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THERMO-MAGNETIC REJUVENATION

Aging and anti-aging strategies

The skin and subcutaneous fatty layer are constantly exposed to a series of naturally occurring mechanical, chemical, and electromagnetic energies whose biological influence is responsible for a highly complex adaptation response of living cells. Cellular response to environmental stress progressively deteriorate with time providing clinically evident signs, universally known as aging. **(Fig.1)** Two main aging processes have been identified: chrono-aging and extrinsic-aging. Chrono-aging is an intrinsic process affecting all cells, tissues, organs, and individuals leading to a progressive decrease in the efficiency of biological homeostasis. Extrinsic aging is characterized by a progressive, random accumulation of functional alterations within cells, lading to an increasing probability of biological malfunction, disease, and death. (14,17,30) When chrono- and extrinsic aging are working together premature aging occurs. Many theories have been proposed to explain the extremely complex mechanisms of aging. One of them focus on the progressive depletion and loss of function of adult stem cells. Adult stem cells have been found in most tissues of adult human organisms. Their role is to provide a constantly active biological source able to guarantee tissue repair and regeneration. Adult stem cells differ from embryonic stem cells which have pluri-potent differentiation capabilities, since they can differentiate into limited lines of cells. They normally reside within specific micro-environments or "niche". Many "niches" have been identified in humans within bone marrow, skeletal muscle, adipose tissue, hair follicle, peripheral circulation, intestinal epithelium, myocardium, lungs, breast, kidney, and brain. Somatic cells have a finite lifespan. They constant loss is compensated by the production of new "daughter" cells originating from adult stem cells. It has been speculated that the acquisition of adult stem cells during evolution in more complex organisms has resulted in a major extension of organismal lifespan – therefore the role of adult stem cells lies primarily in the rejuvenation of aging somatic tissues. Aging of an organism could be linked to a gradual loss of function of adult stem cells leading to a progressive increase of senescent cell population. Chronic environmental insults, inflammatory alterations, oxidative stress, and telomere shortening progressively lead to stem cells dysfunction and/or reduction via senescence or apoptotic death with advancing age. Senescent fibroblasts have been found to secrete matrix metallo proteinases (MMPs) , inflammatory cytokines, epithelial growth factors. Type I collagen is the major structural protein of the body. Collagen destruction, along with other important structural components of the skin, like elastic and reticular fibers, occur over decades. These intrinsic structural alterations are thought to be mainly responsible for the characteristic appearance of aged skin and the additional changes that result from chronic sun exposure. (35) Collagen degradation is due, at least in part, to activation of matrix metallo-proteinases (MMPs) released from epidermal keratinocytes and dermal fibroblasts after UV irradiation. (9,33,34) Heat shock response (HSR) has been proven to effectively protect living cells from progressive cumulative extrinsic- and intrisic-related alterations. Proteins, the functional "bricks" of life, are very sensitive to temperature which strongly influence their performance within and outside living cells. One of the key homeostatic responses involved in maintaining cellular longevity is the induction of a properly efficient heat shock protein (HSPs) response. HSP response is a highly conserved reaction, transversally present in all living cells. This innate cellular reaction must be considered one of the most efficient, primordial, intracellular defence mechanisms against stressful conditions. HSPs can be viewed as "molecular chaperones" synthesized when cells are exposed to potential protein damage. Exposure of cells and organisms to various forms of stress, such as high temperatures, caloric restriction, exercise, oxidative and osmotic stress, heavy metals, proteasome inhibitors, amino-acids analogues, ethanol, glutathione depletion, calcium ionophoresis and metabolic poisons, induce them to preferentially transcribe and translate HSPs. These proteins protect the proteome by folding denatured polypeptides and promoting degradation of severely damaged proteins. In addition to mediating protein quality and functional control, some HSPs such as Hsp27 and Hsp70 directly protect cells against damage-induced entry into death pathways. Optimal HSPs response, in terms of synthesis and activity is essential for cell survival. In contrast,

