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EDITORIAL

THERAPEUTIC APPLICATION OF MUSICALLY MODULATED ELECTROMAGNETIC FIELDS IN THE TREATMENT OF MUSCULOSKELETAL DISORDERS

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Different studies have demonstrated the efficacy of extremely low frequency electromagnetic fields (ELF EMFs) in the treatment of pain. In particular, the positive effects of ELF EMFs seems to depend on their respective codes, such as frequency, intensity and waveform, even if the exact mechanism of interaction is still debated. The most commonly used for extremely low frequency magnetotherapy is a 100Hz sinusoidal field (ELF) with a mean of induction of few Gauss. This article reviews the therapeutic application of a musically modulated electromagnetic field (TAMMEF), a new-generation of electromagnetic field used for extremely low frequency magnetotherapy characterized by variable frequencies, intensities and waveforms. Both clinical and experimental studies, performed by authors of the present review, have demonstrated the efficacy of ELF and the new TAMMEF systems in several musculoskeletal disorders such as osteoarthritis, rheumatoid arthritis, carpal tunnel syndrome, shoulder periarthritis and cervical spondylosis. Moreover, it has been demonstrated that ELF and TAMMEF systems are not only effective, but also safe, from clinical and experimental point of view. In fact, clinical trials did not reported any undesired side effect, while *in vitro* studies showed that ELF EMFs did not induce uncontrolled cell proliferation, did not affect cell viability and did not induce apoptosis. With their efficacy and safety, ELF and even more the new TAMMEF systems represent a valid complementary or alternative treatment to standard pharmacological therapies in reducing both pain and inflammation of patients affected by musculoskeletal disorders.

For many years, numerous authors have investigated the effects of electromagnetic fields (EMFs) on simple systems, such as particles in solutions, colloids and living matter (1, 3). Moreover, electromagnetic fields can be divided into: high frequency electromagnetic fields that produce micro-vibration in the molecules interpreted as resonance phenomena (4, 5), and extremely low frequency electromagnetic fields (ELF EMFs) which are responsible of more modest actions (6). Despite the large amount of studies regarding the interaction of electromagnetic fields with biological systems, the exact mechanism through which electromagnetic fields interfere with molecules, cells and tissues is still debated. Literature reported that the preferred targets of EMFs seemed to be the endorphine modulation (7), enzyme regulation (8), inflammatory pathways (9) and also immune response (10).

It could be hypothesized that different codes (frequency, intensity and waveform) of each

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electromagnetic field could be responsible of different and even opposite effects on cells, even though a meaningful understanding is missing about which frequency, intensity and waveform or their combination could lead to the most positive effects and to the most negative ones. It is very difficult to investigate the entire range of codes of EMFs, because it would require a limitless number of tests and a massive workload. The EMF most commonly used in extremely low frequency magnetotherapy is a sinusoidal field with fixed frequency of 100Hz (ELF) and a mean of induction of few Gauss (11). In order to investigate better the effects of multiple parameters and to overcome the limit of 100Hz-fixed frequency of ELF system, a new apparatus called therapeutic application of musically modulated electromagnetic field has been pioneered at Physics Department of the University of Siena (Italy) and patented in 2002. This new system allows to generate a large spectrum of low frequency EMFs by varying frequency, intensity and waveform since they are generated by a piece of music. TAMMEF system has been used in our institution for several years for both therapeutic (*in vivo*) and research (*in vitro*) purpose to treat patients affected by several diseases, such as osteoarthritis (in particular, primary osteoarthritis of the knee), rheumatoid arthritis, carpal tunnel syndrome, shoulder periarthritis and cervical spondylosis, and the efficiency and effectiveness of the analgesic and anti-inflammatory effects of TAMMEF have been clearly demonstrated (11, 15). Otherwise, the use of ELF EMFs and TAMMEF with respect to the conventional therapies is justified by the evidence that pharmacologic interventions, generally represented by analgesics and/or non-steroidal anti-inflammatory drugs (NSAIDs), are focused mainly on improving symptoms. More recently, new agents (the so-called Chondroprotective or "Structure-modifying" Agents) seem to exceed the limits of a poor symptomatic activity, interfering with the degenerative processes and encouraging normalization of the synovial fluid and cartilage matrix (16, 17).

