clinical treatment of post-menopause women with PEMP of 72 Hz, 10 hours a day in period of 12 weeks led to improvement of bone density (Tabrah, Ross, Hoffmeier & Gilbert, 1998). Trock and associates tested the effects of PEMP in patients with osteoarthritis of the knee and osteoarthritis of cervical spine. Patients were exposed to the field of various parameters from 5Hz, 10-16Gausa, 10 minutes, then 10Hz, 15-25 Gausa 10 minutes and 12 Hz, 15-25 Hz 10 minutes. Exposure lasted 30 minutes 3-5 sessions a week, with 18 sessions in total during the month. This treatment reduced the pain for 37% (Trock, Bollet & Markoll, 1994). In a research conducted by Kocić and associates (Kocić, Lazarević, Kojović et al., 2006) the effects of various protocols in post-operative rehabilitation after total hip replacement in prevention of heterotopic ossification were tested. In group C there were 66 patients/ 79 endoprosthesis who had only kinesitherapy in post-operative rehabilitation. In group B there were 117 patients / 131 hips who had the PEMP involved and interferent electricity on the 14$^{th}$ day after surgery with standard kinesitherapy programme. In group A there were 117 patients / 131 hips who were involved in PEMP on the third day after surgery and after two weeks of standard kinesitherapy. In group A there was only 16,67% heterotopic ossifications whilst in the two others we had 50,63% and 43,51%. An early PEMP treatment significantly statistically prevents the occurrence of heterotopic ossifications. In 2008 the FDA recommended the application of PEMP in treating heavy depression in patients with Parkinson's diseases to decrease antidepressants intake. A

sinergički efekat na osteogenezu. U preglednoj studiji kliničkih istraživanja iz 2013 (Seo,Yun, Kwang i Hyungsun, 2013). je pokazano da iako PEMP nije bio efikasniji od placeba u liječenju bola kod osteoartritisa koljena, ali je efikasniji u poboljšanju funkcije koljena 8 nedelja nakon početka terapije. Međutim, rezultati ovog istraživanja su koristili metodologiju visokog kvaliteta, pružaju dokaz koji podržava efikasnost PEMP-a u smanjenju bola. U zaključku postoji potreba za dobro kontrolisanim randomiziranim studijama sa adekvatnom metodologijom da konačno procijeni efikasnost PEMP-a u tretmanu osteoartritisa. U kliničkoj tretmanu postmenopauzalnih žena sa PEMP-om od 72Hz, 10 sati dnevno u periodu od 12 nedelja je doveo do poboljšanja koštane gustine (Tabrah, Ross, Hoffmeier i Gilbert, 1998). Trock i saradnici su ispitivali efekte PEMP-a kod pacijenata sa osteoartritisom koljena i osteoartritisom vratne kičme. Pacijenti su izlagani polju različitih parametara od 5Hz, 10-16Gausa, 10 minuta, potom 10Hz, 15-25 Gausa 10 minuta i 12 Hz, 15-25 Hz 10 minuta. Ekspozicija je trajala 30 minuta 3-5 sesija sedmično, sa ukupno 18 sesija u toku mjeseca. Ovaj tretman je smanjio bol za 37% (Trock, Bollet i Markoll, 1994). U istraživanju Kocić i saradnika (Kocić, Lazarević, Kojović i sar., 2006) ispitani su efekti različitih protokola u postoperativnoj rehabilitaciji nakon ugradnje totalne endoproteze kuka u prevenciji heterotopičnih osifikacija. U grupi C je bilo 66 pacijenata/79 endoproteza koji su u postoperativnoj rehabilitaciji imali samo kineziterapiju. U grupi B 117 pacijenata/131 kuk kojima je uključen PEMP i interferentna struja 14-og dana nakon hirurške intervencije sa standardnim kineziterapijskim programom. U grupi A je bilo 117 pacijenata/131 kuk kojima je uključen PEMP treći postoperativni dan i nakon dvije nedelje standardna kineziterapija. U grupi A je bilo samo 16,67 % heterotopičnih osifikacija dok smo u ostale dvije imali 50,63% i 43, 51 %. Rani tretman PEMP-om statistički značajno prevenira nastanak heterotopičnih osifikacija. Agencija za hranu i lekove (Food and Drug Administration – FDA) je 2008. godine preporučila primjenu PEMP-a u tretmanu teške depresije kod pacijenata sa Parkinsonovom bolešću, kako bi se smanjilo uzimanje antidepresiva. U preglednom radu se navode i efekti PEMP-a na kognitivne i motorne smetnje kod ovih pacijenata (Vijaysheree, Bever, Bowen et al., 2014). U studiji Leśniewicz i saradnika evaluiran je efekat fizikalnih tretmana na pokretljivost pacijentica sa reumatoidnim artritisom. Smanjenje bola u zglobovima je ustanovljeno nakon primjene joreview study quoted effects of PEMP on cognitive and motor disorders in these patients (Vijaysheree, Bever, Bowen et al., 2014). In a study by Leśniewicz and associates it was evaluated the effect of physical treatments on mobility of female patients with rheumatoid arthritis. Decreasing the pain in joints was established after applying ionophoresis and magnetotherapy. There is no statistically important difference between the group that had just ionophoresis and the other one that used magnetotherapy except ionophoresis (Leśniewicz , Pieszyński , Zboralski et al., 2014). In a tutorial for multiple sclerosis treatment it was indicated that magnetotherapy impacts the decrease of weakness and fatigue ( level B) and it is inefficient for treating depression in these patients ( level B) (Vijaysheree, Bever, Bowen et al., 2014).

