

Comparative Study

Treatment of lymphedema, two methods compared: Ketogenic diet and Endospheres, Ketogenic diet and Vodder lymphatic drainage

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Lymphedema is a chronic disease with an evolutionary and often disabling nature, which represents an abnormal and excessive accumulation of lymphatic fluid on the interstitial side, both due to altered morphology of the lymphatic vessel and excessive lymph formation with difficulty in drainage. This condition is characterized by stasis of water and macromolecules, which, over time, transform the connective tissue into fibrous tissue. Unfortunately, it is a very widespread pathological condition. According to official data in Italy, there are about 40,000 cases per year, especially as a result of surgery, trauma, or radiotherapy such as secondary lymphedema and deriving from lymphatic channels or non-functional lymph nodes or in conditions of non-metabolic homeostasis. Unfortunately, despite the large-scale spread of lymphedema, information on this pathology is quite scarce, and the therapeutic alternatives offered to the patient are often limited and incomplete, forcing the patient to follow constant therapeutic paths. The main therapies are based on anti-inflammatory, vascular drugs, and physiotherapeutic treatments, based on various types of lymphatic drainage, first of all, the lymphatic drainage described by Vodder. It is known that the lymphatic system is a drainage tissue of the macromolecules produced by the cellular activities of the organism. However, it also acts as an important immune organ closely connected to the adipose and metabolic system, affected by the inflammatory processes caused by overweight, intestinal dysbiosis, and visceral obesity. For this reason, lifestyle advice and good nutrition are always associated with lymphatic drainage. One hundred female patients with lymphedema and lipolymphedema were followed by Prof. Bellomo who recommended a ketogenic diet; half were treated with traditional Vodder lymphatic drainage, the other with compressive microvibration method. Both groups maintained suitable compression stockings. The results obtained in the two different experimental groups highlighted the ability of the therapeutic combination between a ketogenic diet and Endosphere Therapy to offer stable results thanks to the draining and vascularizing actions, which are associated with the reduction of inflammatory processes caused by overweight and visceral fat.

In the definition of Campisi to Casley-Smith, lymphedema is described as a pathological picture characterized by tumescence of the soft tissues, usually superficial, due to the accumulation of lymph with high protein content in the interstitial space, due to stasis from primary alterations of the lymphatic ways, or secondary from metabolic alterations, diseases, trauma or surgery.

The main characteristics of lymphedema are evolution, hard and stable edema, cold skin, and joint changes tending to stiffness (1-4).

Lymphedema is sometimes also associated with venous insufficiency, described as phlebolymphe-dema, but in women, it is more often associated with an increase in subcutaneous adipose tissue, so-called lipolymphedema, especially in subjects with

visceral overweight.

Common characteristics of lipolymphedema are the close relationship with the peripheral metabolism of fat tissue and the lower fibrous evolution of lymphatic stasis (5-7).

The main therapies are based on anti-inflammatory and vascular drugs with physiotherapeutic treatments based on various types of lymphatic drainage; first, the lymphatic drainage described by Vodder.

The lymphatic system is a drainage tissue aimed at eliminating macromolecules produced by the cellular activities. However, it also acts as an important immune organ closely connected to the adipose and metabolic system, mostly in the inflammatory processes caused by overweight, intestinal dysbiosis, and visceral obesity. For this reason, lifestyle advice and good nutrition are always associated with lymphatic drainage (8-12).

Manual lymphatic drainage is a non-invasive technique developed to drain the lymph present in the lymphatic system. Among the different lymphatic drainage techniques, the most used is the Vodder method, which is performed by manipulating the tissues with light circular and oval pressures (13-16). The operator must use a delicacy in the movements so as not to cause damage to the blood and lymphatic capillaries. In addition, the manipulation of the skin must be painless and must not cause redness. The Vodder method provides:

1. movements with steady circles
2. pumping movements

3. dispensing movements

4. rotary movements

The first phase begins by pressing the fingers on the person's skin and drawing increasingly larger spiral circles. The direction of the circular movement depends on the lymphatic outflow. In pumping movements, the direction is downwards, and the fingers of the hand, which must be well stretched, draw oval curves, while the fingertips are not used. In the dispensing movements, spiral shapes are drawn by rotating the wrist. Instead, in the rotational movements, the wrist is raised and lowered; simultaneously, placing the hand on the skin, a spiral-shaped rotational movement is performed; this technique is performed during the pressure phase.

