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Review

Generative medicine - towards a systematization of mechanical compressive microvibration treatments in aesthetic, regenerative, and anti-aging medicine: theoretical bases, tissue targets, and classification

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ABSTRACT

Regenerative medicine is the new frontier of medicine, with a high degree of translationality, which involves different medical specializations, engineering, and information technology. It has as a target the human tissues. Lesions not yet irreversible become treatable. Aging can be re-discussed. In fact, preventive treatments arise; among these, the minimally invasive are particularly interesting. Mechanical treatments are included in the latter. A precise new classification of mechanical treatments was performed in this study. In particular, a detailed analysis was performed relating to mechanical compressive microvibration therapy. Both the tissue target and the bio-physical effects of this treatment were evaluated. All the aspects were analyzed to correlate theoretical expectations with the preliminary results of a research project. The regenerative effects appeared clear, and the absence of tissue damage was remarkable. For these reasons, mechanical compressive microvibration therapy can be included in the typology of mechanical regenerative therapies.

INTRODUCTION

New science has increasingly attracted the scientific community's attention in recent years. This is the so-called science of regeneration, which presents aspects that differentiate it from traditional scientific disciplines. Its innovative character places it at the interface between medicine and biology on the one hand and disciplines that appear more distant from the biological sector, such as engineering and information technology, on the other.

The sector that seems most interested in this new discipline is certainly medicine. In this field, the science of regeneration overcomes the traditional boundaries between medical specialties and sees doctors from very different specialties converge. This arises from the approach of regenerative medicine, which presents itself as an actual tissue medicine, as opposed to the currently dominant approaches, which can be defined as systemic as they attempt to influence the health of the entire organism.

The regenerative approach has a tissue target because a tissue presents a nanostructured biological architecture, as its components are molecules, assembled with a typically bottom-up approach, i.e., molecule by molecule. This approach differs from that used in invasive technologies, where the administration of compounds leads to top-down mechanisms in which the initial volume subsequently progresses to nanometric structures (1).

Furthermore, regenerative medicine is fascinating as it firmly pushes technological innovation (2-4). It requires the constant development of new approaches with a degree of technological evolution, probably higher than in other branches. Indeed, research in regenerative medicine goes beyond academic boundaries due to its high degree of translationality.

The great interest aroused in recent times is also due to the solid preventive aspects of regenerative approaches, which are most useful in treating lesions that are not yet irreversible. This aspect is particularly relevant in the discussion of changes due to aging, which typically affect the entire organism, although with different levels of involvement (5, 6). For these changes, it is, in fact, desirable to institute preventive treatments, which begin already at a pre-senile age and should be minimally invasive.

This last consideration makes it clear that mechanical treatments are preferred in this area but must be optimized for maximum effectiveness. The reference parts for these treatments are the skin and underlying tissues, whose aging has a powerful impact on individuals' self-vision and behavior (7, 8). The superficial localization of the problem and the low invasiveness of the treatments limit side effects and complications.

Furthermore, mechanical procedures allow intervention in vast areas and entire anatomical districts compared to invasive treatments.

In aesthetic medicine, there is a widespread belief that invasive treatments allow visible results to be obtained more quickly than those with mechanical procedures. This is undoubtedly true in some cases, such as volumization with a filler. However, mechanical treatments can lead to structural modifications of the tissue in a physiological or para-physiological way. They can, therefore, more easily lead to a *restitutio ad integrum* of the damaged areas or more lasting maintenance of the effects.

In recent years, our group has conducted numerous studies to evaluate the regenerative effects of various skin treatments. The data obtained, based on the analysis of skin and subcutaneous samples from various body regions, suggest a standard aging process. Despite the apparent differences due to operating causes and anatomical characteristics, some aspects seem to accumulate in all areas.

The samples examined came from both cadaveric and living specimens. In particular, the facial, gluteal-femoral, and abdominal areas were examined. Subcutaneous samples were also collected from periarticular sites. The cadaveric samples allowed the analysis of large body parts, highlighting the aging processes. The living specimens were biopsies. The methods used to analyze living men were ultrasound and elastosonography. At the same time, histology, transmission, scanning electron microscopy (TEM and SEM), and magnetic resonance imaging (RMI) at 7 Tesla were used in the tissue samples. Different techniques enabled us to highlight various aspects of the tissues (9), as some pathologies involve the deep layers of the subcutis (10), resulting in other co-morbidities (11).