altered or inefficient HSPs response has been implicated in abnormal growth and development, aging and cellular apoptosis.(5) Triggering controlled, sequential heat-shock responses with subsequent up-regulation of HSPs and extracellular-intracellular signal regulating kinases (ERK; p38 SAPK-2 Stress Activated Protein Kinase; JNK cc-Jun Terminal Kinase SAPK-1) can protect adult stem cells within dermal niches leading to a prolonged "healthy skin aging". (23)
Recently it has been shown that repetitive, controlled pulsed heat exposures can stimulate an increased synthesis of pro-collagen I and pro-collagen III by fibroblasts in vitro. (7) Two seconds heat shocks exposures to 45°C were able to induce fibroblasts to produce pro-collagen I and III with a peak synthesis at 35 days, slowly decreasing after 90 days. Repetitive mild thermal stress has proven effective in providing an hormetic tool to be used in skin rejuvenation, maintaining a good intracellular stress protein profile responsible for reducing accumulation of oxidatively and glyco-oxidatively damaged proteins while stimulating proteasomal activities aiming to degrade damaged proteins and improving cellular resistance to other stressful conditions. Hormesis is a term derived from homotoxicology describing the possibility for potentially noxious events delivered to living cells to actually stimulate cellular function when administered at sub-noxious levels.(26, 27)

Current Anti-Aging Strategies

Overall life expectancy has considerably increased with time along with a paralleled demand for more prolonged social, intellectual and physical activities – future estimate for anti-aging market is enormously increased. Effective rejuvenating procedures should target dermal-epidermal layers as well as subcutaneous tissue with the aim of harmonizing body volumes and overlying external structures. Many rejuvenating procedures have been proposed to slow down or partially reverse skin aging with variable degrees of success. **(Fig. 2)** The majority of patients seeking medical advise to improve their skin prefer to choose from non invasive or minimally invasive treatment strategies associated with minimal side-effects and short recovery time over more aggressive, yet potentially more effective, but riskier procedures. Modern trends tend to take advantage of combination treatments where multiple procedures and energy sources are sequentially or simultaneously combined to produce balanced, three dimensional skin and subcutaneous fat rejuvenation. **(Fig.3)** Personalized rejuvenation strategies should always follow precise patient clinical evaluation in order to provide best possible clinical improvements. Well designed rejuvenating strategies should always take into account the need for a global anti-aging approach. Facial mio-remodelling with BTX-A, bio-volumization with autologous or non-permanent, non-autologous, tissue-compatible fillers, bio-stimulation with PRP and other regenerative strategies have provided a consistent contribution to skin rejuvenation and should be always considered when a balanced 3D skin rejuvenation proposal is to be discussed. Chemical peels, ablative and non ablative full surface or fractional lasers, high intensity polychromatic pulsed light, LED, focused ultrasound, monopolar, bipolar, and multipolar radiofrequency, PDT, subcutaneous fat remodeling have all a definite place in modern anti-aging medicine. (13, 15, 21) Most chemical peels and laser-assisted rejuvenating procedures are associated with variably prolonged down-time and obvious side effects.
Frenetic, highly irregular life style, wrong alimentary habits, and genetic predisposition lead to formation of cellulite and modifications of body fat distribution, mostly associated with localized adiposities. Unfortunately aging is an ongoing, unstoppable process and clinical improvements obtained with rejuvenating procedures gradually return to baseline after a variable amount of time. Preparing patients before more complex rejuvenating procedures and providing effective maintenance treatments to prolong rejuvenating effects should be always an integral part of a well thought rejuvenating plan.

Thermo-magnetic rejuvenation with Multi-Polar RF and Magnetic Pulses

Monopolar, bi-polar, and multipolar RF have proven effective in stimulating collagen synthesis with clinically evident skin tightening effects. (1,4,8,37,38) Properly spaced electrodes allowing deeper RF penetration are able to induce subcutaneous fat remodelling and cellulite improvements. (2, 24) Recently a simultaneous combination of multipolar RF and pulsed magnetic fields has been proposed to induce a three-dimensional thermo-magnetic rejuvenation. **(Fig.4)**
RF passing through living tissue induce a controlled thermal surge along its path going from an active electrode to a return electrode. Water-rich tissue offer less resistance to electricity and warm more slowly than water-poor tissue, like fat, that warm faster and more efficiently. Adipocytes are highly sensitive to

