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Letter to the Editor

Compressive microvibration in the cellulite treatment: retrospective study

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Introduction

In 2006, in the Department of Physical Therapy and Rehabilitation at the University of Chieti, a new medical strategy was presented that used a non-invasive methodology capable of causing microvibrations and microcompressions on the tissues. The new methodology was used for the treatment of neuromuscular pain and in sportsmen rehabilitation (1, 2).
In 2007, a preliminary study was performed to evaluate the possible use of that methodology to reduce the pain and the interstitial edema of the so-called female cellulite (3).
The present work is aimed at a critical and retrospective reflection on that preliminary study in the light of current knowledge and experiences, but it is necessary to review the evolutions of the physiology of the microcirculation and the interstitial matrix on which the new strategy is based.

Microcirculation

The seventeenth century was very important for the history of medicine, especially after the

treatise “De motu cordis” was published in 1628, where blood vessels and the “double circulation” were described for the first time, with the effects of ligatures on blood flow (4).

A few years later, a professor of Medical Physiology at the University of Bologna published the treatise “De polypo cordis”, where the very small vessels of the frog lung were described. Not knowing how to define them for how small they were, he described them as hair, calling them “capillaries”, (in latin, vasa for capillamentare soluta ”, vessels that thin like hair) (5).

Thus was born the first definition of “capillary”, with the discovery of important microvascular functions, not only of the so-called “arteriolar” district (therefore of those blood vessels capable of “pumping” blood into the capillaries: trophic-metabolic function), but also in the venous sector (therefore of those blood vessels responsible for the “removal” of blood: catabolic-purifying function) (6).

By “microcirculation” we commonly mean the functional microvasculotissutal units with vessel diameters from 5 to 100 microns, with the precise purpose of “adjustment” of local blood flows to the needs of the organism, which are always different from moment to moment, both for the activities of parenchymal cells (trophic-metabolic activity) and with tasks of “removal” of catabolites and organic waste in general (catabolic activity).

This fundamental concept introduces an important functional aspect, not only organic, in the sense that it goes beyond the idea of pure and simple organ, but is grafted into a multifactorial framework represented by different interconnected organs operating in the same final direction. All this is aimed at safeguarding tissue homeostasis, meaning by this term all the structures that participate in the life of the human organism in everyday life, and not only the cellular apparatus in the strict sense (7).

The fundamental function of the microcirculation is to provide the tissues with oxygen, nutrients, hormones and immune cells, and to remove waste substances so that they can be eliminated from the body. The function of capillaries is to allow the exchange of metabolites between the blood and the interstitial fluid that bathes the tissue cells. Capillaries have an extremely thin wall formed by a single endothelial cell supported by the basement membrane and pericytes, the endothelium regulates the movement of water and materials dissolved in the interstitial plasma between the blood and tissues, and produces molecules that prevent blood clotting. The pericyte is a mesenchymal stem cell that surrounds the vessel and has the ability to contract, reducing the size of the arterioles and thus regulating blood flow and pressure, but it can also turn into a new vessel or macrophage, thus contributing to the metabolic tissue homeostasis (8).

Microcirculatory blood flow shows a typical vasomotility and presents rhythmic oscillations of vascular tone caused by variations in the constriction and dilatation of smooth muscle, which is controlled locally and systemically. The oscillations are generally 4-10 cycles per minute (cpm) and can change with temperature, but also with wide variations in response to particular stimuli, such as heat (which dilates and creates a blood reserve), compression (which creates reactive post-occlusive hyperemia), vacuum aspiration (which dilates and creates “hypoemia” by slowing down the flow rate), cold therapy (which

contracts the vessel and increases the pressure and flow rate), and then there are drugs, posture alterations or electromagnetic stimulations that have vasodilating and angiogenetic action on capillaries and microcirculation in general (9).
The various types of mechanical or electromagnetic stimulation have proved to be useful in the therapy of various vascular, immune, orthopedic and even aesthetic pathologies, the effectiveness of the stimulus does not depend only on the type of stimulation, but also on the time of the treatment time. The synergy between the type of stimulus, the application technique and the duration of the treatment constitutes the essential factor to promote the harmonious activity of "vasomotion" in the microcirculation and the interstitial matrix.