Endospheres Therapy aims to diffuse “microvibrations and microcompressions” using 55 soft silicone spheres with a diameter of 19.5 mm that rotate inside a cylinder at different speeds, transmitting different mechanical vibratory frequencies in the tissues (17-18).

These microspheres have an active mechanical rotary movement induced by the motor of the roller inserted in the cylinder and managed by the handpiece, while the balls rotate on their axis in a passive movement induced by sliding on the tissues.

Associated with the different types of frequency and the direction of rotation of the spheres, the compression exerted by the operating cylinder contained in the handpiece

produces different elastic responses on the tissues, also stimulating various mechanoreceptors and energy points capable of activating different vascularization, draining, toning and analgesic functional reactions.

Endospheres Therapy is a new interesting methodology useful in vascular medicine, sports, and aesthetic physiotherapy; the novelty lies in the particular mechanism of

action based on the rotation speed variation of the rotating soft silicone microspheres, which determine the frequency of vibrations, from 40Hz to 450Hz.

The direction of rotation of the spheres and the pressure exerted by the handpiece on the tissues creates a “compressive microvibration” that manages to transmit a complex pulsed and rhythmic action that finally produces a “positive/negative pump” effect (Fig. 1).

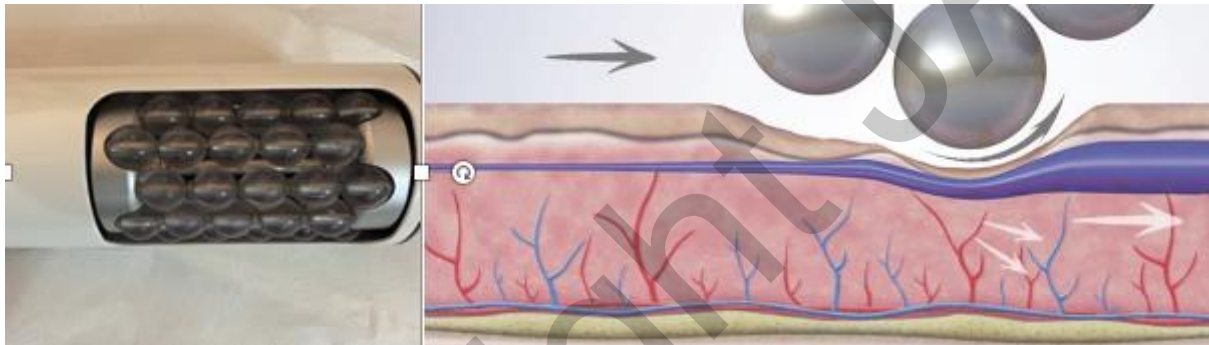


Fig. 1. On the left, the 55 rotating soft silicone spheres housed inside the cylinder; on the right, the rotation of the spheres.

The right combination of the microvibrational and micro compressive forces used determines the intensity of the treatment, which can be adapted to the different clinical conditions of the patient. For these reasons, the method proved to be of interest above all for treating pain in neuromuscular pathologies and clinical and aesthetic treatments of soft tissues, such as lymphedema, lipodystrophy lipoedema, and

cellulite.

Among the most interesting effects of the Endospheres Therapy treatment, we find an important lymphatic drainage action, a significant action of vascularization of the tissues with an increase in body temperature, a constant reduction of tissue pain with a reduction of the inflammatory process, a significant reduction of the superficial adipose layer (19-21).

Materials and Methods

A retrospective, observational case-control study was conducted. We monitored 100 volunteers diagnosed with second-stage lymphedema of the lower limbs.