Although most of these agents have shown promising effects *in vitro*, none has been proven to produce clinically meaningful undisputed structure-modifying effects in humans with musculoskeletal disorders such as osteoarthritis (18). Moreover, it is well known that NSAIDs use cannot be extended to a long time because of the frequent onset of side effects (19). Therefore, the treatments for these particular diseases are usually unsatisfactory at present and the need to create effective and valid alternatives to standard pharmacological therapies rose up (20): in particular, the therapeutic aim is not only limited to reduce pain, but it is mainly directed to interfere with phlogistic and/or degenerative events of the rheumatic disorders. In this area of interest, some investigators have hypothesized before and then demonstrated that the stimulation of bone and cartilage through the application of specific electric and magnetic fields can interfere with various mechanisms such as inflammation, growth and repair (21, 22). Since the extracellular matrix of the hyaline cartilage is piezoelectric and converts electromagnetic oscillations to mechanical vibrations and vice versa (23), several studies have reported that bone and cartilage can be stimulated by electromagnetic fields (EMFs) to increase the synthesis of extracellular matrix. All these findings have lead to the more frequent use of alternative treatments, such as low frequency magnetotherapy and, in our case, the new TAMMEF system, to treat pain and also to slow the progression of pathologies such as osteoarthritis.

Electromagnetic fields production and characterization

The EMFs apparatus consisted of an audiotape player sending signals through a monochannel-microphone to 2 low-frequency amplifiers, A and M, both with adjustable gain. The ELF field was modulated at a fixed frequency of 100 Hz and was generated by an opposing pair of heteronomous polar expansions that made up the characteristic spatial conformation of the setup. The polar expansions consisted of the sides of two iron-silicon nuclei (3×4 cm) joined by a ferromagnetic arc. The coils (4.5 cm long) consisted of 900 turns of copper wire (0.7 mm in diameter). The alternating current power supply was regulated to maintain the effective value of the oscillation amplitude at ~10 gauss at the midpoint of the interpolar distance (30 cm). In order to generate the TAMMEF field, we used a similar audiotape containing a different signal, that is, a musical passage, which produced a

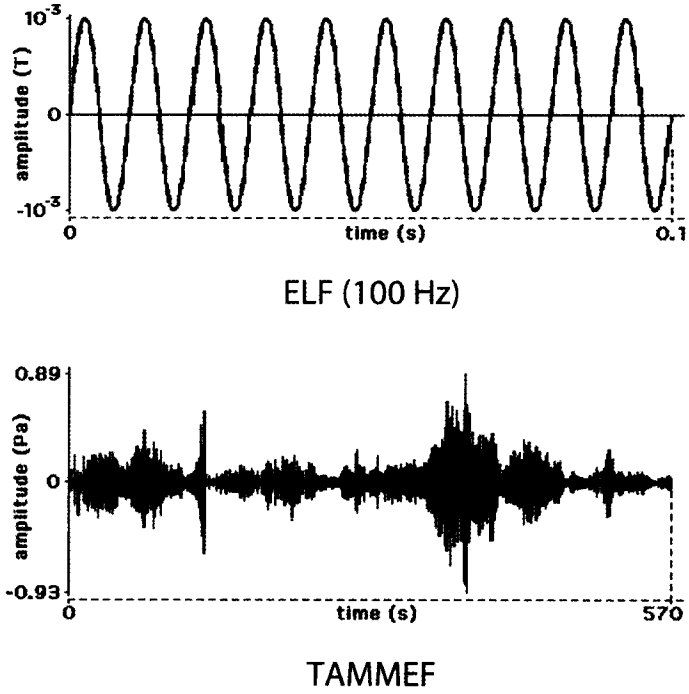

Fig. 1. *Electromagnetic signals generated by ELF field (top) and TAMMEF field (bottom).*

suitably modulated EMF with varying frequencies, intensities and waveforms. We generally used a piece of classical music (i.e., Rachmaninov's Piano Concerto number 2 in C minor Op.18 for piano and orchestra) to generate a microphone signal, with the current from the amplifier going to a loudspeaker that played the musical passage, so that the piece can be contemporary listened during the therapy.