Vasomotion

Vasomotion is the spontaneous oscillation in tone of blood vessel walls, independent of heart beat, innervation or respiration (10, 11).
Vasomotion was first observed by Thomas Wharton Jones in 1852, but the complete mechanisms and its physiological importance were understood later, in the discovery of links between the concentration of intracellular calcium (Ca2) and the oscillations of vascular smooth muscle cells, mediated by the opening of the "calcium channels" that send waves and vibrations along the entire length of the vascular cells (12).
Vasomotion is the harmonic movement of the vibrations in the microvascular side and in the fundamental substance of interstitial matrix, for which there is a need for synchrony between calcium and vascular tone, through an electrical mechanism between vascular smooth muscle cells, endothelial cells and endothelial smooth muscle cells. Then a depolarizing electric current that opens the calcium channels, that have a structural organization very similar to that of sodium channels, with central and accessory subunits in the extracellular side and in the intracytoplasmic side, they guarantee the correct localization and functioning of the channel (13).
Vasomotion is an adaptation and defense mechanism to avoid a possible blood vessel collapse, due to several causes, for example a lack of energy in ATP or in nutrients. In summary, vasomotion ends up being the expression of the reactivation of cellular and regenerative activities of the matrix in those tissues that had reduced the purification and oxygenation processes with the presence of free radicals, tissue acidity, production of inflammatory cytokines and metalloproteases, reduction of activities regenerative stem cells, in conclusion in those tissues that begin to age from the electromagnetic, energetic, biophysical and biochemical point of view. Vasomotion is altered in many pathologies, such as hypertension or diabetes, but also in all those tissues that begin to reduce their metabolic activities, with reduced use of oxygen in the mythocondria and with presence of free radicals, so with a tendency to evolutive fibroedema (14, 15).
Aging begins like this, even all alterations that lead to the aesthetic evidence of cellulite.
Using physiotherapy treatments on the female

thigh to reduce the skin alterations of the cellulite, already at the end of the last century the attentive observers had understood that there was not only a vascular response of drainage or vascularization, but also a general effect on the tissues, from the skin to the muscle fascia, with a restructuring of all tissues. Doctors already knew that the target of any physiotherapy treatment is not only the microcirculatory system, but the fascial system and the interstitial matrix, the so-called "interstitium" which is not a "passive" structure, but absolutely it is an "active, alive and vital structure", an essential system for the activation of the microcirculatory system and the complex regenerative system, working as a real organ.

Interstitial matrix

The interstitial matrix (ECM – ExtraCellular Matrix) represents the mother of all vital reactions, the place where the exchanges between matter and energy take place, "All tissues are connected and functionally integrated to each, not in closed systems, but in open systems; between them there are continuous exchanges that can take place both locally and systemically, exploiting biochemical, biophysical and electromagnetic messages, that is, using the various forms of energy" (16).

The ionic composition of the extracellular interstitial space constitutes the fundamental substance that, not only allows exchanges and life itself, but also acts on the gene expressiveness of each cell: "The cell and the extracellular matrix represent two worlds only apparently separate, because they interact throughout the duration of life and at any moment, in a correct and synergistic way with an extraordinary series of signals followed by an equally incredible series of biological and molecular activities" (17).

The ECM is a structure in perennial and constant morpho-functional "remodeling", both in physiological and pathological conditions, it is an infinite biochemical network able to generate, modulate, change and propagate, even at a distance, millions and millions of information. After years of study, researchers at the Mount Sinai University in New York were able to see and identify the extracellular matrix with confocal laser endomycroscopy (pCLE), that provides histological imaging of human tissues in real time, at a depth of 60-70 µm. The definition of the interstitial matrix, the so-called "interstitium", as the "largest organ of the human body" has opened an important window also in the field of regenerative and aesthetic medicine, given that the main characteristic of the interstitial matrix is the "plasticity", thus acting as a shock absorber, container and harmonizer, in order to favor the various functional activities and microcirculatory actions of the organism (18).

The new knowledge has also brought interesting developments also in regenerative medicine thanks to the characteristics of the matrix, where stem cells, growth factors, pericytes and macrophages act, together with many other elements that work in a harmonious synergy of information transmitted biochemically and biophysically, above all by vibrations. Today we know that "vibrations" are the tool for the communications

between cells, in the fundamental substance and in the microcirculation. In fact, it is precisely in the good relations between matrix and microcirculation that microvascular adaptations develop, both to the various needs of the tissues, and to the physiological angiogenesis, when necessary.

Cellulite

Cellulite is one of the most frequent beauty problems in the female world. Despite the different opinions about the clinical classification of cellulite, the diagnosis is always the fundamental moment, while the treatment is often the result of empirical therapeutic attempts which are not based on a precise rationale included in acknowledged protocols.

The so-called "PEFS" (Edematous FibroSclerotic Panniculopathy) is a dermal and hypodermal alteration starting with venous lymphatic stasis and resulting in fibrosis and after in connective sclerosis. This physiopathological evolution is generally referred to any type of cellulite, although this skin irregularity that visually appears in the form of dimpled skin, may be associated with various types of tissue alterations, as alterations of adipose tissue, connective tissue, venous-lymphatic system and the interstitial matrix" (19).

