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Review

Biological basis of the aesthetic and rejuvenating effects in the skin after the application of the compressive microvibration Endospheres.

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ABSTRACT

Compressive microvibration is a type of stimulation patented as Endospheres therapy. The stimulation, through Endospheres, applied externally to the skin surface, causes changes in the physiological and functional structure of tissues underneath the epidermis, including adipose tissue. Cyclic mechanical stress, induced by this therapy with its particular compressive microvibration, modifies the normal cell cycle of adipose tissue and promotes tissue remodelling due to the activation of the abundantly present mesenchymal-derived stem cells. In this study, a literature revision was performed to elucidate the mechanisms through which the repetitive, cyclic, or modulated/ordered mechanical input of Endospheres, which results in harmonic compressive microvibrations, can have beneficial effects on the skin and all subcutaneous tissues up to the muscles, improving rejuvenation, tissue repair, vascularization, and macro-organization. It was possible to formulate the hypothesis that the ordered frequency and oscillatory dynamics can completely change the chaotic and oscillatory patterns of mitochondria alongside the endoplasmic reticulum membrane in a recently discovered complex known as mitochondria-associated endoplasmatic reticulum membrane complex or mitochondria-associated endoplasmatic reticulum membrane. Analyzing the biochemical and physical characteristics of these structures, it was assessed that the nature of the benefits of the Endospheres stimulation of tissues could include three different origins: mechanical, linked to the transfer of mechanical inputs; biophysical, related to the chaotic biology of mitochondria, the generation of sinusoidal waves, the generation of piezoelectric forces and the thermic effect; and biochemical, linked to the sensory function of adipose tissue. All these forces are discussed in detail.

INTRODUCTION

Compressive microvibration is a type of stimulation patented as Endospheres therapy (Fenix Group srl, Città Sant'Angelo – PE – Italy). Endospheres applied to the skin surface are a typical form of stress, which drastically, but not necessarily in a negative way, modifies the physiological and functional structure of the tissue underlying the epidermis, including the adipose tissue (1, 2). Recently, Biggs et al. highlighted how mechanical forces applied to the skin surface can model the tissues acting on the mechanical properties of the tissues themselves. In fact, the tissues must be considered a complex organization of cells that collectively respond to stimulations. Additionally, the mechanical action determines the alteration in the behaviour of the single cells involved in the stress (1). Skin demonstrates a rapid reactivity to the stress derived from mechanical solicitations, with very high adaptability (3, 4). This circumstance suggests the existence of a great organization, dynamically orchestrated, of the entire skin, from the epidermis up to the deepest layers (1). This adaptability may explain already known phenomena resulting from mechanical injuries and stress, insults, and active stimulations, such as that of Endospheres. The latter seems able to modify the cells of mesenchymal origin underlying the epidermis and their pattern of differentiation/de-differentiation, rejuvenate the tissues, create new adipose tissue, differentiate/de-differentiate resident cells, modulate local staminal cells, and promote angiogenesis (5-7). All these dynamics are correlated to the fact that the cells of the various tissues, particularly the present staminal cells, react to this particular form of mechanical transduction (1, 2, 8-10).

The use of Endospheres to induce effects on tissues and pilot their reaction has already been verified in clinical contexts and appears extremely promising. This utterly non-invasive procedure determines a profound response that can also be exploited in the aesthetic medicine field and anti-aging therapies, as well as in physiotherapy and phlebology. Understanding the biological mechanisms at the base of this action-reaction seems essential. In the present study, we performed a careful literature revision with the aim of clarifying these mechanisms. The literature research was conducted in Pubmed, Scopus, and Google Scholar, using the terms “mechanical stimulation”, “mechanical vibration”, “mechanical microvibration”, and “mechanical massage”, combined with the terms “biological effects”, “adipose tissue”, “mitochondria”, “tissue reaction”. Moreover, cross-references were used.