temperature and their survival was recently found reduced after time-dependent thermal exposures. (10,11,20) **(Fig.5)** RF tissue penetration depends on the distance between electrodes positioned on treatment handpieces. The larger the distance the deeper the penetration. Penetration depth corresponds to half of the distance measured between two electrodes touching the skin. RF is able to produce efficient, controlled three dimensional volumetric tissue heating independently from intrinsic distribution of light-absorbing molecules (chromophores) on which laser-assisted photo-thermal effects depend. Only IR-A (760-1400nm) laser wavelengths can be used to produce a controlled volumetric heating since they are positioned within the so called "skin optical window" where main skin chromophores are not absorbing light. IR-A wavelengths are absorbed at epidermal level by 38%, at dermal level by 48%, and sub-dermal level by 17%. Properly efficient surface cooling systems are needed to prevent excessive epidermal heating when IR-A lasers are used in order to reduce treatment pain, possible burns and post-inflammatory hyperpigmentation.
RF technology can be performed on any skin phototypes and does not require epidermal cooling systems.(16) Monopolar and bi-polar RF devices need to deliver electric energy in a relatively long pulses to obtain properly effective electro-thermal tissue effects. Thermal surge is felt by patients as a relatively painful experience. Maintaining tissue temperature within controlled range of values is quite difficult when larger areas are to be treated since active electrodes and inter-electrode distance are quite small in most monopolar and bipolar devices. (25) Treatment time is proportional to the size of anatomical areas to be exposed to RF and is considerably long when small handpieces are used. Perfect contact of full electrode surfaces with the skin is needed during each electric burst in order to evenly distribute RF penetration. Reducing electrode contact surface may generate thermal burns due to excessive concentration of electricity in smaller areas. Poor electrode contact can also produce an "arching" effect responsible for localized epidermal thermal damage. In order to optimize RF treatments delivered to larger anatomical areas multipolar technology was developed. Multipolar RF handpieces are equipped with multiple electrodes positioned at variable distance among them. Electrodes are spaced far apart allowing deeper penetration. Electrodes are sequentially activated according to a pre-set pattern to produce a gradual temperature increase within exposed tissues enormously reducing risk of burns. Temperature can be easily maintained within an effective treatment range without hyper-thermic bursts. Electric paths follow different depths within tissue, depending on the distance between sequentially activated electrodes.MP_2 technology employed by Venus Freeze implemented all previously described RF technical solutions in its octipolar and tetrapolar handpieces working at 1MHz. **(Fig. 6)** Measuring tissue temperature during RF treatments is not easy. Infrared thermometers can be used to instantaneously measure surface skin temperature during RF applications. Surface temperatures are usually 4°C-to-6°C less than intradermal and subdermal temperatures as was recently confirmed by a precise thermo-couple study performed by Dr. Joseph Ajaka (unpublished data). He inserted thermo-couple needles at fixed depths (10mm and 20mm) and found a baseline difference of +2°C in deeper layers followed by a thermal surge of +4°C during RF treatment and a more pronounced thermal difference (+5.5°C – +6°C) during post-treatment resting phase at 5min, 10min, and 15min. **(Fig. 7)**

The idea of combining RF with pulsed magnetic fields is absolutely new and is based on a solid clinical background. We, and the earth where we live, are constantly surrounded by magnetic fields. Earth magnetism, solar storms, weather changes, human-built electric and electronic devices produce magnetic fields. **(Fig. 8)** Even the human body produces weak magnetic fields generated by chemical reactions within cells and ionic currents in nervous tissue. Electromagnetic fields (EMF) consist of electric and magnetic energies. Electric fields are generated by the presence of charged particles i.e. electrons. Magnetic fields are generated by the movement of charged particles. The human body consists of 50 trillion cells harmoniously working together. Should small energy perturbations arise within isolated cell groups, functional energetic imbalance involving the entire body may ensue. When energetic imbalance lasts longer enough, they may lead to a disease state, chronic illnesses, and premature aging. All living cells need a functional membrane to survive and perform their functions. Cell membrane potential is usually 70-90mV. 50% of cellular energy is used to keep this electric potential within normal range.
Using magnetic fields to influence the course of human diseases is not new. A Swiss physician, Paracelsus, used naturally magnetized magnetite to treat epilepsy, diarrhoea and control hemorrhagic states. He believed in the ability of magnets to attract diseases to eliminate them from the body. Mesmer, an Austrian physicians used magnets to improve body healing capabilities. In 1812 magnetic fields were reported to heal tibial non-unions. Magnetic ointments wee developed to treat headache, inflammatory bowel diseases, burns, fever sores, gout, rheumatic diseases. The advent of modern medicine saw considerable interest in magnetic fields. Fukada and Yasuda discovered piezoelectricity and described electric potential of bone tissue in the 1950s.