Cellulite can be an expression of four "main moments":

- Increase of subcutaneous adipose tissue, with pain, heavy legs and evolutive lipodystrophy, sometimes with edema in the thigh but not in the foot (adipose cellulite and lipoedema).
- Increase of subcutaneous adipose tissue and lymphatic fluid, with pain, heavy legs and edema in the calf and foot (lipolymphoedema).
- Evolutive connective tissue fibroedema, with pain and heavy legs, but without of edema in the calf and foot, and lipodystrophy in the tight (fibrous cellulite).
- Increase of localized fat tissue, without pain or periferical edema of legs (localized adiposity).

From a clinical point of view, the first three forms (adipose cellulite, lipolymphedema and fibrous cellulite) are all characterized by pain in the thigh and heaviness of the legs, all treatments normally begin with a lymphatic drainage or connective massages, to which different therapies are associated depending on the indications, such as carboxytherapy, mesotherapy, ozone-therapy, laser or surgery.

Compressive microvibration

In the tissues of the human body (particularly in dermis and fascia) there are typical corpuscles that function as receptors to various stimuli (mechanical, thermal and painful), for this reason they are called mechanoreceptors, pain receptors and thermoreceptors (20).

When stimulated or compressed, or subject to vibration, these emit signals that favor various

activities thanks above all to the opening of the sodium and calcium channels, resulting in lymphatic drainage, activation of endorphins, better vascularization with increase of physiological temperature, collagen remodeling and regenerative trophic action, but they are also useful both for avoid a greater danger, such as a burn, and for increase the value of certain activities, for example palpation in the medical clinic or at professional work.

The end of the XX and the beginning of the XXI century have seen interesting evolutions in physical therapy, especially in the so-called physiotherapy of well-being, with the improvement of the various types of lymphatic drainage (as Vodder, Földi, Leduc o Casley-Smith), the introduction of acoustic and mechanical waves or the use of vacuum therapy.

In 2007, a new non-invasive methodology was presented, called Endosphères Therapy, which used microvibrations by particular rotating spheres that, sliding on the tissues, obtained draining, vascularizing and analgesic effects (21). After studies performed in the Department of Physical Therapy of the University of Chieti-Pescara, this methodology was initially used to reduce pain in athletes or in neuromuscular pathologies. In 2008, the researches evaluated its use to reduce painful symptoms of the edematous cellulite and adipose cellulite, the work was presented at the Congress of the Italian Society of Aesthetic Medicine and Surgery in Bologna, and constituted the first presentation about the new methodology in the field of phlebo-lymphology and aesthetic medicine. The present work is aimed at the retrospective and critical review of that study in the light of current knowledge.

Materials and Methods

The method used in the study is a new generation electronic device characterized by a mobile handpiece that contains a particular "cylindrical device" with inside 55 small spheres of soft silicone, rotating at different speeds to transmit particular "microcompressive and microvibratory stimuli" at different frequencies to obtain different effects. The operating cylinder has a weight of 1700 gr, which is the ideal weight calculated to transmit the correct working pressure of the balls on the tissues, while each sphere has the diameter of 19.5 mm, which is the ideal measure calculated to transmit the rotation frequency on 1 cm2 per sphere, the "bee-cell arrangement" of the spheres on their axes of rotation favors the transmission of frequencies and creates the effect of vascular gymnastics.

Based on the stimuli of compressive microvibration transmitted to the tissues from the dermis to the fascia by the rotating spheres, the therapeutic effects sought are based on well-defined variables, including the direction of rotation of the spheres and the treatment pressure applied on the tissues. These features create an effect of positive / negative pumping on the tissue itself and a displacement of the interstitial fluids. This microvibration is variable in frequency (from 40 to 255Hz -Tst), where TsT is the estimated time of treatment on each point that changes depending on the movement of advancement of the handpiece in different indications. This variable produces the

different vascularizing, analgesic, draining and / or restructuring effects (Figure 1).