Endospheres consist of a repetitive mechanical input, slight, mild, or moderate, according to the point of application, the tissues to treat, and the wanted results. The particular structure of the device's handpiece, which includes spheres of different materials arranged in a honeycomb and rotating to exert traction and compression on the tissues, generates particular compressive microvibrations. The latter determine tissue responses with increased drainage, vascularization, catabolism and metabolism, and analgesic and trophic effects (5-7). This clinical data lets the authors state that this input may be able to drastically modify the biology underlying the cutaneous tissues in such a way as to enhance healing processes. In that case, it may be hypothesized that this ordered and oscillatory dynamic can influence the chaotic dynamic of mitochondria. More precisely, it is possible to hypothesize that this dynamic elicits the complex of the mitochondria-associated endoplasmatic reticulum membrane (MAM) (12), promoting the mitochondria-dependent activity on cell fates and survival. In this study, this and other hypotheses on cellular dynamics induced by Endospheres were formulated and widely discussed.

The first effects described on dermal adipose tissue

Bigs et al. and Paul et al. reported that mechanical stress compromises the normal cellular cycle of adipose tissue, targeting its proliferation and differentiation (1, 2). This is similar to what happens with the cyclic elongation. Nevertheless, the tissue remodelling mediated by adipocyte-derived stem cells (hASCs) was promoted (2). These authors considered neo-angiogenesis and extra-cellular matrix (ECM) remodelling the leading drivers of tissue renewal under mechanical stress. For them, the action/reaction of adipocytes was secondary (2). On the contrary, Rigotti et al. demonstrated that mechanical stress, arising from mild trauma or traction forces (negative pressure), can activate adipocytes and/or promote the formation of adipose tissue from the mesenchymal stem precursors present (13). Both groups described a significant staminal activation. How is it possible to explain this activation?

The mitochondrial hypothesis

The cyclic stretching, derived from the mechanical traction of Endospheres, induces the expression of CYP1B1 mRNA (2), which is involved in the xenobiotic modulation of mitochondria (14) and cellular proliferation. This last action is done through the induction of the Wnt/β-catenin pathway mediated by the epithelial-mesenchymal transition (EMT). The involvement of CYP1B1 suggests that a mechanism of redox modulation is also present in tissue renewal following Endospheres (15). This redox modulation may be perfectly associated with the chaotic dynamic of mitochondria, as mitochondrial oscillations around the membrane potential are modulated by reactive oxygen species (ROS).

It has been proven that ROS are key signalling molecules for skin regeneration in some clinical treatments and surgical approaches (16). The capability of an entire compartment, such as the skin, to modulate its shape and structure after Endospheres undoubtedly involved mechanical structures (i.e., keratins or other fibrillar protein structures) and small pleiotropic signalling bio-molecules as ROS. The collective cellular response to a stressful or modulating external stimulus is managed, in particular, by the numerous single macro-intracellular structures (i.e., MAM), adequately orchestrated (17-19). The synchronized action of this complex cell system has already been described (20). It is known that the simultaneous presence of low levels of ROS and high levels of antioxidants is fundamental for regular tissue repair. ROS formation influences cell migration, particularly that of keratinocytes and endothelial cells, the formation of fibroblasts and collagen, and cell proliferation. Notably, in wounds, ROS signalling:

- stimulates the release of tumor necrosis factors (TNFs) and platelet-derived growth factors, favouring bacterial death and preventing infections;
- mediates the transferring growth factor TFG-β1, so favouring migration and synthesis of collagen and fibronectin;
- mediates the fibroblast growth factor (FGF) for fibroblast proliferation and migration;
- express the vascular endothelial growth factor (VEGF) to stimulate angiogenesis, endothelial cell division and blood vessel reformation.

These actions have the last result in the development of ECM, keratinocyte growth and migration, and re-epithelialization (21). It must be added that ROS levels that are too high can significantly affect several physiological processes, such as the activity of transcription factors and phosphatases. The results might be the reduction of the effectiveness of the cellular defense mechanisms and the promotion of skin disorders, photosensitivity, and malignancies (22). A bi-stability in a chaotic bifurcation, a final situation of dynamic equilibrium between mitochondrial-produced ROS and buffering ROS, must be reached (23).