### Clinical application of transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation affects the neuroplasticity of cerebral neural tissue and contributes to broadening potentials to the periphery.

In a randomized study of post-stroke chronic phase patients showed the clinically positive effect of rTMS on motor recovery in the upper limb. Low frequency rTMS via unaffected hemisphere is more effective than high frequency rTMS via affected hemisphere which is compatible with a concept of interhemispheric inhibition. In comparison with patients who had cortical stroke, patients with sub-cortical stroke may have more benefit from rTMS. Further and well-designed studies are needed to determine the duration of effect and plastic change of cortical irritation after rTMS protocols (Hsu, Cheng, Liao et al., 2012). Meta-analysis from 2016 confirmed that repetitive transcranial magnetic stimulation has positive effect on disphagia in patients after stroke. In comparison with low-frequency rTMS, high-frequency TMS can be useful for patients. This meta-analysis also supports that rTMS on normal or bilateral hemisphere has a significant therapeutic effect on disphagia (Wagle, Shuster, Chung et al., 2016). Repetitive transcranial magnetic stimulation in patients with Parkinson's disease leads to mild and moderate improvement of motor functions and it has a potential to be used as an additional therapy to treat Parkinson's disease. Future large studies should be projected to isolate specific clinical characteristics of Parkinson's disease that respond well to therapy rTMS (Mark, George et al., 2013). Since 2011 the FDA has been recommending TMS for treating depression. References recommend the stimulation of the left prefrontal with TMS in the course of 3 to 6 weeks which has statistically important anti-depressive

noforeze i magnetoterapije. Nema statistički značajne ralike između grupe koja je imala samo jonoforezu i druge grupe koja je uz jonoforezu koristila i magnetoterapiju (Leśniewicz , Pieszyński , Zboralski i sar., 2014). U vodiču za liječenje multiple skleroze navedeno je da magnetoterapija djeluje za smanjenje slabosti i malaksalosti (nivo B) i da je neefikasna za tretman depresije kod ovih pacijenata(nivo B) (Vijaysheree, Bever, Bowen i sar., 2014).

### Klinička primjena transkranijalne magnetne stimulacije (TMS)

Transkranijalna magnetna stimulacija djeluje na neuroplastičnost moždanog nervnog tkiva i doprinosi širenju potencijala ka periferiji.