With this new TAMMEF system, users are able to vary the generated EMFs simply by changing the music passage. Therefore, this method allows to includes 100Hz field in the omni-comprehensive code, according to our previous data. Moreover, this system includes also different codes used by other authors (2, 11), so the objections related to therapeutic use of different codes should be totally overlapped. Figure 1 shows the codes of the two different electromagnetic fields (ELF and TAMMEF). Fig. 2 shows the EMFs apparatus with the audiotape player put in the frontal mask connected to the two magnetic poles. To conduct an *in vivo* experiment, the hip, finger,, wrist, or knee joints were positioned between the magnetic poles, while to conduct *in vitro* experiments a 75-cm^2 flask containing the biological sample was positioned between the polar expansions in order to be directly in the generated EMF (Fig. 3). The time of procedures for both *in vivo* and *in vitro* experiments was 30 min/day at room temperature for 1-2 weeks.

TAMMEF system in the treatment of osteoarthritis, carpal tunnel syndrome, cervical spondylosis and shoulder periarthritis

Osteoarthritis (24) is one of the most frequently occurring rheumatic diseases. It is a slowly progressive degenerative disorder, characterized by gradual loss of articular cartilage due to disruption of chondrocyte-matrix interactions and alterations of metabolic responses in the chondrocytes (25). Also the pharmacological approach is usually unsatisfactory (26). Starting from these assumptions, we used and compared both ELF and TAMMEF systems in the treatment of knee OA (14). In this study, ninety patients, affected by primary OA of the knee, were enrolled and randomly divided into three groups of 30 patients each: A exposed to TAMMEF; B exposed to ELF; C exposed to a simulated field. The procedures were authorized by

Fig. 2. *The apparatus used to generate ELF and TAMMEF fields. The experiments were carried out at room temperature at time (30 minutes) for two weeks.*

Bioethics Commission and all patients signed their written informed consent. Moreover, all the patients were not informed about the differences between ELF and TAMMEF treatments and also about the division into groups. All subjects underwent a cycle of 15 daily sessions of 30 minutes each and a clinical examination upon enrolment, after 7 days of therapy, at the end of the cycle and at a follow-up 30 days later.

All the patients of groups A and B completed the therapy without the appearance of side effects. They presented a significant improvement of the subjective pain and the functional limitation, which remained stable at the follow-up examination, while in group C, there was no improvement of the pain symptoms or articular functionality. Moreover, in this work no clinically relevant adversities were recorded. This first study suggests that ELF and TAMMEF systems are suitable for the control of pain and in the reduction of functional limitation in treated knee OA patients. Particularly relevant seemed the efficacy of ELF EMFs over time (follow-up): so, the authors hypothesized that ELF EMFs are able to interfere with the pathogenetic mechanisms of the disease, justifying their prolonged action not only limited to the symptoms. In another of our previous clinical studies (15), 30 women (mean age 58+/-3.2 years; duration of disease 2.1+/-2.2 years) affected by a mild-to-moderate form (according to electrophysiological data) of idiopathic carpal tunnel syndrome, one of the most common entrapment neuropathies (27), were exposed to ELF EMFs consisting of 2 cycles, distanced 3 months one from another, each composed by 15 daily applications lasting 30 minutes. The clinical parameters significantly improved in the course of treatment in 28 patients, in particular pain, paresthesias, numbness and functional loss showed a significant decrease. Also, the electrophysiologic findings (from time 0 to the end of treatments) showed a significant improvement in 22 patients, in fact the ratio of the reduced sensory velocity and the increased motor latency in the median nerve significantly enhanced at the end of EMFs application.