It is also fundamental to detail the role of keratinocytes, particularly their keratin type II K16 and type I K6 genes, in regulating mitochondrial function, and structural turnover must be considered. This role has been described using a Krt16 null mouse strain, an animal model for palmoplantar keratoderma associated with congenital pachyonychia. The intermediate filaments K6/K16 network is responsible for mitochondrial cristae formation, respiration, and dynamics in skin keratinocytes. Their lack (keratinocytes null for both) involves the impairment of mitochondria and the disruption of mitochondrial-keratin interaction, with consequences on the redox homeostasis (increase of ROS levels and alteration of metabolic fluxes). In wounds, the K6/K16 network promotes cellular structural integrity, cell migration, keratinocyte differentiation, innate immunity regulation, and redox homeostasis (24).

Murine models have also allowed Wawersik and Coulombe to discover the particular and predominant role of K16 in the adhesion, differentiation, and migration of Keratinocytes (25).

Finally, a role of fundamental importance in response to Endospheres may also be that of a liker of the nucleoskeleton and cytoskeleton complex (LINC), which integrates cellular nuclei and ECM through the control of intra- and extracellular dynamic and homeostasis (26).

Theoretically, the Endospheres action on mitochondria and MAM should tune mitochondrial oscillation, influencing the intracellular decision-making, including the expression of the survival genes rather than autophagy/apoptosis, the differentiation rather than the de-differentiation.

Summarizing, the biomolecular mechanism that induces the already demonstrated tissue variations, from differentiation to rejuvenation, following the activation Endospheres-induced, should include both a fibrillar thin, regular, and highly ordered organization among the cellular layers and ECM of the dermis and ordered fluxes of signaling biomolecules and of grow/modulation factors. Chaotic sources of ROS signaling, such as MAM, would induce a final tuning of these fluxes as synchronous waves.

Consequently, we may formulate the fundamental hypothesis that the periodicity of Endospheres' frequency interrupts chaotic systems, leading to mitochondrial autophagy and further mitochondrial biogenesis. On the other hand, the interaction between periodic waves and tissues induces the propagation of aperiodic and chaotic waves in the tissues, amplifying the chaotic control of cellular survival and morphogenesis in treated tissues (Fig. 1).