U randomiziranoj studiji kod pacijenata u hroničnoj fazi nakon moždanog udara pokazani klinički pozitivan učinak rTMS na motorni oporavak u gornjem ekstremitetu. Niska frekvencija rTMS preko nepogođene hemisfere je efektivnija od visoke frekvencije rTMS preko zahvaćene hemisfere što je kompatibilno sa konceptom interhemisferične inhibicije. U poređenju sa pacijentima koji su imali kortikalni udar, pacijenti sa subkortikalnim udarom možda mogu imati više koristi od rTMS. Potrebne su daljnje dobro osmišljene studije da se odredi trajanje efekta i plastična promjena kortikalne nadraženosti nakon individualnih rTMS protokola (Hsu, Cheng, Liao et al., 2012). Meta-a analiza iz 2016. godine potvrđuje da ponavljajuća transkranijalna magnetna stimulacija ima pozitivan efekat na disfagije kod pacijenata nakon moždanog udara. U poređenju sa niskofrekventnom rTMS, visokofrekventne TMS mogu biti korisne za pacijente. Ova meta - analiza takođe podržava da rTMS na normalnoj ili bilateralnoj hemisferi ima značajan terapijski efekat na disfagije (Wagle, Shuster, Chung i sar., 2016). Repetitivna transkranijalna magnetna stimulacija kod pacijenata sa Parkinsonovom bolešću dovodi do blagog i umjerenog poboljšanja motornih funkcija i ima potencijal da se koristi kao dodatna terapija za liječenje Parkinsonove bolesti. Buduće velike studije trebaju biti projektovane tako da izoluju specifične kliničke karakteristike Parkinsonove bolesti koje dobro reaguju na terapiju rTMS (Mark S. George i sar., 2013). FDA od 2011. godine preporučuje TMS za tretman depresije. U literaturi se preporučuje stimulacija lijevo prefrontalno sa TMS u toku 3-6 sedmica koja ima statistički značajan antidepresivni efekat u odnosu na placebo grupu sa minimalnim neželjenim efektima. TMS ima mogućnost i za liječenje drugih psihijatrijskih oboljenja, kao i u liječenju akutnog i hroničnog bola (Vrbanić i Ćurković, 2012).

effect in relation to placebo group with minimum adverse effects. TMS has a possibility for treating other psychiatric diseases as well as treating acute and chronic pain (Vrbanić & Ćurković, 2012).

## Contraindications

Contraindications in applying physical agents are divided into absolute and relative as well as on special precautions in applying certain procedures. Also, for each modality vulnerable and sensitive tissues and organs are indicated whose understanding is also necessary in everyday clinical practice. Actual contraindications for magnetotherapy are: malignant diseases, acute infective diseases, bleeding, coagulation disorder, thrombosis, occlusive diseases of aortas, coronal decompensation, coronal pacemaker, the presence of ferromagnetic metal implants and pregnancy (Batavia, 2006). Precautions are in carrying hearing aid and insulin pump and it is recommended to remove devices during magnetotherapy (Klein, 2015). Additional contraindications for transcranial magnetic stimulation are the presence of high intracranial pressure, epilepsy and carrying various stimulators with microprocessors in the area of the neck.

## Conclusion

Magnetotherapy has been successfully applied for more than 60 years in physical medicine and rehabilitation in treatment of a wide range of diseases. As in vitro, in vivo and clinical studies proved, magnetotherapy has osteogenetic, anti-inflammatory, chondroprotective and analgesic effect and potential to regenerate the damaged tissue. Despite reports on useful effects of magnetic fields in treating bone fractures, osteoporosis, rheumatoid arthritis, osteoarthritis, neurological damages, adenosine triphosphates, we are only half way to explain the mechanism by which magnet therapy strengthens regenerative capabilities of pathological and damaged tissue. It is up to future researchers to clarify the mechanisms of activity which would contribute to the clearer clinical application and actuality of magnet therapy in the future.