Thus, the treatments seemed to result useful in the initial phase of the disease as analgesic-antiphlogistic

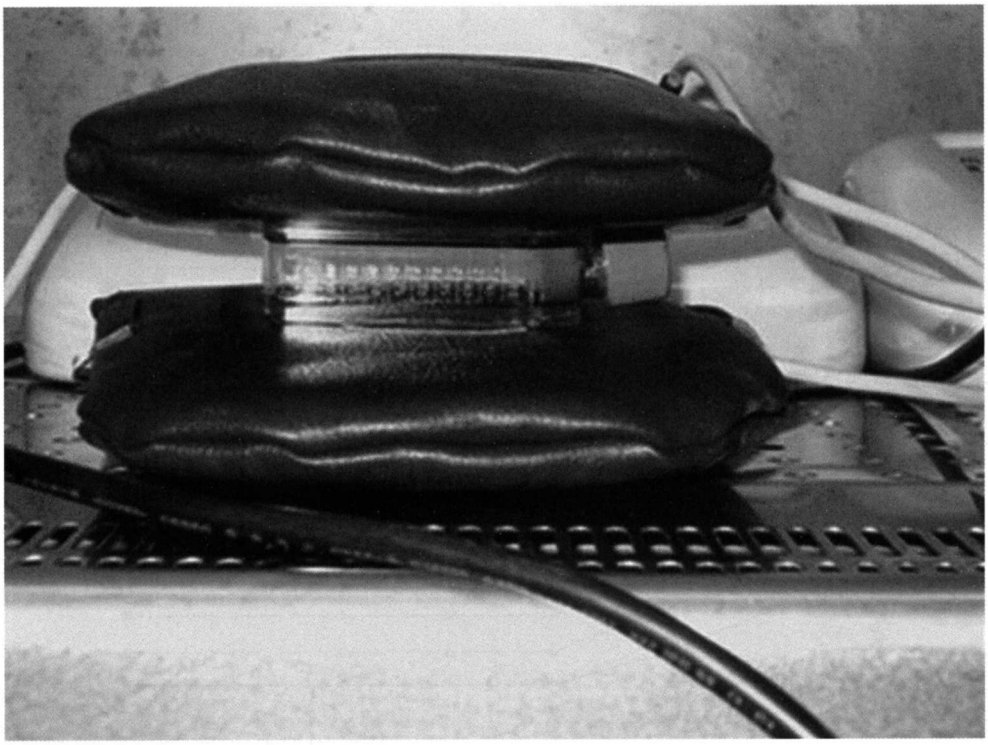

Fig. 3. *Cell culture flask exposed to ELF EMFs. To conduct an experiment, cells samples were positioned between the polar expansions in order to be directly in the generated EMF. Sham Exposed cells were maintained at a distance far from the EMF, thus it served as a control.*

instrumental therapy, alternatively to other palliative treatments such as NSAIDs and/or night splints and corticosteroid injection. The efficacy and tolerability of ELF and TAMMEF systems have been assessed also in patients affected by cervical spondylosis or unilateral non-calcified shoulder periarthritis (13). These patients were divided into three groups: A=50 patients exposed to TAMMEF; B=50 patients exposed to ELF; C=50 patients exposed to a simulated field (placebo). All the patients were exposed to a cycle of 15 daily sessions of 30 minutes each by applying the magnets to the sites affected by pathologies (cervical spine or shoulder joint), stopping non-steroidal anti inflammatory drugs (NSAIDs) two weeks before the treatments. Clinical examination was performed according to Scott's analogue scale that is specific for clinical evaluation of pain (28). The clinical examination also included the execution of semeiological maneuvers to define the functionality of the single regions affected. At the end of the cycle, 28 patients of the TAMMEF group (14 with cervical spondylosis and 14 with shoulder periarthritis) showed a total recovery of the articular functionality, while the other 19 patients of the group (19 with cervical spondylosis and 3 with shoulder periarthritis) showed a significant improvement even though they did not achieve a total functional recovery (Fig. 4A). Moreover, 27 patients of the ELF group (16 with cervical spondylosis, 11 with shoulder periarthritis) showed a total function recovery after the cycle, while the other 23 patients presented the same pattern of functionality demonstrated in TAMMEF group (Fig. 4B). Fig. 4C explains the pattern of functionality of the control group (C). First of all, these findings pointed out that none of the patients of the groups A and B had to take NSAIDs during the treatments and also that all the patients presented a statistically significant improvement of the functionality.