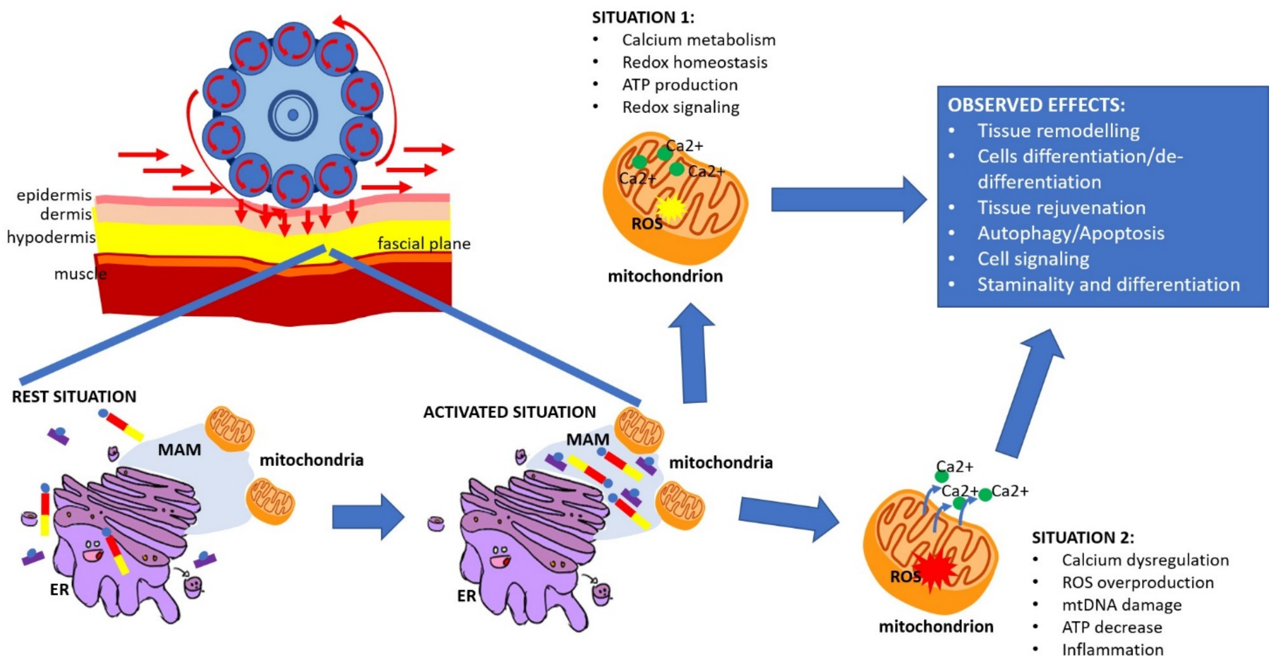

Fig. 1. *Interpretation model of the Endosphere's effects on tissue remodeling and rejuvenation. The continuously exerted vibrational and mechanical forces, typical of Endospheres, elicit a fibril-mediated stochastic resonance in the fibrillar systems of the epidermal and dermal layers. Stochastic resonance is driven to a chaotic dynamic via organized fibrillar systems and relatively disorganized fibrils. Due to prolonged mechanical stress, the chaotic dynamic originates strange attractors (deterministic chaos), which affects the mitochondria oscillating system, thus regulating the chaotic dynamics ruling the activity of ROS and calcium ions as signaling molecules for a long series of cellular functions.*

For this hypothesis to be valid, two fundamental conditions must be verified:
a) mechanical movements of Endospheres must induce slightly aperiodic waves (chaotic waves);
b) the dermal adipose tissue must be a sensitive/transfer organ.
These conditions are discussed below.

Condition a - Mechanical compressive microvibration of Endospheres as oscillatory inputs

The chaotic origin of the mitochondrial dynamic implies that every function of mitochondria, such as redox equilibrium, the bio-energetic function, autophagy, and apoptosis, is on the edge of the chaotic behavior, i.e., these organelles work on the boundary of an unstable dynamic (27). This signifies that deterministic chaos is essential for mitochondria to function optimally as stress-responsible organelles. When mitochondria oscillate in a chaotic condition, a slight but very regular sinusoidal redox and a forced perturbation, as happens with ROS, trigger chaotic dynamics. The described condition maintains the bio-activity of mitochondria in a group of controlled functional phenomena, but with an extensive global impact, e.g., the renewal or the rejuvenation of the tissues, the ordinate maintenance of functions, the functional re-evaluation (through actions/feedback reactions) (20).

Few anatomical and functional studies support this hypothesis. However, it is well known that the sinusoidal input in a chaotic system such as that of ROS, generating a stochastic resonance in many chaotic signalling pathways, guides regular waves of bio-molecules and exosomes (28). This means that a non-chaotic input, such as that of Endospheres, determines a reaction on the tissues stimulated, according to the nature of the components of the tissues. A non-chaotic stimulation of mitochondria involves their chaotic reaction.

Plant studies have demonstrated that ROS, in conjunction with piezoelectric signals, plays a morphogenic role under periodic mechanical stimulation (29). This may also be applied to animal tissues, which involve the chaotic signals of calcium (30).

The complex functional organization of calcium flux of ROS and the bio-electricity presence might represent the main motor through which every cell, with its MAM, contributes to the macroscopic change of wider anatomical compartments.

In other words, a simultaneous microscopic texture of myofibrils and fibrillar proteins acts as the transfer unit of these oscillatory mechanisms, gathering the cells in an overall redundant and ordered action (1, 2).