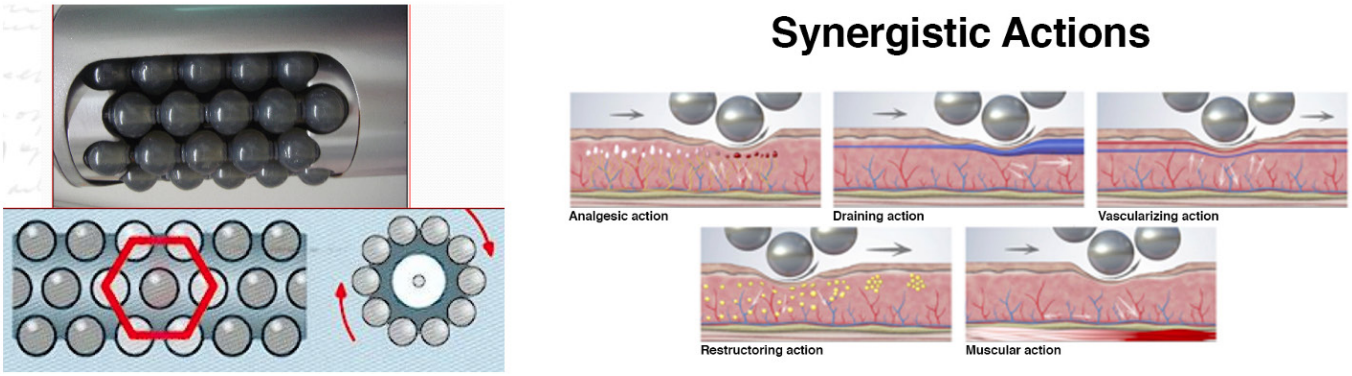

Fig. 1. *To the left, the bee-cell arrangement of the 55 spheres in the cylinder, on the right, different therapeutic effects.*

Endospheres methodology is capable of stimulating and modifying the resistance and elasticity of the connective tissue in order to restore the correct functional fluidity, consequently creating a deep muscle relaxation through mechanical oscillations, these vibrations are obtained through the particular honeycomb-like arrangement of the spheres which rotate on themselves rapidly and cause a pulsed and rhythmic movement. This methodology, referable to "compressive microvibration", also allows you to work on the main muscle groups, resulting in a significant sedative action on the hyperexcitability of the nerves, both motor and sensory.

These receptors are functionally joined to mechanosensitive nerve endings that exist in the skin, in the muscle, in the periosteum, capsules and joint ligaments, do not all respond to the same vibration and there are differences in the response according to the frequency of the stimulus. Receptors react mainly by reducing the pain symptom and stimulating the connective tissue restructuring. The pressure with which the vibration is exerted can greatly affect the results and the result is also linked to a physiological increase in temperature.

The foundations of the "Endosphères Therapy" are aimed at obtaining a draining action on lymphatic stasis together with an increase in tissue vascularization, thus an increase in the number of vessels used by the microcirculation to have an increase in perfusion and tissue oxygenation, with an increase in local temperature and improvement of metabolic and cellular activities (22).

The metabolic activation associated with the stimulation of particular energy points, finally leads to the reduction of pain and heaviness in the lower limbs.

Methods

The study identified 20 female patients between the ages of 20 and 48 who had spontaneously presented themselves to undergo treatment for painful cellulite. These patients presented clinical pictures of "Dimpling skin" in edematous-adipose cellulite, in the absence of primary lymphedema, systemic edematous pathologies or current therapies. The authors did not receive financial support, industry had no role in the analysis and interpretation of data. The authors declared no conflicts of interest.

Of these twenty patients, 10 patients had an adipose cellulite with interstitial edema at the thigh (adipose cellulite) and were slightly overweight (BMI 25-28), the other 10 patients had a lipolymphedema with edema of the legs and normal weight (BMI 20-24). All patients referred heaviness of the lower limbs with a soft edema in the evening or after prolonged standing. All patients had two and three stages of cellulitis, with fine granularity and micronodularity of the subcutis, due to evolutive fibroedema.

The treatment was performed in all patients with standard protocols, with a cycle of 20 sessions, of which three sessions in the first week and two sessions from the second onwards. Each session lasted 40 minutes according to protocol which indicated in the anterior region of the thigh the treatment of the adductive zone, of the lateral band, of the quadriceps and of the anterior tibial zone, as well as in the posterior region of the buttock, the lateral band, the gastrocnemius and plantar fascia. All treatments were carried out in caudocranial direction, the recommended frequencies were 80, 110 and 130Hz repeated in the same area three to five times.

Results

All treatment sessions were well tolerated. The results were evaluated on a scale of 1 to 10 represented by the VAS numerical scale that is used to assess the extent of pain reported by a patient.

The used VAS numerical scale indicates values from 1 to 10, where 5 is the border point between insufficiency and sufficiency, with 1 being the minimum and 10 being the maximum.

Patient evaluations:

In the study carried out, 90 % of the twenty patients were satisfied (18 patients), the two unsatisfied patients performed the treatment discontinuously. In the ten patients with an adipose cellulite of the thigh and slightly overweight, 100% declared themselves satisfied in terms of pain reduction, with a rating of 9 in the VAS scale, and improvement of the skin appearance of cellulite with satisfaction of 8,5 on a scale of 1 to 10 (Figure 2).