The results led to the definition of a classification of mechanical procedures, which was presented for the first time in this work. This classification could be used for all aesthetic, regenerative, and anti-aging procedures.

Furthermore, the results highlighted how mechanical factors that are not generally considered are present in the various treatments.

Finally, as part of a joint project (Joint Project – call for application n. JR2021, CUP B33C21000210008, with the authorization of the University Ethics Committee, n. 6.R1/2022) between the University of Verona and an industrial company (Fenix Group srl, Città Sant'Angelo, PE, Italy), a study of a mechanical compressive microvibration treatment was performed to highlight how its effects could extend to the deep tissues located under the muscle fascia. As tissue targets of this treatment are also interested in other mechanical and chemical or physical treatments, their knowledge has a general value for specialists involved in regenerative or aesthetic treatments.

Classification

Mechanical treatments can be distinguished based on the type, mechanism, and site of action.

Based on the type, exclusively mechanical treatments can be distinguished from combined treatments, in which other intervention methods are associated with the mechanical part. Among the former, manual therapies such as massage can be considered, distinguishing them from those operated with instrumental techniques such as compression, for example, bandages (12, 13), compressive microvibration (14-16), and shock waves (17-19). Among combined treatments, it is necessary to consider the mechanical component operating in parenteral therapies, such as the injection of fillers (20, 21), biostimulants (22, 23) or gases (24, 25), and intradermal radio frequencies (26-28). However, there are also mechanical aspects to treatments performed outside the body, such as capacitive or resistive radio frequencies (29-33), high-intensity focused ultrasound (HIFU) (34-37), and laser treatments (38-40).

As regards the mechanism of action, biological (vascular, muscular, osmotic) or physical (gravity, piezoelectric effect) interventions can be distinguished.

Regarding the site of action, direct interventions operating on the structure itself must be distinguished from indirect ones operating on the surrounding structures and subsequently active on the structure of interest. However, it should be considered that the morphology of the site of action is not static but changes during the treatment if this presents an intense interaction with the tissues. For example, previous work has shown that a mechanical stimulus can induce adipose tissue development. This result is probably due to an action on the stem niches as the tissue created appeared structurally normal, and it was not a simple hypertrophy of the adipocytes. The results obtained on animal models, confirmed by MRI, were clear (41). The possibility of inducing human structural changes has also been demonstrated in the breast and used in clinics for years (42).

Compressive microvibration: analysis of tissue targets

The term compressive microvibration comes from the words microvibration and compression. It is an Italian patent titled Endospheres Therapy (Fenix Group srl, Città Sant'Angelo, PE, Italy).

It involves using a handpiece of spheres arranged in a honeycomb, rotating at a variable frequency. The spheres are produced in different materials depending on the type of effect to be obtained on the tissues.

The rotation frequency of the handpiece balls determines microvibration. The compression is given both by the anti-clockwise rotation movement of the spheres and by the handpiece's traction on the tissues. It is correct to speak of tissues in the plural because this instrument's action involves all tissues, from the epidermis to the muscle, passing through the fascial plane.

Microvibrations range from 29 to 384 Hz, depending on the area to treat, the tissue thickness, and the patient's needs. Higher frequencies were applied to reach the deeper tissues. Therapy lasts from 20 minutes to 1 hour, according to the area and the specific problem to treat.

Regarding the compressive microvibration action, one of the main effects is expressed through the modification, in the target tissues, of what is defined as a fibrotic state, in which there is an increase in cross-links between collagen fibers. The mechanical stretching action generated by the spheres produces a realignment of the fibers, probably following the breaking of the intermolecular bridges. This determines a significant structural alteration of the extracellular matrix (ECM), which also affects the elastic fibers, which become misaligned concerning the collagen fibers. A restructuring of the matrix then occurs with the restoration of mobility and the formation of new cross-linked bonds.

The stretching and vibration actions cause the membrane dipole sensors to activate. In this case, the membrane potential appears to change due to the involvement of calcium channels, which results in an increase in intracellular calcium concentration. This may lead to a contraction of vascular smooth muscle, and subsequently, the effect may extend to cell proliferation and differentiation due to the stimulus on perivascular regenerative units (43).