In this same perspective, the external mechanical solicitations, specific to Endospheres, and the consequent internal solicitations determine structural micro-deformations (diameters of collagen fibrils and fibrillar meshes (31)) and activation of the transforming growth factor-β (TGF-β), which induces a contractile phenotype in the ECM.

Condition b - Role of the dermal fat as a sensor

Since the major part of the ROS signals are correlated with external stimuli, in humans, it is possible that the dermal fat, or dermal white adipose tissue (dWAT), acts as a useful ROS "bio-sensor" to boost the renewal and rejuvenation of tissues, the wound healings and other plastic functions (32). The principal transfer activity of the signal from the dWAT is not of bio-molecular origin but, instead, of bio-physic/frequential nature. Ultrasonography of human dWAT revealed its distinctive structure (Fig. 2), infiltrating the inferior dermis. This structure was interpreted as a sensory structure that capture signals from superior layers.

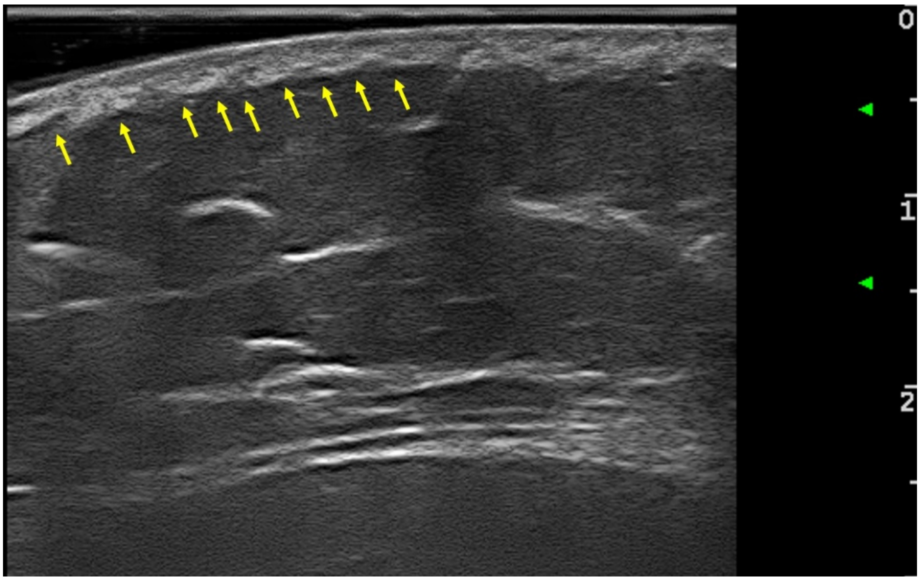

Fig. 2. *18 MHz ultrasound of gluteus maximus reveals the presence of uniformly distributed dermal papillae at the level of the dermal-hypodermal junction (yellow arrows). Segalla et al. (32) have well elucidated the role of these structures as sensors of the adipose tissue (Explicative image. Personal authors' data collected at the University of Verona as part of the master's thesis in "Aesthetic Medicine" by Dr. Kamel Anton).*

The simplest hypothesis about the type of signal that the dWAT might receive and transfer is that its sensorial structures "perceive" fluctuant perturbations from the superior layers and can "inform" the underlying layers of adipose tissue in such a way that action/reaction are orchestrated in the entire adipose tissue, of some its components or of single layers. The adipose tissue behaves like a buffer tissue for ROS activation and as an amplifier of ROS signalling, mainly thanks to its hypoxic microenvironment. For this reason, it is possible that, from superior to inferior layers, the ROS and calcium inputs moved from the dWAT in a hypoxic/normoxic equilibrium, converting ROS's chaotic/oscillatory mechanism into a hypoxic/normoxic dynamic (33). Therefore, the dWAT would perform the converting function of a biophysical mechanism in a biochemical mechanism.