The subjects were divided into two groups; the “Diet and Endosphères Therapy” protocol was applied to the first group, while the “Diet and LDM (manual lymphatic drainage with Vodder method)” protocol was applied to the second group. All subjects underwent 8 sessions with a frequency of twice a week. This study showed a significant improvement in reducing lymphedema and painful symptoms; it also showed an improvement in vascularity and aesthetic appearance.

The ketogenic diet initially formulated to treat drug-resistant childhood epilepsies favors the metabolic use of fats and ketones when glucose is no longer available as a normal source of energy (22). It is, therefore, a hypoglucidal (20 g / day of CHO), normoproteic, and hyperlipidic (PUFA and MUFA of vegetable and fish origin) nutritional approach (23-24).

Carbohydrates represent the main energy source for our body, but they are also the macronutrient most responsible for the postprandial glycemic peak. Therefore, they are identified with the abbreviation CHO, representing a unit of measurement used to choose the right insulin dose to inject. By comparing the weight in grams of the food and the percentage of carbohydrates in it, the formula is used: Total weight (gr.) $\times$ % of

specific carbohydrates for each food / 100 = gr. of carbohydrates (25). Polyunsaturated fatty acids (called PUFAs) are fatty acids characterized by more than one double bond along the carbon chain. Those with only one double bond are called monounsaturated (MUFA); in the absence of double bonds, the fatty acids are called saturated (26-27).

From the early stages of treatment, the subcutaneous edema is reduced: the lack of glucose introduced with food prevents its conservation in the form of glycogen, which would require up to a ratio of 1:17 with water.

Furthermore, the increased permeability of the lymphatic vascular endothelium, which negatively affects the correct drainage of the interstitial fluid, is improved thanks to the high levels of circulating NO (nitric oxide), associated with the presence of L-arginine, whose supply is guaranteed by the ketogenic regimen (28).

The transition from a “glucocentric” to an “adipocentric” energy metabolism causes a net decrease in circulating insulin levels, contributing to an improvement in the condition of insulin resistance. Instead, in response to high fat intake, leptin levels increase along with relative brain sensitivity. The individual perceives the sense of satiety with the effect of improving compliance with the diet for long periods. At the same time, neuronal activation in response to any tactile stimulus will decrease with a reduction in neuropathic and nociceptive pain (29).

The resistance of hypertrophic adipocytes to a normal hypocaloric regimen lies in their need for insulin levels, useful for inducing lipolysis, many times lower than those required by the normal fat cells of an obese subject (30). Such minimum concentrations can only be achieved with the ketogenic diet. In this way, although delayed concerning the reduction of edema, we will also reduce localized adiposity in the target areas, such as the lower limbs. This element is essential to progressively reduce the mechanical compression of the lymphatic pathways and peripheral nerves. The subjects examined were treated with the following specific methods:

- ketogenic diet
- Endosphères Therapy
- Vodder manual lymphatic drainage
- After treatment, all patients continued to maintain the elastic compression devices normally used.

The evaluation methods used were:

- Centimeter measurement of the lower and upper limbs
- BMI (Body Mass Index)
- Weight

The assessments were performed at T0, immediately before the start of the rehabilitation protocol, and at T1, following the 8 sessions required by the protocol. Centimeter measurements are anthropometric measurements that represent the transverse dimensions of the various body segments. In this specific case, they were recorded at the level of the lower limbs in an orthostatic position using metric tape. In the

protocol mentioned above, 100 female subjects were included. The subjects were equally distributed in the two different therapeutic combinations.

- 50 sessions of Endosphères Therapy and a ketogenic diet
- 50 sessions of lymphatic drainage by the Vodder method and a ketogenic diet.

Inclusion criteria:

- Female sex with overweight between 24 and 30 BMI
- Bilateral lymphedema with overweight
- Bilateral Lipolymphedema with overweight
- Bilateral lymphedema with Chronic venous insufficiency and overweight.

Exclusion criteria:

- Obesity with BMI above 30
- Diabetes mellitus and Metabolic syndrome
- Evolutive lipoedema
- Thrombophlebitis
- Active tumor or metastasis
- Major heart problems: angina pectoris, coronary thrombosis, heart failure.