## Kontraindikacije

Kontraindikacije u primjeni fizikalnih agensa su podijeljenje na apsolutne i relativne, kao i na posebne mjere opreza kod primjene pojedinih procedura. Isto tako za svaki modalitet se navode i koja su vulnerabilna i osjetljiva tkiva i organi čije poznavanje je takođe nužno u svakodnevnoj kliničkoj praksi. Aktuelne kontraindikacije za magnetoterapiju su: maligna oboljenja, akutna infektivna oboljenja, krvarenje, poremećaj koagulacije, tromboza, okluzivne bolesti arterija, srčana dekompenzacija, srčani pejsmejker, prisustvo feromagnetnih metalnih implantata i trudnoća (Batavia, 2006). Mjere opreza su kod nošenja slušnog aparata i inzulinske pumpe i preporučuje se skidanje aparata tokom magnetoterapije (Klein, 2015). Za transkranijalnu magnetnu stimulaciju su dodatne kontraindikacije prisustvo povišenog intrakranijalnog pritiska, epilepsija i nošenje različitih stimulatora sa mikroprocesorima u području vrata.

## Zaključak

Magnetoterapija se više od 60 godina uspješno primjenjuje u fizikalnoj medicini i rehabilitacije u liječenju širokog dijapazona oboljenja. Kao što su pokazale in vitro, in vivo i kliničke studije magnetoterapija ima osteogenetski, antiupalni, hondroprotektivni , analgetski efekat i potencijal da obnovi oštećeno tkivo. Uprkos izvještajima o korisnom učinku magnetnog polja u tretmanu koštanih preloma, osteoporoze, reumatoidnog artritisa, osteoartritisa, neuroloških oštećenja, tek smo na pola puta u razjašnjavanju mehanizma putem kojeg magnetoterapija ojačava regenerativne sposobnosti patološkog i oštećenog tkiva. Na budućim istraživanjima je da se razjasne mehanizmi djelovanja koji bi doprinijeli jasnijoj kliničkoj primjeni i aktuelnost magnetoterapije i u budućnosti.

## References

Basford J.R. (2001). A historical perspective of the popular use of electric and magnetic therapy. *Arch Physic Med Rehab*, *82*, 1261-9

Batavia, M. (2006). Contraindications in Physical Rehabilitation-E-Book: Doing No Harm. Elsevier Health Sciences.

Gilbert W. De Magnete. (1991). (written in Latin, Translated and published by Dover Publication.p.368

Lažetić B. (2004). *Osnovi magnetobiologije*. Novi Sad: Medicinski fakultet

Fukada E., & Yasuda I. (1957). On the piezoelectric effects of bone. *Journal of Phys Soc of Japan*, *12*, 1158-62.

Friedenberg ZB. (1966). Brighton CT. Bioelectric potentials in bone. *J Bone Joint Surg* . *48*(5): 915-23

Bassett, C. A. L., Pawluk, R. J., & Pilla, A. A. (1974). Acceleration of fracture repair by electromagnetic fields. A surgically noninvasive method. *Annals of the New York Academy of Sciences*, *238*(1), 242-262.

Linovitz, R. J., Pathria, M., Bernhardt, M., Green, D., Law, M. D., McGuire, R. A., ... & Faden, J. S. (2002). Combined magnetic fields accelerate and increase spine fusion: a double-blind, randomized, placebo controlled study. *Spine*, *27*(13), 1383-1388.

Leśniewicz, J., Pieszyński, I., Zboralski, K., & Florkowski, A. (2014). The effect of selected physical procedures on mobility in women with rheumatoid arthritis. *Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiego*, *37*(222), 335-337.

Kocić, M., Lazović, M., Kojović, Z., Mitković, M., Milenković, S., & Ćirić, T. (2006). Methods of the physical medicine therapy in prevention of heterotopic ossification after total hip arthroplasty. *Vojnosanitetski pregled*, *63*(9), 807-811.

Vadalà, M., Vallelunga, A., Palmieri, L., Palmieri, B., Morales-Medina, J. C., & Iannitti, T. (2015). Mechanisms and therapeutic applications of electromagnetic therapy in Parkinson's disease. *Behavioral and Brain Functions*, *11*(1), 26.