In particular, in TAMMEF group the pain regressed completely after the treatments in 38 (76%) of the 50 patients, while pain decreased relevantly in the remaining 12 patients in respect to the basal values. Furthermore, both patients treated with ELF and TAMMEF presented the so called "tail effect", since their improved functionality and reduced

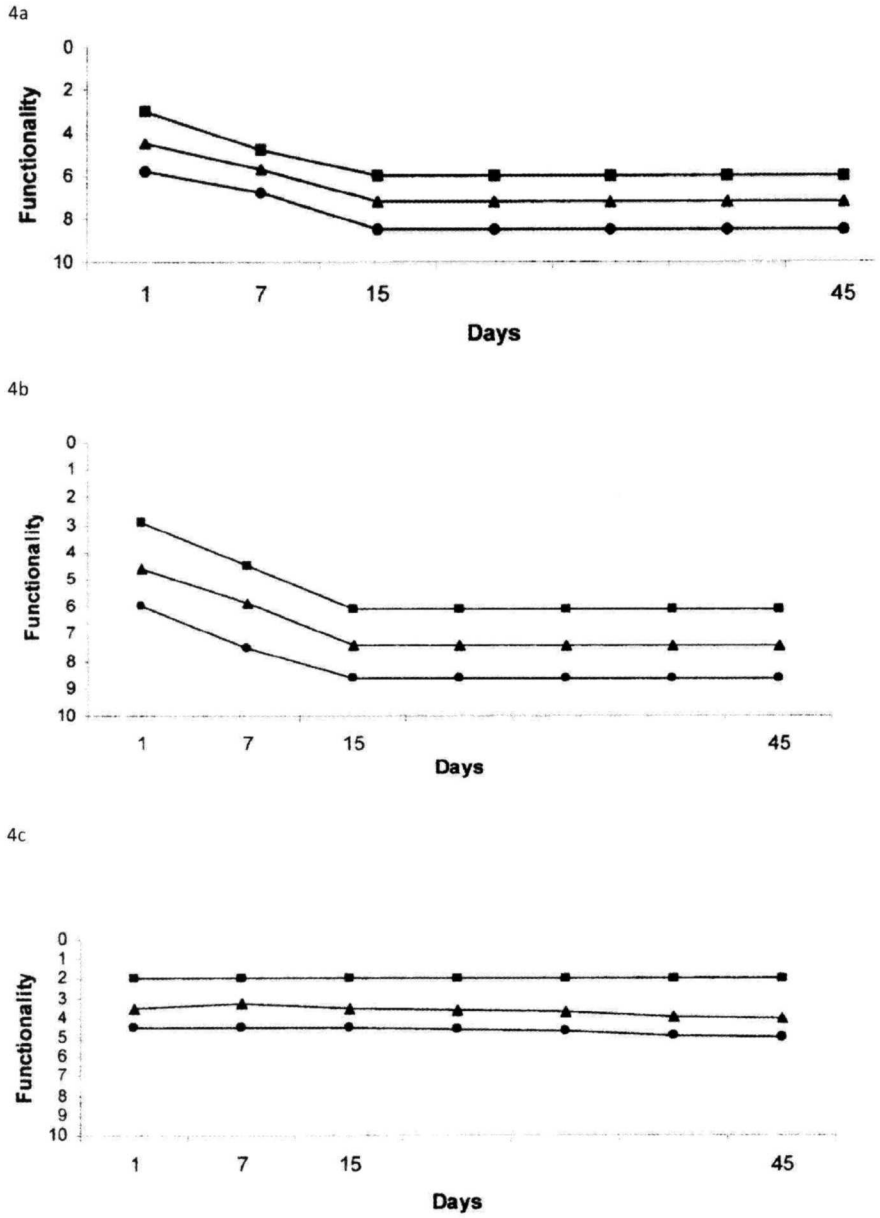

Fig. 4. *Evaluation of Functionality (expressed as mean) from the start to 45 days after treatments in the three group: TAMMEF (**a**), ELF (**b**), PLACEBO (**c**).* ● *Slight disease,* ▲ *Moderate disease,* ■ *Serious disease.*