The mechanical effect also seems to influence pain sensitivity. The stretching and vibration action of the large-caliber Aα and Aβ myelinated fibers, i.e., the activation of the mechanoreceptors, involves two consequent actions. First of all, according to the gate control theory, the nociceptive Aδ (poorly myelinated) and C (non-myelinated) fibers are inhibited, and the painful sensation does not reach the thalamus. Secondly, the activation of mechanoreceptors determines the release of endogenous opioids, i.e., the increase in morphine-like mediators, and there is an absolute reduction in pain.

The activation of the smooth muscles determines a vasomotor reaction of the treated tissues, with activation of the thermoreceptors and dilation of the arterioles and capillaries. There is an increase in circulation and metabolic and catabolic reactions, with an increase in both reparative processes and the "cell kill" phenomenon, i.e., the elimination of senescent and non-repairable cells.

Thermal action is widespread in all the tissues affected by the treatment. In particular, in the muscles, it determines an increase in metabolism and catabolism, an increase in relaxation, and a reduction in inflammatory and pain states. In the connective tissue present both in the hypodermis and at the muscular level, it determines the restructuring of the ECM, as already stated, with the realignment of the collagen and elastic fibers and an increase in the elastic modulus, i.e., the elasticity of tissues. Furthermore, since connective tissue is the body tissue with the greatest piezoelectric properties, electrical energy production occurs, and, once again, it determines an increase in metabolism and catabolism.

Imaging evaluations

The tissue reaction of modification of the ECM is immediate after Endospheres treatment (Fig. 1).

The ultrasound study highlighted how the handpiece's vibration spreads to all tissues, up to the bone. The vibrational effect extends, involving multiple tissues and activating the connective tissue in particular. The action is very deep, with notable involvement of the muscle fascia as well. An increase in echogenicity was noted.

Elastosonography confirmed the immediate structural modification, with softening of the tissues, resolution of contractile states, and redistribution of the structural components (collagen and elastic fibers).

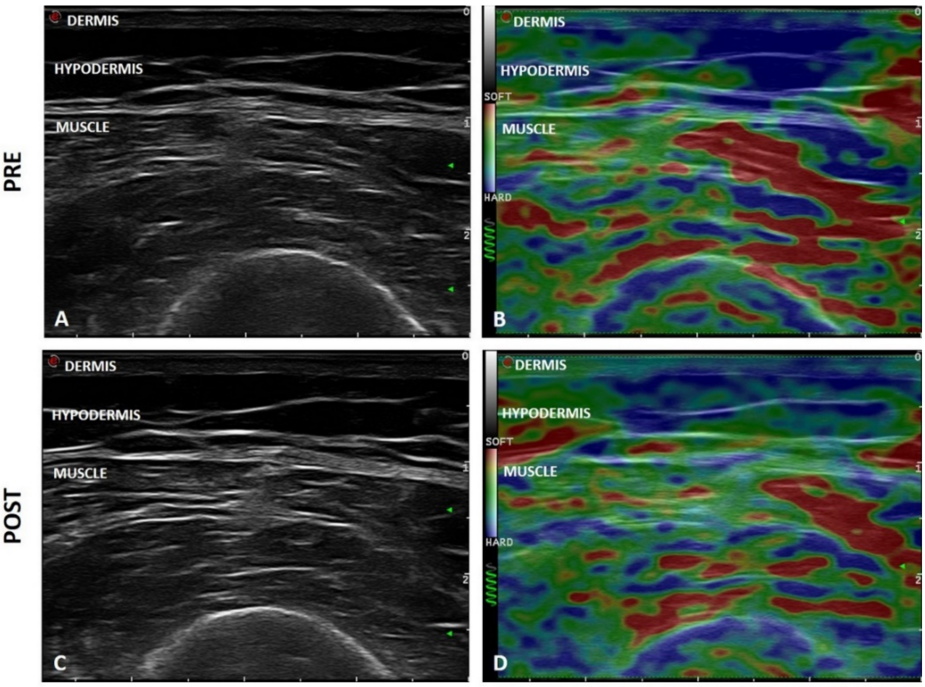

Fig. 1. *Ultrasonography (A, C) and elastosonography (B, D) of pre and post Endospheres Therapy. The therapy was performed on the back for 20 minutes at a frequency correlated to the patient's pain, ranging from the lowest to the well-tolerated one. Ultrasonography highlights an increased echogenicity of connective tissue and ECM, a widening of connective tissue fibers, and a structural modification of the ECM. According to ultrasonography, elastosonography shows a softening of all tissues, the resolution of contractile states, and a structural modification.*

First research line: thermal action evaluation

Thermography allowed us to identify different phases in the responses. The reaction of the tissues to the treatment was characterized by a first initial thermal phase of increase in temperature, probably following the mechanical release of histamine by the mast cells. This is followed by an orthosympathetic phase of vasoconstriction, probably resulting from the action of the autonomic nervous system and determining a reduction in temperature, and a homeostatic phase, in which a rebound phenomenon occurs, i.e., a return to normal conditions.