Hsu, W. Y., Cheng, C. H., Liao, K. K., Lee, I. H., & Lin, Y. Y. (2012). Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke. *Stroke*, *43*(7), 1849-1857.

Yadav, V., Bever, C., Bowen, J., Bowling, A., Weinstock-Guttman, B., Cameron, M., ... & Narayanaswami, P. (2014). Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*, *82*(12), 1083-1092.

Markov, M. (2015). XXIst century magnetotherapy. *Electromagnetic biology and medicine*, *34*(3), 190-196

Adey, W. R. (2004). Potential therapeutic applications of nonthermal electromagnetic fields: ensemble organization of cells in tissue as a factor in biological field sensing. *Bioelectromagnetic medicine*, 1.

Kirilov J.B., Uhov J.I., Lastučkin A.V., Sučkova Ž.V., & Karpov E.M. (1995). Mehanizam dejstvija magnitnoga poja na živoj organizam. *Vopros Kurort, 3:*43-45.

Barnothy, M. F., & Sümegi, I. (1969). Effects of the magnetic field on internal organs and the endocrine system of mice. In *Biological effects of magnetic fields* (pp. 103-126). Springer, Boston, MA.

Markov, M. S., Todorov, S. I., & Ratcheva, M. R. (1975). Biomagnetic effect of the constant magnetic field action on water and physiological activity. In *Physical and Chemical Bases of Biological Information Transfer* (pp. 441-449). Springer, Boston, MA.

Liburdy, R. P. (1995). Cellular studies and interaction mechanisms of extremely low frequency fields. *Radio Science*, *30*(1), 179-203.

Pilla, A. A. (2015). Pulsed electromagnetic fields: from signaling to healing. Electromagnetic Fields in Biology and Medicine, 29-48.

Cho, M. R., Thatte, H. S., Silvia, M. T., & Golan, D. E. (1999). Transmembrane calcium influx induced by ac electric fields. *The FASEB journal*, *13*(6), 677-683.

Ikehara, T., Park, K. H., Yamaguchi, H., Hosokawa, K., Houchi, H., Azuma, M., ... & Yoshizaki, K. (2002). Effects of a time varying strong magnetic field on release of cytosolic free Ca2+ from intracellular stores in cultured bovine adrenal chromaffin cells. *Bioelectromagnetics*, *23*(7), 505-515.

Markov, M. S. (2004). Myosin light chain phosphorylation modification depending on magnetic fields. I. Theoretical. *Electromagnetic Biology and Medicine*, *23*(1), 55-74.

Berg, H. (1995). Possibilities and problems of low frequency weak electromagnetic fields in cell biology. *Bioelectrochemistry and bioenergetics*, *38*(1), 153-159.

Sreedharan, V., & Zhang, D. (2003, March). Finite element modeling of cellular responses of gap junction connected osteocytes under extremely low-frequency electromagnetic fields. In *Bioengineering Conference, 2003 IEEE 29th Annual, Proceedings of* (pp. 160-161). IEEE.

Vander Molen, M. A., Donahue, H. J., Rubin, C. T., & McLeod, K. J. (2000). Osteoblastic networks with deficient coupling: differential effects of magnetic and electric field exposure. *Bone*, *27*(2), 227-231.

Zečević-Luković, T., Milošević, O., & Ristić, B. (2007). Electromagnetic field and osteogenesis. *Vojnosanitetski pregled*, *64*(10), 701-706.

Lukac, T., Matavulj, A., Matavulj, M., Rajković, V., & Lazetić, B. (2006). Photoperiodism as a modifier of effect of extremely low-frequency electromagnetic field on morphological properties of pineal gland. *Bosnian journal of basic medical sciences*, *6*(3), 10-16.

Glaser, R. (1992). Current concepts of the interaction of weak electromagnetic fields with cells. *Journal of Electroanalytical Chemistry*, *342*(3), 255-268.

Santoro, N., Lisi, A., Pozzi, D., Pasquali, E., Serafino, A., & Grimaldi, S. (1997). Effect of extremely low frequency (ELF) magnetic field exposure on morphological and biophysical properties of human lymphoid cell line (Raji). *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, *1357*(3), 281-290.