pain remained after a month from the treatments, suggesting a potential "structure-modifying" activity (13).

TAMMEF system in the treatment of human primary osteoarthritic chondrocytes

As mentioned above, the apparatus for EMFs stimulation is suitable both for *in vivo* and *in vitro* studies. Starting from the results already obtained *in vivo* (11, 14), in order to remove any doubt regarding the potential interference of placebo effect in patients treated with ELF and TAMMEF, we performed further cellular investigations.

First of all, we want to underline that in our previous *in vivo* studies we considered as placebo effect the slight improvements of pain, bearing

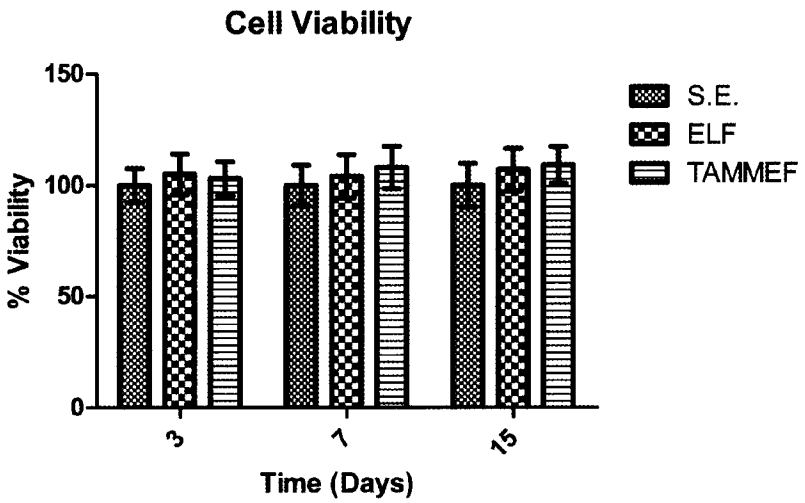

Fig. 5. *Cell viability recorded after 3, 7 and 15 days of treatments. Data are reported as % viability referred to S.E (100%).*

in mind the well-known interaction between pain pathways and psychic habitus (29, 32). Based on the necessity to deeply analyze the interactions between ELF EMFs and human cells, in our recent study (33) we isolated human primary osteoathrtitic chondrocytes from 20 OA patients (12 males and 8 females, age 68±10 yrs) undergoing total femoral head replacement. In order to reproduce the same conditions for our previous *in vivo* studies (11, 14), chondrocytes were divided into three groups: A exposed to TAMMEF, B exposed to ELF; and C sham exposed (S.E). In the S.E group the cells were removed from the incubator and maintained at a distance far from the EMFs. The cells of groups A and B received 30 min/day of treatments for 15 days, while cells of group C did not receive any treatment. Cell viability assays performed at days 3, 7 and 15 showed that ELF EMFs did not affect cell viability for all the time of the treatments compared to untreated cells (Fig. 5). It is known that some cytokines (such as interleukin-1β and interleukin-6) may be responsible of the catabolic process that involves OA cartilage (34, 35). Moreover, literature reports that insulin-like growth factor-1 (IGF-1) acts in contrast with the above-mentioned cytokines (36). Consequently, in order to mimic closely *in vitro* the imbalance between the degenerative role of the inflammatory cytokines and the protective role of IGF-1 we cultured the chondrocytes of the three groups (A, B and C) in presence of 5ng/ml IL-1β and 5ng/ml IGF-1, performing further metabolic tests such as reactive oxygen species (ROS) production, glutathione (GSH) production and mitochondrial transmembrane potential. While some investigators demonstrated that cell exposure to ELF EMFs could lead to the production of reactive oxygen species (ROS) (37),we found that chondrocytes treated with TAMMEF and in the presence of IL-1β showed 50% ROS lower respect to chondrocytes on ELF and S.E alone; no significant differences were found between untreated and treated cells in presence of IGF-1 (Fig. 6A).