The thermal action was verified on the thigh and face, and just 45 seconds of treatment on the thigh resulted in a 6-hour thermal reaction. At the cheek level, just 20 seconds of treatment results in the same type of effect we have seen for the front of the thigh, with a 3-phase treatment response and a total duration of effect of 6 hours. A variation in the homeostatic phase was observed between the two anatomical sites since the tissues of the two treated areas differ. While the thigh has much fatty tissue, the face has more fibrous tissue (Fig. 2).

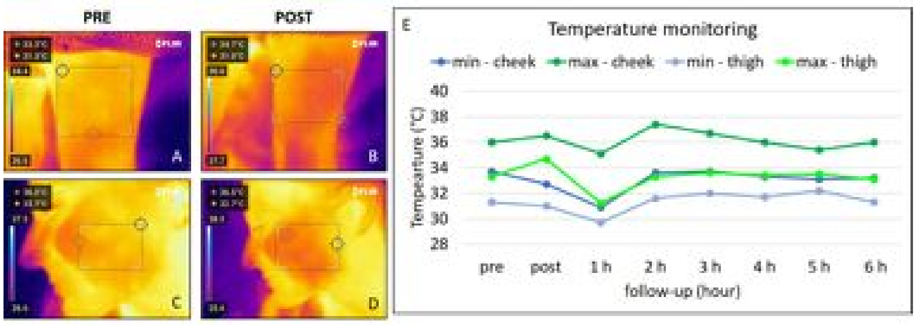

Fig. 2. *Thermographic evaluation of the effects of Endospheres Therapy immediately after the treatment and with a follow-up of 6 hours. The treatments were experiments to evaluate the thermal effect lasting. The treatment was performed on the leg for 45 seconds at a high frequency to reach the deeper structures. The treatment was performed on the face with the face probe at a low frequency for 20 seconds. The evaluation pre-treatment (A, C) lets us appreciate the skin's temperature increase as an immediate reaction to the treatment (B, D). The return to the basal temperature levels is not linear (D).*

Second research line: evaluation of effects on muscle contraction and trigger points

Once again, treating contracted backs with sore muscles resulted in an immediate reaction, always visible, particularly with ultrasound at the connective tissue level. The increase in echogenicity was seen with enlargement and redistribution of the collagen fibers, and with elastosonography, the softening of the tissues was seen. However, it was noted that at 3 months of follow-up, the back tended to return to the initial situation because the muscle contracture was linked to incorrect posture (Fig. 3).