The first group subjects carried out a re-educational protocol with a ketogenic diet and Endosphères Therapy, with a frequency of two sessions per week for four weeks. The subjects who performed Endosphères Therapy were cared by 4 frequencies, of 127Hz, 150Hz, 170Hz, and 190Hz (31).

At 127 and 150 Hz, the weight of the handpiece is supported by the operator to obtain a pressure that stimulates the more superficial corpuscles (the free endings of the dermis, the Meissner's

corpuscles, the Merkel corpuscles, and the superficial nervous plexus) and the superficial lymphatic structures. These first two frequencies act mainly on the lymphatic system with lymphatic drainage action, so a disto-proximal linear gait is required.

At 170 and 190 Hz, the weight of the handpiece is exploited by the operator to obtain a continuous and prolonged tensive action on the muscle that arranges the fibers in series, resulting in an elongation of the connective tissue elastic and eliminating muscle contractures in very few sessions.

With these latter frequencies, the action obtained is a deep vascular and muscular action; for this reason, an oscillatory gait is always distoproximal. The patient first lies in the supine position during the treatment, relaxed with the lower limbs slightly apart. After treatment, all patients continued to maintain the elastic compression devices normally used.

Application 1: opening of the inguinal lymph nodes (Fig. 2).

- Time: 10-12 seconds
- Direction: centripetal, towards the heart
- Frequency 127 Hz

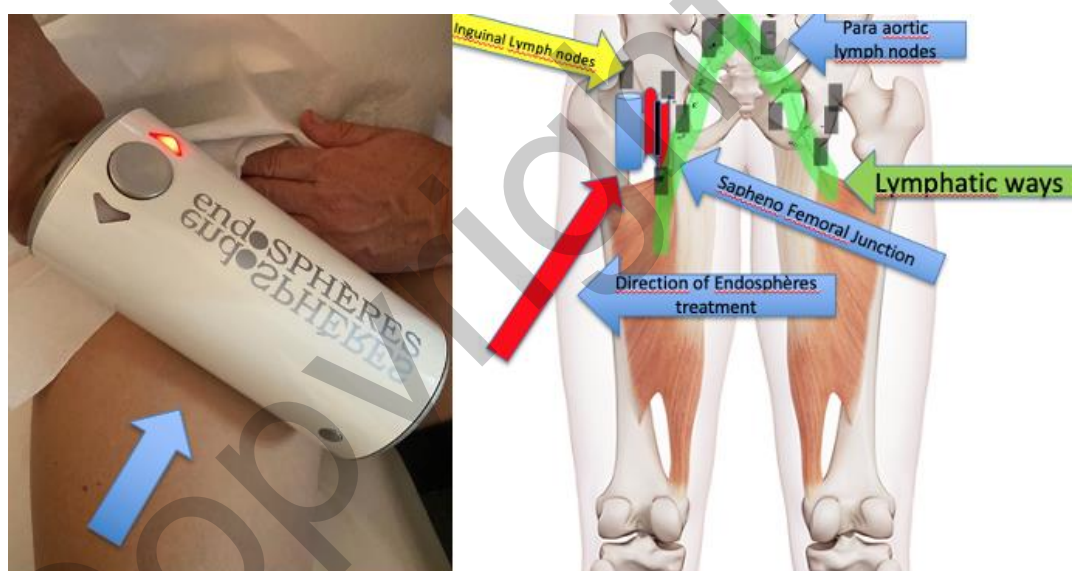


Fig. 2. Opening lymph nodes in the *Endosphères* treatment.

Application 2, treatment in the adductor area (Fig. 3).

- Time: 10-12 seconds
- Direction: centripetal
- Frequency: 127Hz - 150Hz - 170Hz 190Hz

Application 3 - the patient is placed in the prone position for application 3 to open the popliteal lymph nodes.

- Time: 10-12 seconds
- Direction: centripetal
- Frequency: 127 Hz



Fig. 3. *On the left: the application in the adductor area; on the right: the application in the popliteal area. The arrows indicate the direction of treatment along the lymphatic pathways.*

The adductor area was treated both in the supine and in the prone position as it appears to be the area richest in both lymphatic and lymph nodes of the lower limb.