The production of intracellular GSH increased significantly in chondrocytes after ELF EMFs exposure, as by IGF-1 cells stimulation as by IL-1β one (Fig. 6B). Literature reported also that mitochondrial dysfunction seems to interfere with cartilage degradation process (38). Our study showed a restoration of the mitochondrial transmembrane potential of treated chondrocytes and stimulated by IGF-1 and IL-1β, in respect to untreated cells. This fundamental change in mitochondrial membrane permeability has been induced by both ELF and TAMMEF treatments, but in a higher percentage by the latter (Fig. 6C). In our opinion, these findings contribute to justify the results already obtained in

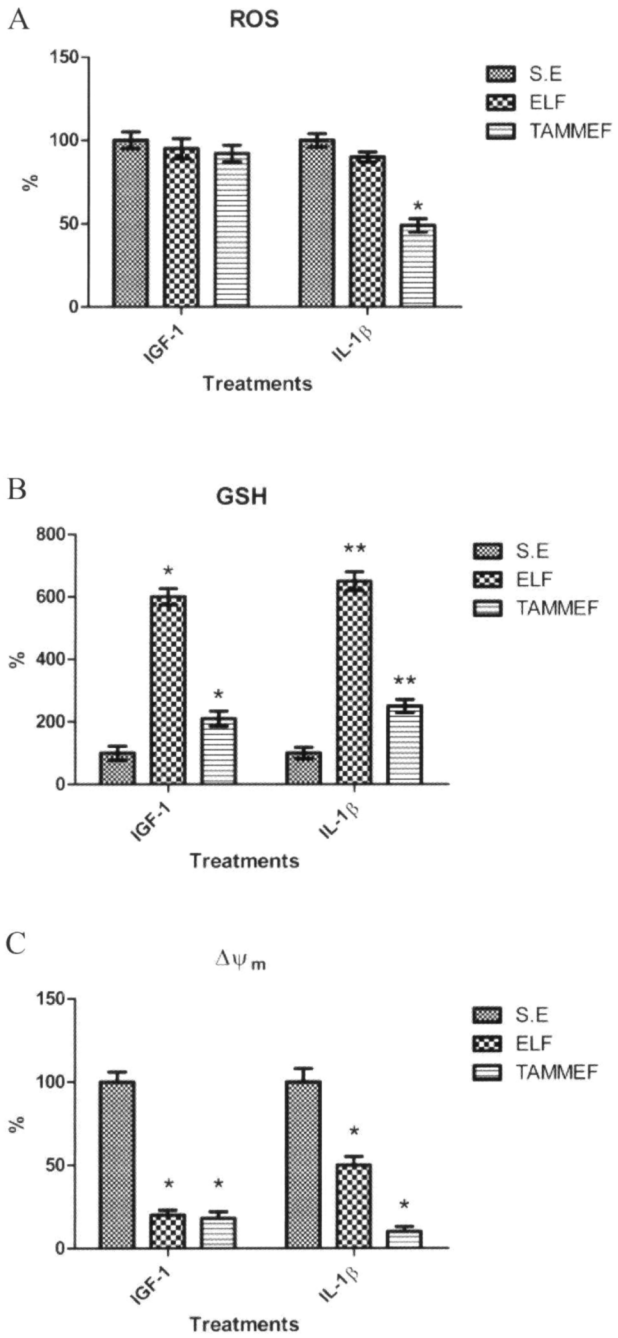

Fig. 6. *ROS (**a**), GSH (**b**) and ΔΨm (**c**) production by cells treated with IGF-1 (5ng/ml) (left) and IL-1β (5ng/ml) (right) exposed to electromagnetic fields. Data are expressed as % ± SD.*