Basset used specific bi-phasic low frequency signals to treat non-union and delayed healing fractures in in 1964. Non invasive devices using pulsed electro-magnetic fields (PEMF)obtained FDA approval to stimulate bone growth in 1979. The same treatment was subsequently approved in 1991 to treat post-operative pain and soft-tissue edema. Since then PEMF was successfully used in many different fields of medicine and surgery. Orthopedic surgeons use them to reduce post-op pain, stimulate bone formation, and treat non-healing fractures.(18, 29) Plastic surgeons use PEMF to reduce post-op edema and ecchimoses. (19, 22,31) Traumatologists use them to reduce muscular-skeletal pain. Dermatologists prescribe them to treat chronic and diabetic ulcers since PEMF induce vasodilatation and angiogenesis.(6,12) Neurologists use PEMF to treat degenerative and post-traumatic neuropathies, depression, dystonia, migranes. PEMF produces eddy currents within treated tissues. Eddy current is an electrical current generated in conducting systems by changing magnetic fields. These currents oppose the direction of magnetic field responsible or their generation. PEMF uses electrical energy to deliver magnetic pulses through living tissue. Each magnetic pulse induces an electric signal that stimulate cellular activity through a positive interaction with cellular membrane function. (3) Intra-membrane protein distribution was found modified in cellular cultures by 50Hz PEMF, positively influencing trans-membrane ion channels, enzyme production, and receptors. Cultured fibroblasts were found to be stimulated to produce new collagen when exposed to low-frequency PEMFs. Cultured endothelial cells exposed to PEMFs were able to increase their secretion of Fibroblast Growth Factor-2 (FGF-2) three folds, and cultured medium applied to wounds has proven to considerably speed up healing processes. In vitro and in vivo PEMF-related angiogenesis was found to be dependent on endothelial release of FGF-2. Angiogenesis is a biological process consisting of sprouting of new vessels from already existing vascular structures to provide higher oxygen supply to low perfusion anatomical regions. (28,32,36) PEMFs have been considered safe after extensive studies challenging single and repeated exposures using clinical and supra-clinical doses. No cytotoxic or mutagenic activities were detected.

Thermo-magnetic rejuvenation: a time-dependent technique

We had the impression, from preliminary observations, that thermo-magnetic rejuvenating effects were directly proportional to RF+PEMF application time. We therefore studied a group of 16 female patients (age 42-68 – mean 53) affected by premature facial aging performing a different duration split-face RF+PEMF treatment limited to their cheek regions. The study were conducted in accordance with the ethical principles from the Declaration of Helsinki and Good Clinical Practices. After obtaining properly detailed informed consent and pre-treating all patients with the same skin-care regime, the same RF and PEMF parameters were used on both cheeks. Right cheeks were treated first, for a duration of 7 min. and left cheeks later, for a duration of 5 min. Venus Freeze (Venus Concept, Canada) and a tetra-polar MP2 handpiece were used on all patients. PEMF parameters were pre-set by the system at 15Hz, 15 Gauss (1.5 mTesla), 5ms pulse duration. A total of 10 treatment sessions were performed on all patients scheduling 2 sessions per week for five weeks. Clinical images were taken with a Visia Complexion Analysis standardized photographic system with Visia 5 software (Canfield Imaging System – Canfield Scientific, Inc. 253 Passaic Avenue, Fairfield, NJ, USA). Skin erythema was measured using a ColorMeter II (Cortex Technology, Plastvaenget 9, 9560 Hadsund, Denmark). Elastometry values were measured using a Dermacheck Multi Skin Center MC750 (Courage-Khazaka Electronic GmbH Koln, Germany). All measurements were taken on standardized facial anatomical landmarks immediately before treatment (T-1), 60 days (T-2), 90 days (T-3) and 120 days (T-4) after treatment. Subjective assessment was evaluated by analyzing treatment and immediately post-treatment acceptability questionnaires. The majority of patients confirmed an acceptable intra-treatment tolerability grading their experience as good (47%) and fair (47%) while only 6% regarded treatment as barely tolerable. Post-treatment tolerability was reported progressively increasing with time, at one, two, and three hours. No unacceptable tolerability levels were reported. Effective treatment working temperature, measured on skin surface, was set at 40.8 °C ± 0.5°C – corresponding to a dermal-hypodermal temperature of 44.5 ± 0.5 °C according to data provided by Dr. Joseph Ajaka. Surface temperature was measured with a dual laser targeting, non-contact infrared thermometer ZI-9688 (ZicoTech, Kadima, Israel). A pre-warming interval of 61-79 seconds (mean 70 sec.) was necessary to reach an effective working temperature on the right cheek. The left cheek required a pre-warming interval of 50-67 seconds (mean 56 sec.) confirming the induction of contiguous vasoactive reaction deriving from the previously PM2 treated right cheek. Average surface working temperature was 40.72 °C (40.20 – 41.30°C) on the left cheek, and 40.62 °C (40.20-41.00 °C) on the right cheek. **(Fig. 9)** Erythema, interpreted as an indirect sign of increased tissue vascular perfusion, was found more pronounced at T-2 on both cheeks: + 5.58% on the left cheek, and +3.16% on the right cheek.