In the hypoxic dWAT, the endospheres' actions should be explained by activating oxygen-detecting sensors, which regulate the whole compartment. The sole important signalling factor of tissue biology is oxidative stress. In such context, it is well known that hypoxia-inducible factor 1-alpha (HIF-1α) is the switch that permits cells to reply to oxygen starvation. When this last situation occurs, HIF-1α is not hydroxylated and is not degraded by proteasomes. In the cell nucleus, HIF-1α associates with the similar protein HIF-1β and, together, the two combined proteins bind to DNA sites and promote the transcription of the genes involved in the metabolism of oxygen deficiency and the remodelling of the circulatory system, with the aim to improve the oxygen transport (34). HIF-1α, as a bio-marker in the cell economy of O2, permits cells to synchronize with mitochondria (35).

HIF-1α is intensely involved in wound healing mechanisms, considering wound hypoxia level. Its activation from dWAT, following Endospheres, should justify the induce mechanisms of regenerative type both a superficial level, in the epidermis, dermis, and superficial hypodermis, and deeper, in the deep hypodermis (36).

DISCUSSION

The hypothesis that Endospheres' action on tissues determines a mitochondrial reaction and a consequent remodelling of the treated tissues seems logical. The biological basis of the effects observed after the application of this therapy is not completed, whether two other aspects are not taken into consideration:

- the piezoelectric action;
- the thermal action.

How is the piezoelectric force generated in treated tissues, and what does this imply? The stress correlated to Endospheres determines structural micro-deformations of collagen fibers and cellular membranes. Like many other biological materials, these structures have piezoelectric properties (37-39). Collagen type I, in particular, is the kind of collagen more present in the human body (in muscle, skin, bone, and tendon) and is equivalent to 25-30% of the entire body's proteins. It is abundant in ECM. Collagen fibers and cellular membranes have piezoelectric properties, so they mechanically alter their structure in response to a stimulus. In this case, the stimulus is the Endospheres' therapy, which determines the development of piezoelectric forces. The action of these forces is the re-aligning of the collagen fibers of the entire ECM, in a direction parallel to the skin surface, according to a coherent behaviour (Fig. 3) (40). The role of piezoelectric signals in bone regeneration and wound healing has already been amply studied (29, 40).