our *in vivo* studies. Finally, in another *in vitro* study (data not published) we investigated the proteomic expression of human osteoarthritic chondrocytes exposed to TAMMEF, ELF and sham exposed (S.E). What we found was a different expression of proteins involved in specific biological mechanisms (such as metabolism, inflammation, oxidative stress, protease inhibition, cytoskeletal regulation and apoptosis), before and after ELF and TAMMEF treatments, respect to S.E. In particular, we evidenced that proteins involved in the anti-inflammatory response like S100-AA family proteins (39) are significantly overexpressed in TAMMEF respect to ELF and S.E (data not shown). Moreover, proteins related in the protective role to stress response like Mn-superoxide dismutase (SODM) (40) are significantly overexpressed in TAMMEF compared to ELF and S.E (data not shown).

We believe that some of these proteins need to be studied more accurately, since they could express tissue changes due to the pathological process, representing also useful diagnostic and prognostic biomarkers of the disease.

DISCUSSION

In the past, much effort has been devoted to understanding the possible benefits of electromagnetic fields in the treatment of musculoskeletal disorders (41). For many years, the goal of research has been represented by the standardization of the best method able to reduce pain and improve articular functionality. This need has been further emphasized by debated findings regarding the large number of variables or codes (frequency, intensity and waveform) to set up in order to create a EMF which is safe and effective (14). However, several observations have underlined that the ideal EMF profile for one patient may be far from the ideal profile for another (42). Starting from these assumptions, it could be reasonable that the EMF used as the gold standard in extremely low frequency magnetotherapy, generally the ELF field with fixed frequency of 100Hz, could not represent the ideal field for all patients affected by musculoskeletal disorders because of its single frequency (43, 44). Thus, it is likely that different types of ELF EMFs, each with different codes, might be rationally applied to various patients according to their needs.

As mentioned above, it is very difficult to investigate the entire range of codes of ELF EMFs

because it would require a limitless number of tests and a massive workload. In this context, the idea of an apparatus able to create multiple codes in a single application rose up. Due to its capability to generate multiple codes (always in the range of extremely low frequency electromagnetic fields) thanks to a piece of music, TAMMEF system seems to be the right solution to overcome the limits presented by the old systems that were unable to satisfy the needs of each patientand the best solution for each disease. In our experience, TAMMEF systems showed an undoubted efficacy in patients affected by different rheumatic disorders such as osteoarthritis, cervical spondylosis and shoulder periarthritis.

The beneficial effects of TAMMEF system include the decrease of pain and improvement of articular function during the 15 days of treatment, the so called "tail effect" until one month after the end of the therapy, and lastly the possible suspension of any analgesic-anti-inflammatory drugs during the treatment period until one month later. A strong confirmation of these positive clinical results is provided by our *in vitro* studies: they demonstrated that TAMMEF system is not only safe for cells (does not affect cell viability), but also it seems to produce benefits in terms of protection toward the oxidative stress and of modulation of the anti-inflammatory response. Lastly, our *in vitro* study, in particular those on proteomics of chondrocytes treated by ELF-TAMMEF, seem to indicate that they can interfere positively not only with the inflammatory response but also with the tissue repair and growth.

This prospected pleiotropic activity of ELF EMFs is confirmed by different, recent studies performed in other experimental conditions, in which ELF-TAMMEF seem to modulate purine metabolism of human peripheral blood mononuclear cells (45) and also to improve lipolysaccharide (Lps)-induced tumor necrosis factor-alpha (TNF-a) release in human lymphomonocytes (46). Returning to our clinical and experimental studies, we want to conclude this review underlining the need to validate alternative and/or complementary therapies to standard pharmacological ones in the treatments of musculoskeletal pathologies where the reduction of pain and the improvement of functionality represent without doubts the final goals. In this context, TAMMEF system represents a helpful therapeutic means in terms of efficacy and tolerability.

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