The second group subjects carried out a protocol with manual lymphatic drainage with the Vodder method and a ketogenic diet. With a frequency of two sessions a week for four weeks, the subjects performed manual lymphatic drainage with the Vodder method. The operator makes light touches on the skin, in a centripetal direction, from the periphery towards the center of the trunk to help the lymph in its path.

The Vodder school provides for the execution of four movements: circular thrusts, rotations, pumping, and dispensing movements. The

circular movements must always be applied in a light but, at the same time, consistent way. The massage continues with rotational movements, in which the expert operator performs movements with the wrist, raising and lowering it, rubbing the hand on the skin in a circular way. Subsequently, lymphatic drainage involves pumping movements: the pressure of the tissues is altered to allow better circulation of the lymph (the operator moves the patient's skin, trying to "draw" a sort of oval circles by moving the fingers in the same direction). All these movements are alternated with a dispensing clutch, which consists of movement rotation of the wrist on the patient's skin.

Results

In compliance with statistical analysis, the normality of the distribution for all measured variables was tested by normal probability plots and the Jarque-Bera test (32).

Data are presented as the mean (standard deviation, SD). Student t-test was used to test differences in the main characteristics of the patients. Two-way mixed ANOVA assessed the effects of time, group, and interaction for all variables.

The contrast analysis was assessed using correction. All statistical tests were 2-sided, with a significance level of $p < 0.05$. All analyses were performed with the open-source statistical R environment (version 3.4.3, the R Foundation for Statistical Computing). Groups did not differ in age, sex, weight, BMI, and Height at baseline.

The mean value for BMI for both treatments is

reduced, but not more in one group than in the other. In Group 1, the basal value of BMI is 26.5 (2.24) and in Group 2 is 27.0 (4.00). At the follow-up, the mean BMI value is 25.8 (3.01) for Group 1 and 26.8 (3.17) for Group 2 (Table I).

Table II shows the interaction term for the Right and Left Lower limb variables; indeed, the post-hoc shows a difference between groups at the follow-up (Table II).

At the baseline, for Group 1, the mean value for the Right Lower Limb is 31.6 (4.74), and for the left lower limb, it is 30.2 (4.48); at T1, the mean value is 31.7 (4.91) and 30.3 (3.93) for right and left respectively.

In Group 2, the mean value at baseline for the right lower limb is 30.2 (4.48), and 30.4 (3.81) at follow-up. For the Left Upper Limb, the mean value at T0 is 30.4 (3.81) and 29.0 (3.93) at T1.

Table I. Descriptive statistics of patient characteristics. P-value result from t-test.

Variables	Group 1	Group 2	p-value
	N=50	N=50	
Age (years)	39.6 (4.97)	39.7 (4.97)	0.920
Weight (Kg)	71.2 (10.4)	71.3 (10.1)	0.930
Height (cm)	163 (8.08)	162 (8.14)	0.594
BMI (Kg/m ²)	26.5 (2.24)	27.0 (4.00)	0.420

Table II. Two ways mixed ANOVA and contrast analysis for (Panel A) Right and (Panel B) Left lower limb variables. Significance code: **= $p < 0.01$, *= $p < 0.05$.