Subsequent measurements revealed a progressive decrease at T-3 and T-4. Melanin readings revealed increased values at T-2: +9.60% on the right cheek and + 11.13% on the left cheek. Values progressively decreased at T-3 and T-4 confirming a moderate activation of temperature-related melanogenesis. Elastometry values decreased at T2 and progressively increased at T-3 and T-4 reaching +5.79% on the R cheek and + 2.87% on the L cheek. (**Fig. 10)** Textural variations revealed a slight increase at T-2 followed by a decrease at T-3 and an upward swing at T-4. Wrinkle count showed a moderate increase at T-2 followed by a progressive decrease at T-3 and T-4. Right cheek revealed a more significant decrease (-4.29%) than the left cheek (-3.45%). **(Fig. 11)** Data analysis of our split-face study confirmed the effectiveness of MP2 technology in rejuvenating prematurely aged skin. Treatment was well tolerated. No down-time, side effects, and complications were reported except for an isolated case of previously unreported temporo-mandibular-joint syndrome which worsened after the first application of MP2. Treatment was stopped and patient was replaced by another subject. Our study demonstrated also the importance of stretching treatment time to obtain better and more durable results concerning both wrinkle reduction and elasticity.
After our first pilot study confirming the time-dependent long-term effectiveness of thermo-magnetic technology, new treatment schedules have been proposed with the aim of optimizing cellular and tissue response according to their natural biological rhythms. Our present treatment formula consists in one seven-minute treatment per 15 cm^2 body area per week for a total of 6-8 sessions followed by a maintenance treatment scheduled every 30-45 days.

Combination treatments with thermo-magnetic technology

Thermo-magnetic technology has been successfully used also in combination with liposuction surgery preparing surgical areas before procedures and helping treated areas to smoothly recover during post-op time. MP2 technology has been effectively used in fibrotic and fibro-edematous cellulite either alone or in combination with mesotherapy. Bio-stimulation with hyaluronic acid and multivitamins has been improved pre-treating skin with MP2 technology. This technology may also temporarily increase specific light absorption by difficult-to-treat vascular targets like resistant port-wine-stains (PWS) immediately before selective laser micro-coagulation. It can be used to optimize photo-dynamic therapy (PDT) either before the application of photosensitizer precursors or immediately before specific light irradiation.

Conclusions

Aging is a highly complex, integrated biological process progressively affecting all cells and living tissues. Anti aging strategies have become more efficient after modern research allowed a better understanding of some of the mechanisms responsible for natural and induced cellular degeneration. Today non-invasive and micro-invasive procedures are widely preferred by the majority of patients seeking medical advice. Thermo-magnetic rejuvenation with MP2 technology has shown to induce collagen synthesis following fibroblastic activation by endothelial FGF-2, optimise collagen remodelling and extracellular matrix functional activities, increase tissue perfusion, activate effective heat shock protein thermal response able to induce a hormetic rejuvenation when periodic thermal treatments are performed. Treatment is safe and extremely easy to perform. Patient acceptability is high both during treatment sessions and immediately after. Biological response to thermo-magnetic technology is slow and considerable time is required to observe improvements. This is due to the physiologic cellular behaviour induced by sub-lethal stressful conditions which will ultimately contribute to improve their long-term endurance.