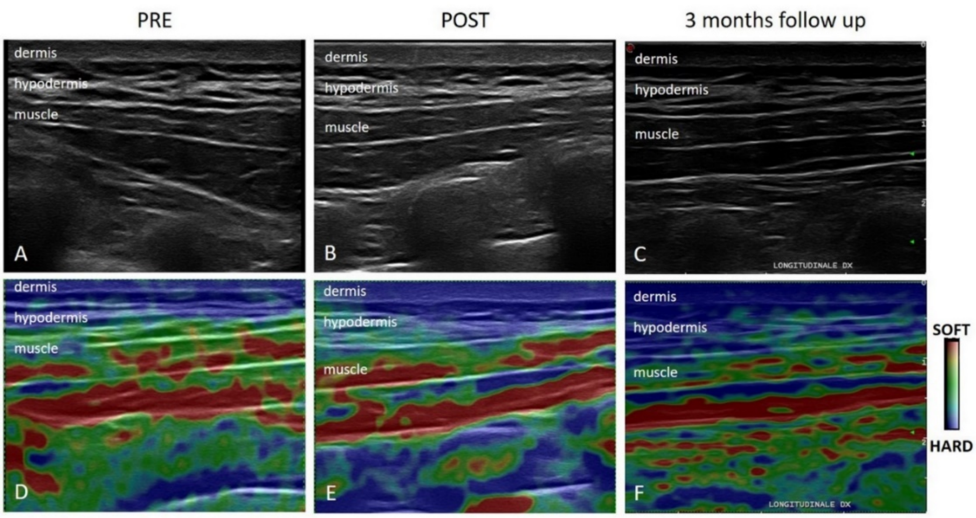

Fig. 3. *The treatment of back-contracture (A, D) results in an immediate response of all the tissues, particularly connective tissue (B, E). The treatment lasted 20 minutes and was focused on the contracted area. Microvibration was performed from a low to a well-tolerated and not painful frequency. After 3 months, the situation seems to regress because the contraction is probably related to postural defects (C, F).*

However, in the case of backs with painful trigger points, the same responses were found both at an ultrasound and elastosonographic level. In this case, however, at 3 months of follow-up, there was no recovery from the painful situation. The action of the mechanical compressive microvibration seems to have resolved the fibrotic state linked to the trigger (Fig. 4).

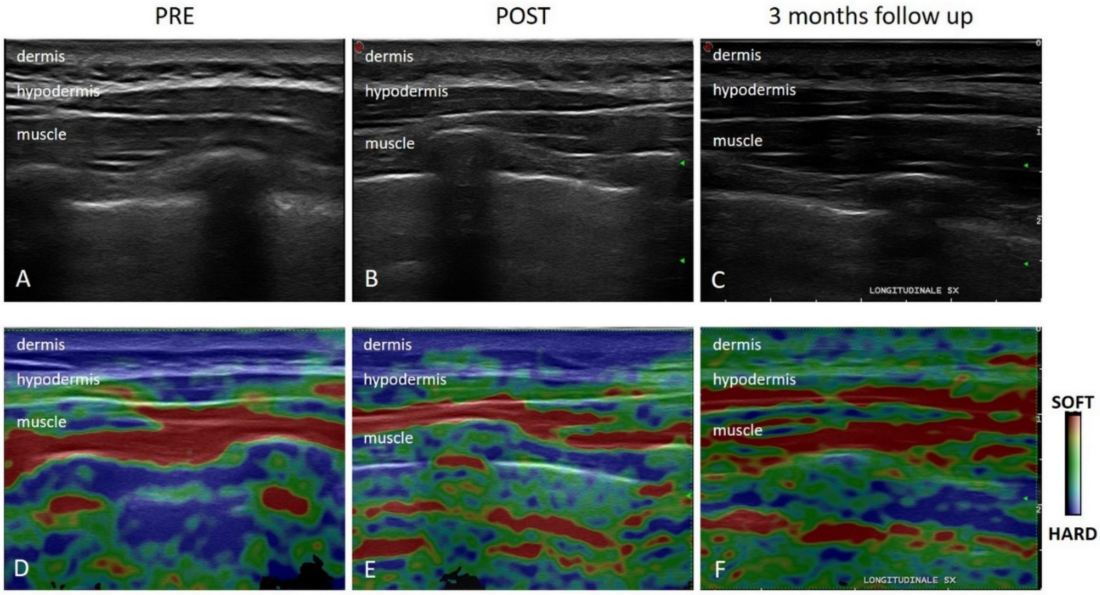

Fig. 4. *The treatment of trigger points of the back (A, D) results in an immediate response of all the tissues, particularly of connective (B, E), as seen for the back's contraction. The treatment was the same as that conducted for the latter, with the same frequencies. Contrary to the latter, the clinic situation seems to improve over time (C, F).*

Third research line: reduction of localized fatty deposits

Activation of the connective components has always been determined in areas with a high adipose tissue content. Already halfway through the treatment, a reduction in the thickness of the hypodermis was observed, i.e., a volumetric reduction of the adipose tissue. At an elastosonographic level, an increase in rigidity was found, which is interpreted as firming of the treated tissues.

This type of reaction was observed both at the gluteal-femoral area (*culotte de cheval*) level and in the abdominal areas (Fig. 5).