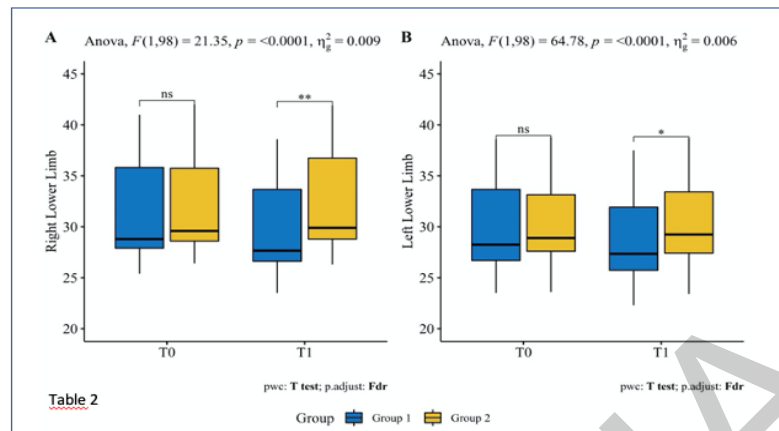
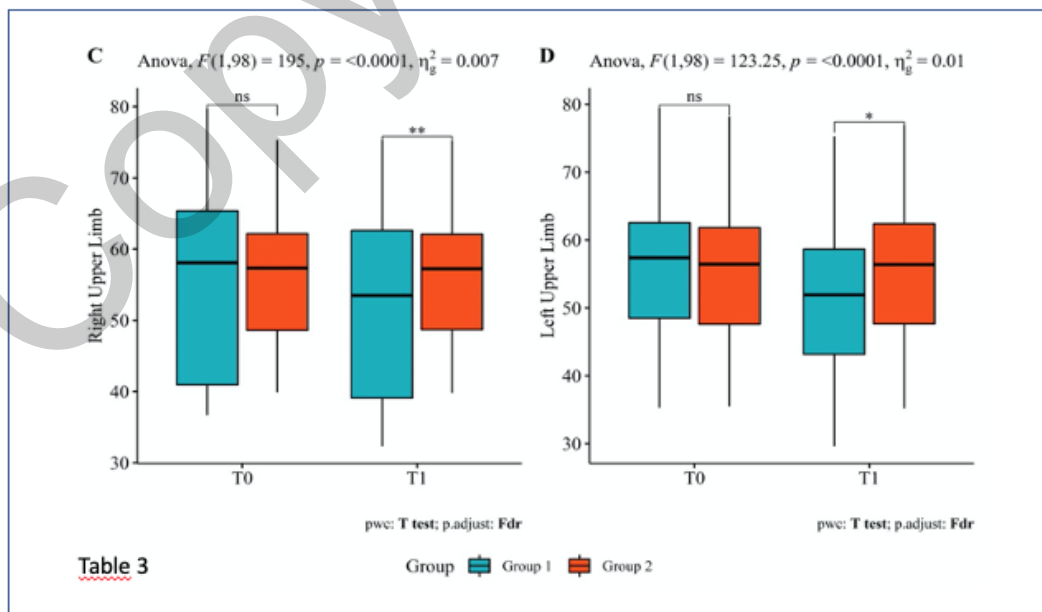


Table III shows the two ways mixed ANOVA results for the right and lower upper limb variables reveal a larger mean improvement for Group 2. For the Right Upper Limb variable, we have 55.1 (13.1) in Group 1 and 57.4 (8.64) in Group 2 at T0 and 54.0 (11.5) for Group 1 and

54.7 (10.4) for Group2 at T1. For the Left Lower Limb variable, the mean value at T0 is 56.2 (10.9) for Group 1 and 51.1 (9.00) for Group 2. At the follow-up, the mean value for the latter variable is 56.2 (10.9) in Group 1 and 51.1 (9.00) in Group 2 (Table III).

Table III. Two ways mixed ANOVA and contrast analysis for (Panel C) Right and (Panel D) Left Upper limb variables. Significance code: **= $p < 0.01$, *= $p < 0.05$.



Discussion

In the studies of De Godoy (2019), we can read that the alterations of adipose tissue towards overweight and obesity are associated with generalized edema of the extremities and trunk, with an increase in intracellular and extracellular fluids starting from the lower limbs, thus suggesting a new concept of lymphedema defined as “systemic subclinical lymphedema”.

Studies show that the evolution of overweight and obesity leads to alterations in the lymphatic system and microcirculation with alterations in the motility of lymphatic vessels, with activation of inflammatory processes, capillary permeability, and the immune response (33).