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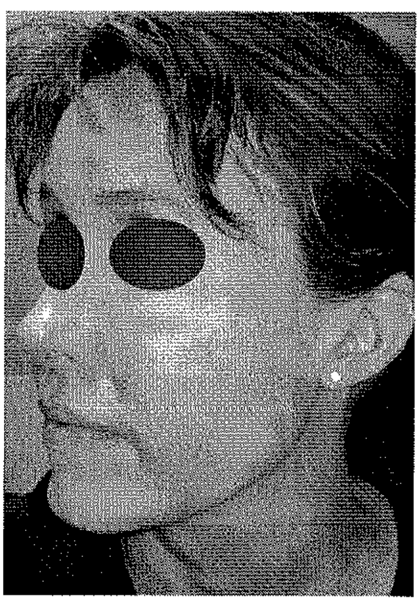

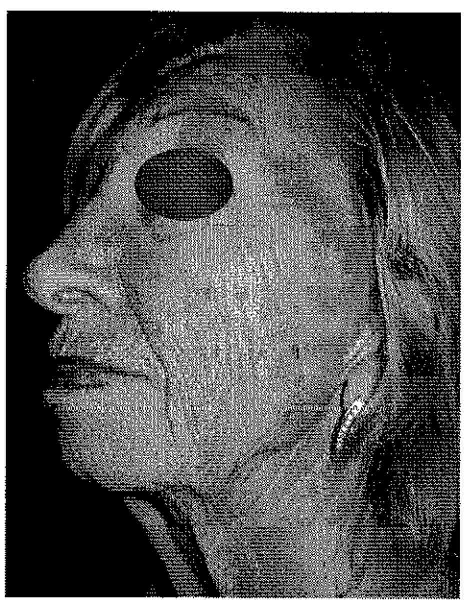

Fig. 1 Fitzpatrick phototype 1-2 young, functionally active skin (left) and deteriorated chrono- + photo-aged skin (right)

Fig. 2 Full face conventional CO_2 laser resurfacing: pre-op clinical image (left) and post-op clinical result at 120 days (right)

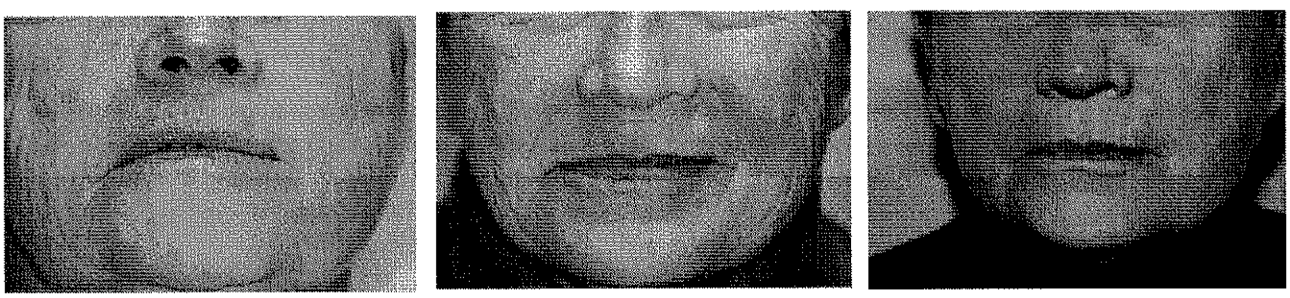

Fig. 3 Single photo-thermal rejuvenation treatment with sequentially combined multiple laser wavelengths according to SPF-RR technique: 1064nm short and long pulse volumetric heating followed by 2940nm Er:YAG fractional resurfacing. Pre-op image (left) and post-op clinical results at 30 days (center), and 90 days (right)

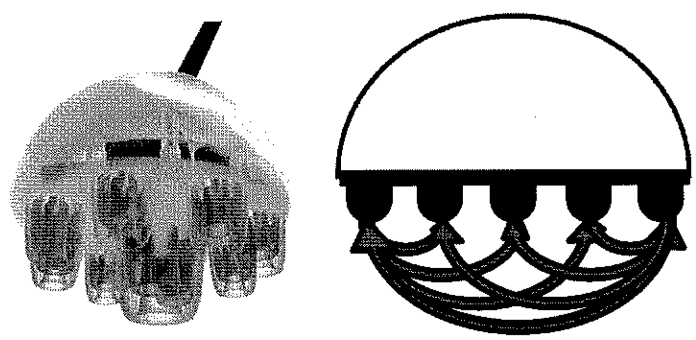

Fig. 4 Multipolar combination of pulsed magnetic fields (left) and matrix-pattern RF (right) within the same effector handpiece as proposed by MP_2 technology. Multipolar electrode array is able to induce a smooth, highly tolerable, three-dimensional volumetric tissue heating.