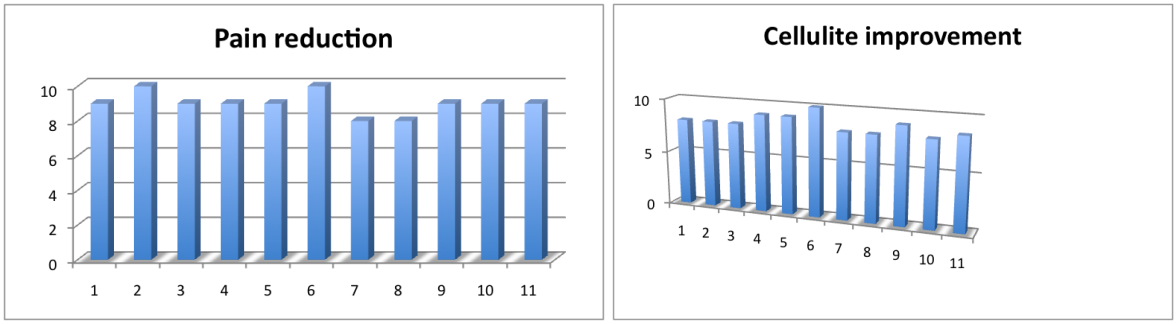

Fig. 2. *Adipose cellulite: Pain reduction and aesthetic improvement after Endosphères by VAS scale (n.11 is the total average).*

In the ten patients who had lipolymphedema with peripheral edema, the level of satisfaction was 80%, because two patients had not followed the treatment correctly, the other patients reported reduction of painful symptoms and heaviness, with a rating of 7 on the VAS scale. From the point of view of "Orange peel", the level of satisfaction was 8.4 on a scale from 1 to 10 (Figure 3).

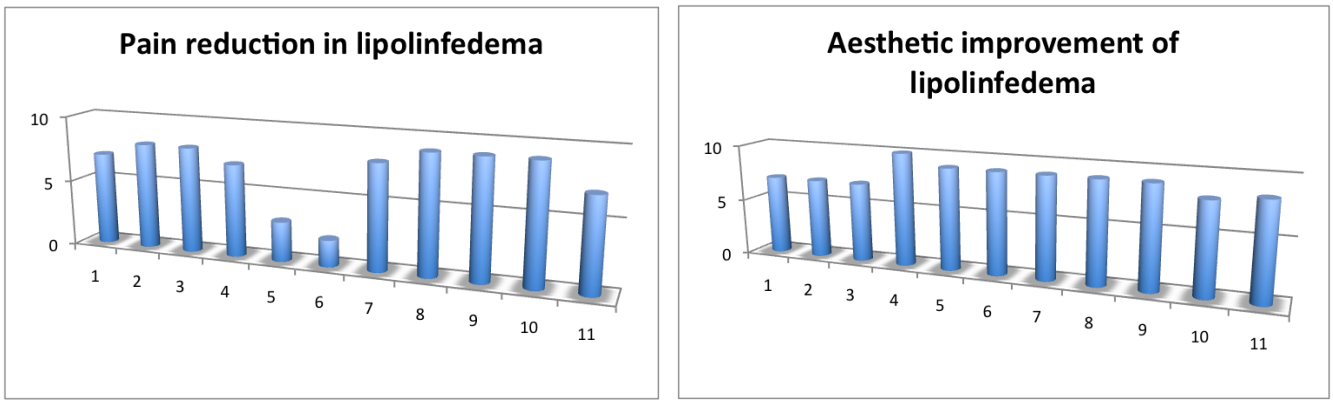

Fig. 3. *Lipolymphedema: Pain reduction and aesthetic improvement after Endosphères by VAS scale (11 is the total average).*

The study shows a general satisfaction of the patients, with reduction of pain and improvement of the unsightly skin irregularities in both cases of cellulite, as VAS scale shows in the result of the improvement of cellulite, with 8.5 in adipose cellulite and 8.4 in lipolymphedema, while the pain reduction is instead more evident in adipose cellulite, with 9 compared to 7.

This data is very important and confirms that pain is not only given by lymphatic stasis, but by hypoxic alterations that are associated with free radicals, tissue acidity and tissue energy decrease, in summary by the reduction of cellular activities in the interstitial matrix. The lymphatic stasis is certainly important, but cells react first to the vascularization and increase of temperature than to lymph reduction.