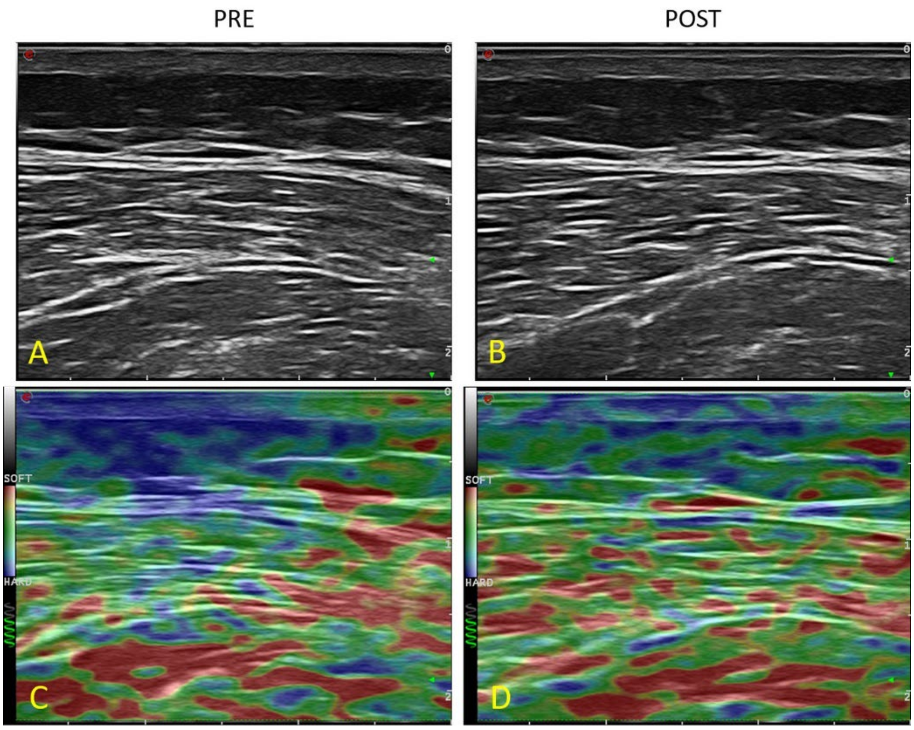

Fig. 3. *18 MHz ultrasound (**A, B**) and elastosonography (**C, D**) pre (**A, C**) and post (**B, D**) treatment with the Endospheres on the anterior thigh in a 44-year-old female. The ultrasound image shows alterations in the distribution of collagen fibers, especially at the level of the muscular fascia. The elastography image shows a change in the elasticity properties of tissues from the epidermis to the muscle. At the dermis and hypodermis level, there is an increase in elasticity, probably linked to the stretching of the tissues. At the muscle level, the increase in elasticity is compatible with an increase in vascularization, induced by both mechanical and thermal effects (Explicative images. Personal authors' data collected at the University of Verona as part of the Joint Project – call for application n. JR2021, CUP B33C21000210008, with the authorization of the University Ethics Committee, n. 6.R1/2022).*

The effects of temperature rise induced as a therapy (thermotherapy) on tissue are well known (41). Classic massages are defined as mechanic massages and cause a limited increase in temperature (42). Endospheres are similar to an evolved mechanic massage (43), and their thermal effect has already been demonstrated (11). So, the Endospheres' vibrational energy applied externally on the skin is transferred as thermal energy to internal tissues from proteins such as Usherin USH2A (44), again causing the ROS formation and the propagation of sinusoidal waves to the underlying layers. Tissue healing is inversely proportional to the depth of the same tissues (42), denoting major effects on the dermis and the superficial hypodermis more than other deeper tissues. Therefore, at the protein level, beyond keratins, the Endospheres' action involves other dermis and ECM proteins (45).

Last, but not least, it is essential to highlight that no side effects have been reported in the published studies on Endospheres' therapy. This means that although the action it provokes is broad and diffuse, it respects, at the same time, normal body homeostasis. The caused redox action is probably within the limits of ROS levels that favour a trophic action on tissues. Moreover, the piezoelectric and thermal actions increase the positive effects of this therapy.

CONCLUSIONS

Further targeted clinical studies are needed to thoroughly verify and deepen the hypothesis and considerations formulated in this study. For instance, to explain how Endospheres inputs act so deeply on skin tissues, it should be done an integrated investigation on how the forces it induces, applied to the skin, permit the renewal and/or the reshaping of the different skin layers, including hypodermis and the fascia-muscular structure, which has been proved to be wholly involved in skin pathologies. This investigation should involve the study of a macroscopic mechanism of cell-controlled synchrony. The last mechanism should subsequently be transduced in a cell-controlled chaotic dynamic held by mitochondria and MAM, and that pilots the leading decision on cells' fate.

Further clinical studies should relate to the possible alterations of the chemical-physical-mechanical properties of the skin, the underlying adipose tissue, and, eventually, the muscles, with the identification of specific biomarkers activated after Endospheres.

The performed review confirms that endosphere inputs may have beneficial effects on the skin and all the subcutaneous tissue, including the muscles. The nature of these benefits may involve three different origins: a) mechanical, that is, the transfer of mechanic inputs through keratins and other micro-structures to mitochondria and MAM; b) biophysical, that is, the creation of a sort of stochastic resonance of ROS in the chaotic biology of MAM, and the generation of sinusoidal waves, the release of signalling molecules, the transmission of piezoelectric forces and the increase of local temperature; c) biochemical, that is the frequency transfer from ROS oscillation to the hypoxic/normoxic dynamic of the underlying adipose tissue, through the dWAT sensorial function.

Authors' Contributions

SV: Writing - Original Draft, Writing - Review & Editing, Visualization. SC: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Visualization. PAB: Writing - Review & Editing. LAQS: Visualization. AP: Writing - Review & Editing, Visualization. AS: Writing - Review & Editing, Supervision, Project administration.

Author Disclosure Statement

No competing financial interests exist.

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