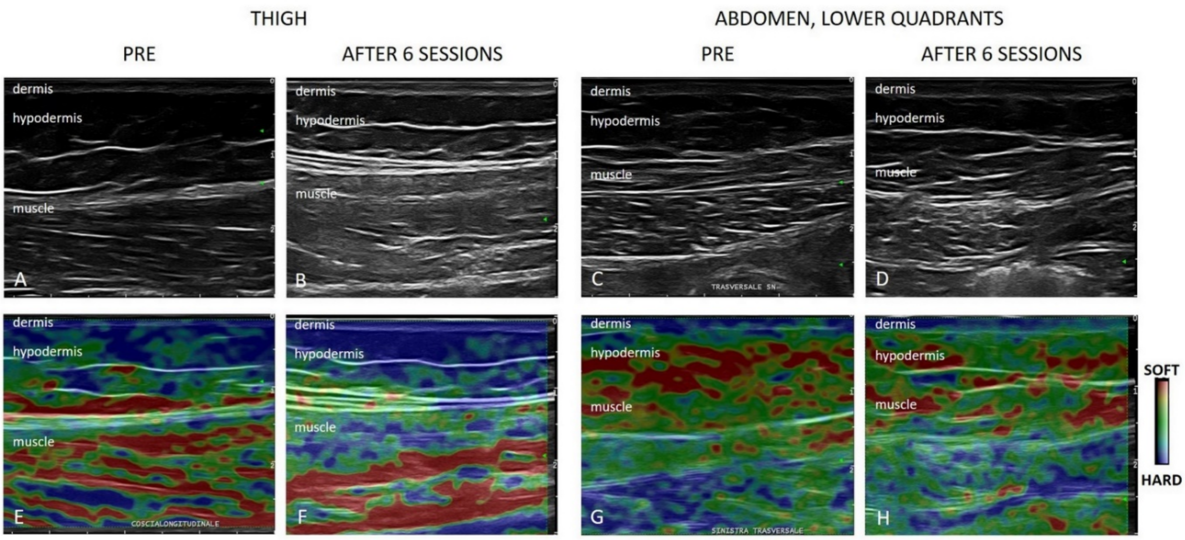

Fig. 5. *In both the thigh and abdomen, an initial laxity (A, E), with softening of tissues (B, F), improves just after 6 sessions of treatment, with a restructuring, in particular, of the hypodermis (C, G) and a tissue recomposition (D, H). The treatment was performed for 20 minutes at a high frequency in both areas to obtain a profound action.*

DISCUSSION

The above considerations and the initial preliminary experimental data show how non-invasive interventions can be combined with injection procedures or with surgical interventions to promote regenerative processes.

In fact, mechanical compressive microvibration could be used as a preventive treatment before another treatment to increase the receptive capability of the tissues and improve the effectiveness of the second treatment, favoring a long-lasting effect. Recently, for instance, the mechanical impact of shock waves was used to activate the fat before fat grafting in saddle nose corrective non-surgical treatments (44). Results demonstrated the efficiency of this preventive treatment.

Moreover, the mechanical treatments might be performed after another treatment to pilot the response of treated tissues. For example, in hand rejuvenation, it is a well-known practice to perform a light massage after a hyaluronic acid filler or fat grafting to distribute the injected product and even out the effect of the treatment (45, 46).

If the three pillars of regenerative medicine are stem cells, scaffolds, and growth factors, this work demonstrates that compressive microvibration acts in a particular way on the scaffold.

It is important to note that Endospheres Therapy is a mechanical technology that exerts a regenerative effect without causing tissue damage (47). Other methods based on mechanical waves, such as microfocused ultrasound, generate a fibrotic state by passing through tissue damage caused by focused microcoagulations, with a consequent repair stimulus. The tissue damage might not be entirely regenerated. For this treatment, the occurrence of side effects is rare. Still, in the 2% of cases, there might be dysesthesia (numbness or hypersensitivity), bruising and stinging, mandibular burns, striations, and contact dermatitis (48). The mechanical effect induced by radio frequency equipment always occurs in conjunction with the thermal effect, which is the *primum movens* of equipment based on this technology. Therefore, the mechanical effect always accompanies and is always secondary to the phlogistic activation resulting from the release of the Heat Shock Proteins. Many different types of radiofrequency are employed in aesthetic medicine and applied in various ways for various conditions. The thermal effect is not always controlled. Major side effects such as burns are described for percutaneous radio frequencies (49), but in some particular conditions, they may occur even with transcutaneous radio frequencies (50).

CONCLUSION

The action of Endospheres therapy determines a complete restructuring effect, not influenced by tissue damage. For its characteristics, it can be considered a mechanical methodology that can be included among the regenerative medicine techniques.

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