Typical Sources of Electromagnetic Fields

Frequency range	Frequencies	Some examples of exposure sources
static	0 Hz	VDU (video displays); MRI and other diagnostic/scientific intrumentation; Industrial electrolysis; Welding devices
ELF	0 - 300 Hz	Powerlines; Domestic distribution lines, Domestic appliances; Electric engines in cars, train, and tramway; welding devices
IF	300 Hz – 100 kHz	VDU; Anti theft device in shops, hand free access control systems, card readers, and metal detectors; MRI; Welding devices
RF	100 kHz – 300 GHz	Mobile telephony; Broadcasting and TV; Microwave oven; Radar, portable and stationary radio transceivers, personal mobile radio, MRI

Fig. 8 Table illustrating some commonly encountered electromagnetic fields induced by modern technologies

Time-Dependent Reduction in Adipocyte Viability

Exposuretime (minutes)	Temperature (°C) 45	50	55	60	65
1	89 ± 9	20 ± 3	15 ± 1	17 ± 2	
2		16 ± 2	16 ± 1	17 ± 2	11 ± 4
3	40 ± 19		13 ± 2		7 ± 7

Fig. 5 Table illustrating time-dependent, in-vitro adipocyte viability response to thermal exposures 72 hours post-treatment.. Deep, trans-epidermal RF volumetric heating (working range of 45-50 °C) can remodel subcutaneous localized adiposities by selectively decreasing adipocyte mass and number. Modified from: Franco *et al.* **Hyperthermic Injury to Adipocyte Cells by Selective Heating of Subcutaneous Fat With a Novel Radiofrequency Device: Feasibility Studies.** *Laser Surg Med.*2010; 42:361-370

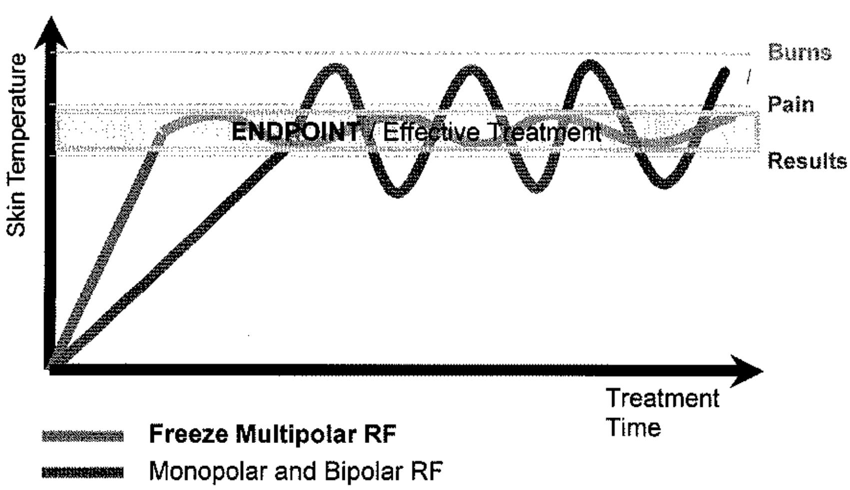

Fig. 6 Graphic scheme illustrating different RF-induced skin temperature variations produced by different RF technologies. Multipolar RF with matrix pattern polar activation is able to reach effective volumetric treatment temperatures faster than monopolar and bipolar technologies. Multipolar RF can keep tissue temperature within effective treatment range more constantly than other RF technologies avoiding excessive and insufficient thermal variations during energy delivery.