The early diagnosis of systemic subclinical lymphedema can certainly slow down the evolution of clinical lymphedema of the limbs, so the search for the causes and the implementation of integrated non-invasive treatments of a physical and nutritional type can therefore constitute an important moment of preventive medicine (34-35). For this reason, among other objectives, the purpose of the study was to be able to identify a valid treatment that could also be used as a preventive therapy; therefore, overweight but not obese female patients were chosen (with BMI between 24 and 30), especially without endocrine and cardiovascular diseases, and not in diabetes or metabolic syndrome.

Furthermore, the average age of the patients was 39 years, a range of overweight and lymphedema unfortunately very common in modern society.

The choice of the so-called ketogenic diet was dictated by the experiences and studies of this nutritional technique on visceral fat and inflammatory processes that are always associated with the functional slowdown of the lymphatic and connective systems (36-38). In addition to this, the characteristic of this diet is the “temporariness”, a targeted nutritional scheme that must be adopted for short periods, to then be replaced by generic nutritional schemes with control of the various nutrients.

This nutritional need also dictated the choice of the four weeks; for this reason, an intense integrated treatment in a short period was chosen as protocol, with two treatments per week for four weeks, without drug therapy support but only nutrition.

The manual lymphatic drainage treatment was performed with the traditional Vodder method, while the Compressive Microvibration treatment followed the basic indications that have proved to be valid and adequate over time. After the treatment, all patients continued to wear the compression device normally used.

This study showed that the effect of the Endospheres Compressive Microvibration associated with the ketogenic diet was positive for the decrease in weight and loss of centimeters compared to the treatment with the Vodder method.

From 2007 to today, both the first clinical experiences and current practical knowledge, all

connected by the same thread, indicate the activation of tissue metabolism as the main effect of treatment, thanks to the vascularization induced by the microspheres rotating at precise frequencies (39). Therefore, it is correct to speak of the “main effect” of this methodology because all the other actions (analgesic, draining, or restructuring actions) are consequent to this primary activity, which uses “micro vibrations” and “microcompressions”, induced by the microspheres rotating at different frequencies, in order to obtain an elastic response of the tissues that favors a positive/negative local pump action

Conclusion

The present study is a retrospective investigation that is often hampered by biases in its statistical significance.

Among the observational studies, even the retrospective ones aim to observe how a specific risk factor acts, provide information on the possible causes of a key event, or identify therapeutic activities to reduce the evolution of the disease. The difference between the various types of study is the observation point of the key event.

Scientific research uses all possible points of view to examine the relationship between two events, both to ensure the correct temporal and functional framing of the entire phenomenon and leave nothing to chance in terms of cause and effect (42-43).

capable of opening the microshunts and allowing greater quantity of blood. This vascularised activity increases the speed of the blood in the vessels and capillaries, leads to a physiological increase in temperature and consequent better metabolic activity and reduction of pain (40-41).

The interesting data of all the surveys is subjective and objective clinical observations that demonstrate the constant relationship between an increase in physiological temperature and an improvement in patient satisfaction, both clinical and aesthetic.

In retrospective studies, the risk of prejudice is always present and sometimes justified. However, the correct identification of the temporal and functional order between the events and the relationship between them very often allows for correcting knowledge and any errors, even during construction, and setting up more performing and meaningful scientific studies, rather than confirming data and experiences.

Comparing the results obtained in this study's two different experimental groups, we can see how the therapeutic combination obtained by associating the ketogenic diet to the treatment by Endosphere Therapy is more effective. Therefore, the proposed work gave positive results found not only from the objective analysis of the measurements carried out but also from the testimonies of the patients who recorded a

pleasant sensation of lightness in the lower limbs from the first session. However, given the complexity and involvement of the disease and its typical chronicity along with its marked tendency to spontaneous evolution, it is essential to associate a correct diet.

Therefore, we conclude by saying that, since lymphedema is one of the most frequent

pathologies and has such a striking psycho-social impact, it is important in scientific research to continue the studies and research of innovative methods for its treatment. The new treatment proposal “Endosphères” responds to current scientific knowledge and is indicated for the current requests of patients regarding clinical and aesthetic pathologies related to lymphedema.

Acknowledgements

The authors declare that there is no conflict of interest. The necessary precautions were applied

in carrying out the observational study, and laws in force were respected.

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