Selvam, R., Ganesan, K., Raju, K. N., Gangadharan, A. C., Manohar, B. M., & Puvanakrishnan, R. (2007). Low frequency and low intensity pulsed electromagnetic field exerts its antiinflammatory effect through restoration of plasma membrane calcium ATPase activity. *Life sciences*, *80*(26), 2403-2410.

Anbarasan, S., Baraneedharan, U., Paul, S. F., Kaur, H., Rangaswami, S., & Bhaskar, E. (2016). Low dose short duration pulsed electromagnetic field effects on cultured human chondrocytes: An experimental study. *Indian journal of orthopaedics*, *50*(1), 87.

Popović T. (2007). Poređenje djelovanja pulsnog elektromagnetnog djelovanja i medikamentozne terapije na kost u eksperimentalnoj osteoporozi. Neobjavljena doktorska disertacija.

Yan, J. L., Zhou, J., Ma, H. P., Ma, X. N., Gao, Y. H., Shi, W. G., ... & Chen, K. M. (2015). Pulsed electromagnetic fields promote osteoblast mineralization and maturation needing the existence of primary cilia. *Molecular and cellular endocrinology*, *404*, 132-140.

Li, J. K. J., Lin, J. C. A., Liu, H. C., & Chang, W. H. S. (2007). Cytokine release from osteoblasts in response to different intensities of pulsed electromagnetic field stimulation. *Electromagnetic Biology and medicine*, *26*(3), 153-165..

Chang, K., Hong-Shong Chang, W., Yu, Y. H., & Shih, C. (2004). Pulsed electromagnetic field stimulation of bone marrow cells derived from ovariectomized rats affects osteoclast formation and local factor production. *Bioelectromagnetics*, *25*(2), 134-141.

Bassett, C. A. L., Mitchell, S. N., Norton, L., Caulo, N., & Gaston, S. R. (1979). Electromagnetic repairs of nonunions, electrical properties of bone and cartilage, experimental effects and clinical applications. *Grune & Stratton Inc, New York*, *605*.

Ryang We, S., Koog, Y. H., Jeong, K. I., & Wi, H. (2012). Effects of pulsed electromagnetic field on knee osteoarthritis: a systematic review. *Rheumatology*, *52*(5), 815-824.

Tabrah, F. L., Ross, P., Hoffmeier, M., & Gilbert, F. (1998). Clinical report on long-term bone density after short-term EMF application. *Bioelectromagnetics*, *19*(2), 75-78..

Trock, D. H., Bollet, A. J., & Markoll, R. (1994). The effect of pulsed electromagnetic fields in the treatment of osteoarthritis of the knee and cervical spine. Report of randomized, double blind, placebo controlled trials. *The Journal of Rheumatology*, *21*(10), 1903-1911.

Liao, X., Xing, G., Guo, Z., Jin, Y., Tang, Q., He, B., ... & Mu, Q. (2017). Repetitive transcranial magnetic stimulation as an alternative therapy for dysphagia after stroke: A systematic review and meta-analysis. *Clinical rehabilitation*, *31*(3), 289-298.

Shukla, A. W., Shuster, J. J., Chung, J. W., Vaillancourt, D. E., Patten, C., Ostrem, J., & Okun, M. S. (2016). Repetitive transcranial magnetic stimulation (rTMS) therapy in Parkinson disease: a meta-analysis. *PM&R*, *8*(4), 356-366..

George, M. S., Taylor, J. J., & Short, E. B. (2013). The expanding evidence base for rTMS treatment of depression. *Current opinion in psychiatry*, *26*(1), 13.

Schnurrer-Luke-Vrbanić, T., & Ćurković, B. (2012). The new technologies in physical and rehabilitation medicine. Medicina Fluminensis, 48(4), 346-353.

*Primljen: 12. jun 2017. / Received: June 12, 2017*
*Prihvaćen: 26. oktobar 2017. / Accepted: October 26, 2017*