Discussion

This retrospective study is aimed at the critical review of the first presentation done in 2008 about the effects of a new non-invasive physical therapy used for edematous and adipose cellulite treatment. The present study intends to interpret that our work, both in its scientific rationale with the knowledge of the time, and in the reflections that can be deduced in the light of current knowledge and experiences, fifteen years later.
The study was born on the wave of curiosity and enthusiasm created by a new treatment that had proved interesting in reducing pain and promoting fasciomuscular rehabilitation, but the first observations indicated effects that could also be used in other sectors, such as phlebolymphology and lymphatic aesthetic pathologies.
If today we evaluate that preliminary study only by the methods and the results obtained at that time, it is certainly difficult to find evidence and a scientific value, but if we change the point of view, we can find many points that must absolutely be re-evaluated with deep reflections, in particular if we observe that work referring to the period in which it was performed, to the premises, to the reasons and purposes for which it was performed, above all considering that new methodology as one unknown and in some aspects revolutionary technique. In addition to this, it is interesting to understand that presentation, made in a Congress of Aesthetic Medicine in 2008, as the first presentation of the so-called "Compressive Microvibration", with some effects over time, both on scientific knowledge and on the possibilities of professional work that opened up in the following.

The work

The preliminary study used a classic scheme for non-experimental observational clinical works, with an appropriate number of patients undergoing the same therapy, for a suitable period of time to obtain a result that can be assessed subjectively and objectively. In the work in question, the purpose of the study was to evaluate the reduction of the thigh pain and heaviness in the legs in cases of edematous and adipose cellulite.
The VAS scale was the method used for the assessment, the treatment performed was a new and unknown non-invasive therapeutic technique of physical therapy that used a new tool with a new, and in some respects revolutionary mechanism of action.

The methodology

In 2006-2007 the new Endosphères Therapy was only a bioengineering project based on the classic knowledge of manual lymphatic drainage, on vacuum therapy and on manual and mechanical methods of non-invasive physical therapy, but also on the new knowledge of trigger point and

of the energy point of stimulation, in addition to the new knowledge about the interstitial matrix and cell biology. Compressive microvibration was not known, without scientific publications or presentations at conferences, but only some technical observations made in University or medical centers of reference.

In 2008, after the first presentation of the new methodology as a useful physical therapy for muscle recovery, the attention shifted to the field of phlebolymphology and related aesthetic pathologies, where the first observations showed interesting results in the reduction of pain in the various forms of cellulite, to which was added a constant vascularizing effect. The vascularizing effect with thermal increase has resulted over time the main action's mechanism of Endosphères Therapy.

The variable frequency of oscillation of the "compressive microvibration" device mounted on the handpiece that works on the skin level with a predetermined protocol, creates a "positive/negative pump effect" which allows a displacement of liquids reducing stasis, also a significant vascularization that activates the "Vasomotion".

In the fundamentals of bioengineering of Endosphères Therapy, the goal of the treatment was the possibility of obtaining a "vascular gymnastics" by micro-vibrations and micro-pressures, with "micro-lifts" of the skin and subcutaneous structure as a whole, working simultaneously on the lymphatic areas and on the arteriolar microshunts to increase the vascularisation and local temperature.

On this basis, already at that time it could be deduced that the Endospheres Therapy could have counteracted the imperfection of cellulite, acting by microcompression and microvibration to realise passive mouvements on different tissue layers and on the mechanoreceptors, in order to inhibit the tendency to fibroedema of the interlobular-adipocyte septa.

Observing the results of those first twenty cases of the study, united only by the imperfection of cellulite with thigh pain, makes us understand the historical value of that first preliminary work in the field of so-called aesthetic medicine, because it highlighted the importance of the "vibrations" in tissue and cellular exchanges.

In particular, he highlighted the possibilities of a non-invasive method of using microvibrations and microcompressions to stimulate receptors, open calcium channels, drain lymphatic stasis and increase tissue vascularization, essential characteristics for tissue repair and regeneration activities.

The work shows the satisfaction of patients in both cases of cellulite, which the patients noted in the improvement of the external appearance of the orange peel and in the sense of well-being of the legs. This is an indicative and significant figure due to the importance that vascularization and the physiological thermal increase can have on the metabolic activities of tissues with stasis and fibroedematous alterations, all characterized by a reduction of use of oxygen in cells and mitochondria.

The work also shows the satisfaction of patients in both cases of cellulite in reducing the pain of the tissue panniculus. At the same time, we can observe the importance that already in 2008 was given to the stimulation of mechanoreceptors for the opening of calcium channels and for

the production of endorphins, all effects that participate in the reduction of pain together with the increase in tissue temperature.

Regenerative effects

The study shows a general satisfaction of the patients, with reduction of pain and improvement of the unsightly skin irregularities in both cases of cellulite. The VAS scale shows the result of the improvement of cellulite, with 8,5 in adipose cellulite and 8,4 in lipolymphedema in overage, while the pain reduction is instead more evident in adipose cellulite, with 9 compared to 7.

Why?