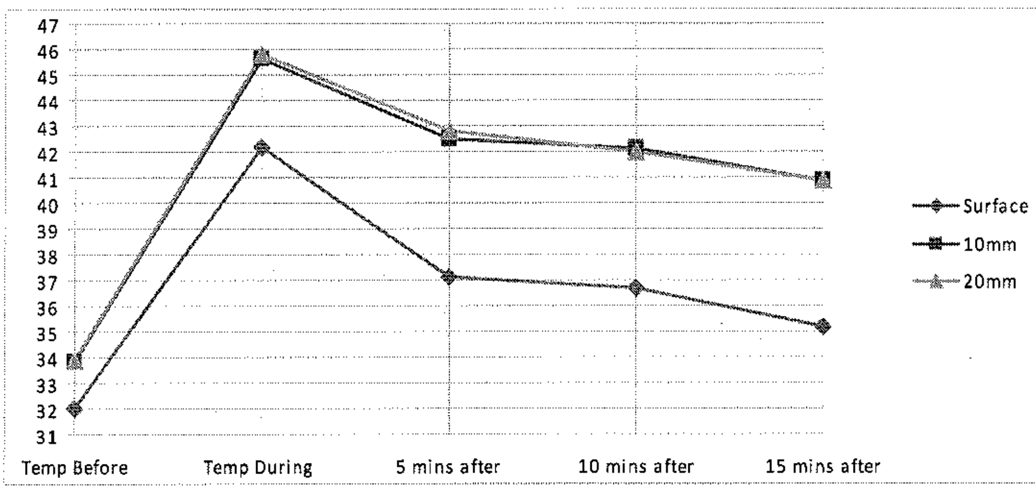

Fig. 7 Surface and sub-surface skin tissue temperature readings during, and immediately after trans-epidermal multipolar RF treatment at 5, 10, and 15 minutes. Thermocouple needles were positioned at 10 and 20mm of depth. Courtesy of Joseph Ajaka, MD

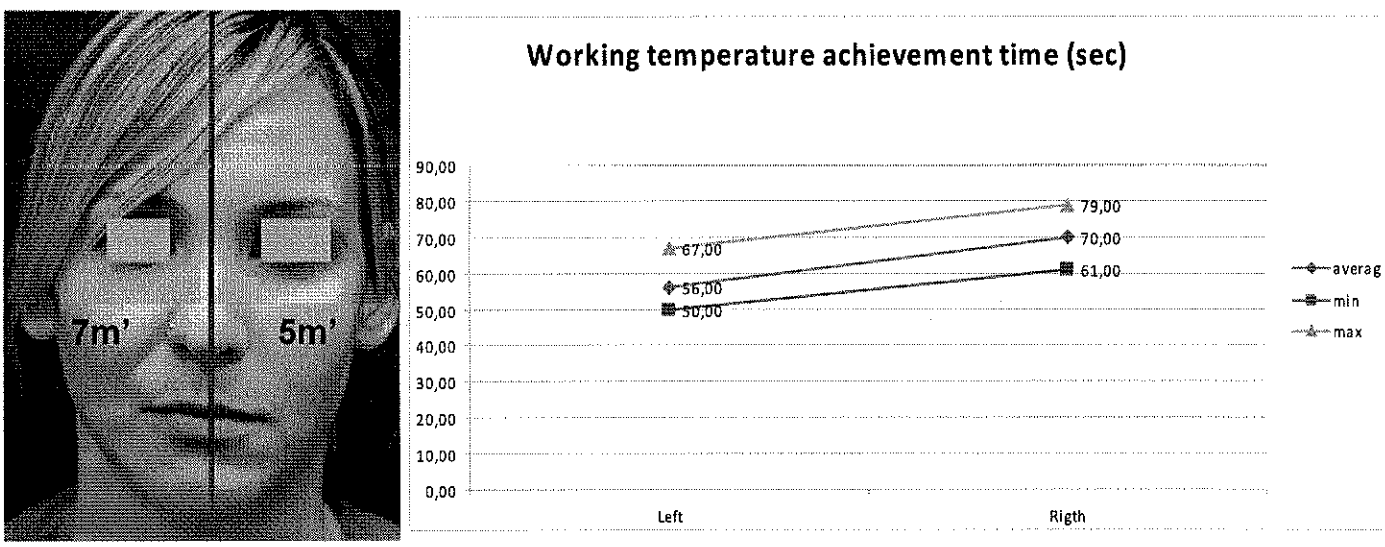

Fig. 9 Split face study with different MP_2 technology treatment times. Effective working temperatures (40.8 ± 0.5 °C) measured by non-contact skin surface IR thermometry was maintained for 7 minutes on the R cheek and 5 minutes on the L cheek. Working temperature achievement time since beginning of MP2 tissue delivery (right)