This data is very important, because all practical experiences confirmed it over time, corroborating the physiopathological premises. This data is very important because pain is not the direct consequence of the lymphatic stasis, but of a complex series of alterations in the microcirculation and in the extracellular matrix characterized by inversion of cells polarity, difficulty in information and all biophysical alterations that lead to changes in the biochemical molecular state.

In the clinical expression of tissue pain, the presence of free radicals, tissue acidity and decrease in tissue energy are important, in short, a complex alteration of the activities in the interstitial matrix due to a reduction in the use of oxygen in the cells. For these reasons, an integrated vascularizing and biostimulating treatment is useful for the treatment of lipodystrophy and adipose cellulite, because the cells react earlier to vascularization and temperature increase than to lymph reduction (23).

In human tissues, in particular in the extracellular matrix, a perfect homeostasis is necessary to keep cells healthy, removing heavy metals, slags and fatty acids in excess. To this end, the body has some vascular pathways, especially the lymphatic ones, which collect major molecular wastes by bringing them to kidneys for elimination, but there are also other interesting elements that function as "waste-to-energy plants" by a process of autophagy, transforming these excess or unused molecules into energy.

These organelles are called "lysosomes", they live in the cellular cytoplasm and are the digestive system of the cell, making part of the immune system, their biological task is to break down organic compounds by reducing them into smaller amino acids, fatty acids and monosaccharides. Together with "peroxisomes", other enzymatic organelles that degrade free radicals and carry out oxidation reactions, lysosomes transform these wastes into ATP energy, thus avoiding a toxic warehouse with the transformation of biological waste material into an immediately usable energy source.

An interesting study by the Department of Medical Genetics of the University of Naples "Federico II" showed that lysosomes are activated or deactivated by a single control unit under the control of a single gene, called "TFEB" (Transcriptor Factor EB) (24).

All chronic and degenerative diseases begin with "tissue pollution" and reduction of the mitochondrial oxygenation, with inflammatory

activity and then evolutive responses towards fibroedema. Recent acquisitions on aging indicate this perspective which would also confirm the evolutive hypotheses of cellulite, placing at the base the hypoxic alterations of the microcirculation and of the interstitial matrix due to a purification system that does not have the ability to maintain homeostasis in balance, ultimately causing inflammation and reducing the activity of stem cells. Cellulite as a degenerative skin disease, where it is interesting to observe the role played by mesenchymal stem cells isolated from the stromal vascular fraction of adipose tissue affected by cellulite, which demonstrate the role of the interstitial matrix in the regenerative process (25).

This hypothesis would also confirm the genesis of pain in adipose and edematous cellulite, enhancing the therapeutic approach performed by a vascularising, draining and restructuring physical therapy, perhaps with microvibrations and microcompressions that create stimulus signals for receptors responsible for cell regeneration.

This data is in harmony with the reflections on the microcirculation, on the interstitial matrix and on the tissue receptors, highlighting how the activation of vasomotion is more important than the reduction of stasis, most likely the activation of the metabolic pumps, managed by mitochondrial activities and by calcium channels, favor lymphatic drainage and the activation of the scavenger gene (TFEB) which allows tissue purification, an essential moment for cellular activities, also for the reduction of pain.

Maybe that stimulation of receptors and increase in tissue vascularization can also help the cells purification by a metabolic reactivation, influencing the pain reduction too.

Conclusion

In the light of current knowledge, we can deduce that hypotheses and conclusions of the preliminary study of 2008, can now be considered congruent and pertinent with the objectives that new methodology had initially indicated, as pain reduction, vascularization and tissue trophism.

In these fifteen years, "Endosphères Therapy" has spread all over the world and thousands of "Compressive Microvibration" treatments have been carried out for the clinical and aesthetic treatment in different forms of cellulite, lipolymphedema and lipodystrophy of the lower limbs, demonstrating its therapeutic utility, indications, advantages and contraindications in daily practice and in patient satisfaction: but this is not the aim of the present study.

The goal is the desire to share doubts, questions and reflections that we felt the need to ask ourselves first of all:

- Why do the same authors want to review one of their submissions after fifteen years?

In 2008, the "Endosphères Therapy" practically did not exist, it was totally unknown and also the action's mechanism had to be understood and identified. The first patents were the expression of years of research by the Italian FenixGroup industry in the field of the medical sports and rehabilitation, but they were only

bioengineering projects and ideas based on the scientific knowledge of the time and on professional experiences about physical therapy for neuromuscular or lymphatic pain. Those new patents, however, contained an indisputable novelty that at the time represented a sure "technical revolution" compared to the methods normally used, since in fact we passed from the physiotherapy concept of "tissue palpation and rolling by the fingers" and from methods that used " the vacuum therapy made by a mechanical suction to pull the connective fibers and move the tissues ", to a totally different concept that used" microvibrations and microcompressions " obtained using 55 soft silicone microspheres that, rotating both on their own axis and on the axis of the operating cylinder in which they are inserted, produced vibrations that spread at certain frequencies to obtain different results.

The fact that each microsphere had a precise diameter, that the silicone had to have a certain type of softness, that the weight of the handpiece was the established weight of 1700 grams and that the rotation frequency of the balls had to be in a certain speed range a depending on the type of tissue, it often made understanding difficult.

For these reasons, even with deep scientific curiosity for the interesting novelty and with sure enthusiasm for the results obtained in the preliminary studies, the early days were more of observation than of scientific production, both by technical researchers and by sanitary consultants.

The first conclusions in the treatment of pain in rehabilitation made at the University of Chieti opened new spaces that led to the presentation made in 2008 at the Congress of Aesthetic Medicine for the treatment of tissue pain in cellulite.

Over the years, that first presentation was followed by many other presentations in national and international congresses or university courses, there was no lack of contributions and observations from doctors and operators of different specialist backgrounds and from various countries, there was no lack of articles in books or magazines of various types, only official publications in indexed journals were lacking.

Above all, the testimony and scientific visibility of that 2008 presentation was lacking.

This work is intended in part to be the answer to the first question, to fill the "historical void" of the scientific visibility of the first work.

- Why do the authors themselves wish to publish a retrospective study after fifteen years?

However, the real reasons are more complex, and it is fair to ask why the authors themselves wish to publish a retrospective study of that first presentation which, due to the methods and execution, certainly does not have particular scientific relevance. Why a retrospective work of that almost forgotten study?

Fifteen years of observations and experiences have led to the confirmation of the mechanism of action of the method and the protocols used, but the last few years, especially in the pandemic period, there has been an incredible and unthinkable push to the evolution of our generation and of life itself, in its various forms.

Society has changed, geopolitics has changed, social and work organization has changed, lifestyles and health care have changed, new scientific knowledge of great value has emerged in the knowledge of the cell and biological life, such as stem cells, inflammation, oxidative stress, the interstitial matrix, the vascular endothelium and

ion pumps, light and electromagnetic energy, the role of water and light, the concept of nutrition and purification from genetic and metabolic point of view, the structure and function of fat cells, aging processes, energy points and vibrations. All this required reviewing their knowledge by updating it in the light of new discoveries.

This cultural revolution also took place in phlebolymphology and aesthetic medicine, highlighting the role of the endothelium and inflammation, the role of the interstitial matrix and the role of intercellular information through waves and vibrations. The modern technologies are based on this knowledge, which propose the use of therapeutic waves and vibrations. This is the answer to the second question, since the revision of that first presentation allows the authors to "review themselves" in a serene, profound and critical process, dutifully sharing the conclusions and the path made in scientific reflections.

- What could be the scientific value of the retrospective study on that type of study?

The answer to the third question is more complex because it requires an evaluation of the possible value of this retrospective study.

University has sacred "academic laws" based on the universal transmission of "knowledge", understood as the final outcome of a continuous process of revision based on doubt and on the "thesis-antithesis" dualism, followed by the conclusion, after a peaceful and objective discussion.

The preliminary study of 2008 was above all a "working hypothesis" based on clinical and technical observations associated with medical sensitivities, the present retrospective study is instead the final expression of fifteen years of thesis / antithesis, a continuous revision that led in the time to perfect the methodology and protocols, but leaving the basic principles practically intact.

Today we can confirm that working hypothesis, in the premises and expectations of use of the method, but we are especially interested in sharing that revolution of the time, integrating it with current knowledge about adipose tissue, the interstitial matrix, the cell biology and regenerative medicine, all biological elements characterized by information systems that are sensitive to stimuli and vibrations.

To the third question we answer that the value of the study does not lie in the results of the treatment, in the numbers or in the statistics, but in the path taken to arrive at those numbers, especially in the choice to share one's own paths and reflections, a choice that constitutes the 'final goal" of this work.

Some studies are currently underway on the direct effect of compressive microvibration on trigger points in relation to angiogenetic and modulatory action, in the hypothesis of direct effects of vibration on adipose tissue and tissue remodeling. The "Endosphères Therapy'' is based on the vascularizing and angiogenetic action favored by the increase in skin temperature and cellular oxygenation, but also by the stimulation of the energy points for the opening of calcium channels, with consequent improvement of the metabolic activities in their complexity, including anti-inflammatory and immune regenerative ones.

If these are the conclusions and future prospects, the data offered by the 2008 study are congruent and coherent, above all, this retrospective study has allowed us to take time to review and update our knowledge.

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