Lymphology 56 (2023) 13-26

DEFOCUSED AND RADIAL SHOCK WAVE THERAPY, MESOTHERAPY, AND KINESIO TAPING EFFECTS IN PATIENTS WITH LIPEDEMA: A PILOT STUDY

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ABSTRACT

The aim of this pilot study was to investigate the effects of defocused and radial shock wave therapy, mesotherapy, and kinesio taping on pain, circumferences of lower limbs, echographic/ elastosonographic pattern of subcutaneous adipose tissue (SAT), and quality of life in patients with lipedema. Fifteen women affected by lower limb lipedema in stage II were treated with shock wave therapy, mesotherapy, and kinesio taping on thighs and legs (eight sessions, twice a week). The primary outcome was pain, as assessed by Numeric Rating Scale (NRS). Secondary outcomes included the limb circumferences measurements, the SF-12 Health Survey for quality of life, the International Classification of Functioning (ICF) for disability, and echographic/ elastosonographic changes of SAT. Significant reductions of pain and circumference measurements were seen in patients at each follow up. This was associated with significant reduction of thickness, echographic pattern improvement, and increased elasticity of SAT, with consequent positive impact on the quality of life and disability reported by the patients. The results demonstrate improved clinical and functional ultrasound findings in patients affected by lipedema in the early stages of lower limbs, and this combination therapy needs to be investigated in larger populations at multiple centers to confirm the findings.

Keywords: lipedema, disability, shock wave therapy, mesotherapy, kinesio taping

Lipedema is a painful chronic adipose tissue disorder characterized by symmetrical swelling of the extremities due to subcutaneous adipose tissue (SAT) deposition in the buttocks, hips, thighs, legs, and arms, sparing the trunk and feet. The etiology and pathogenesis are unclear. It may be associated with impairment of an estrogen-related hormonal axis, since lipedema mainly affects females and its onset, is primarily around the time of puberty. It also can be aggravated with hormonal changes such as in pregnancy or in menopause (1).

Lipedema is a strongly suggested genetic condition as self-reported positive family history of lipedema has been found for up to

64% of women (2). Prevalence in the general population has been estimated to range from 15 to 18.8% across several studies and has been reported as high as 39% in German women (2). A missense variant p. (Leu213Gln) in the gene encoding for an aldo-keto reductase (AKR1C1) seems to be involved in a less efficient reduction of progesterone to hydroxyprogesterone and in an increased subcutaneous fat deposition in variant carriers (2). Symptoms include spontaneous or pressure-induced pain, tenderness, physical limitations, and easy bruising (1). Lipedema is also accompanied by local circulatory abnormalities such as microangiopathy and increased blood capillary permeability that leads to protein-rich fluid extravasation, which can further enhance lymph formation (3).

Pain is the common and leading complaint in lipedema. This can be brought forth by touch or minor pressure or may occur after standing or sitting for a prolonged period (4). It significantly impairs quality of life and is correlated with mental disorders such anxiety and depression in lipedema patients (1). Adipose tissue inflammation that characterizes lipedema induces dysregulation of locoregional sensory nerve fibers causing increased perception of pain (5).

Dayan et al recognized four stages of lipedema through which the disease progresses, and five types, depending on the location of excess adipose tissue (6). Diagnosis of lipedema is usually made by medical history and physical examination. However, lipedema is often misdiagnosed as obesity, lymphedema, and other conditions characterized by edema of the limbs and fat accumulation, such as Dercum's disease. For a proper and timely diagnosis, it is necessary to investigate the medical history of the patient and to conduct a careful clinical examination (5). Imaging investigations are usually not necessary to diagnose lipedema but may have a role if there is diagnostic uncertainty (7). Lipedema must be mainly distinguished from two entities with which it is usually confused, obesity and lymphedema, although the three conditions can and do coexist (5). Ultrasound (US) measurement of dermis and hypodermal thickness may help to differentiate lymphedema and lipedema (7).

Lipedema management consists of conservative treatment and surgical interventions largely depending on the stage of lipedema. In advanced stages surgical treatment remains the most decisive in the control of symptoms, reducing adipose tissue, and improving quality of life. Advanced stages are also often associated with pathological obesity, which therefore need to be treated as associated comorbidity. The first aim of management is to relieve symptoms, in particular pain and the underlying inflammation, and prevent disease progression. Surgery is performed to reduce fatty tissue and improve patient's disability, although it is limited to advanced stages (1). In the last few years, evidence has emerged suggesting that extracorporeal shock wave therapy (ESWT) reduces pain and inflammation in musculoskeletal disorders by potentially inducing neoangiogenesis and promoting lymphatic drainage (8). Radial shock wave has also been shown to improve function and quality of life (8). Furthermore, the use of shockwaves in several skin and subcutaneous pathologies is growing, considering the effects on the improvement of the aspect of skin and body contour, thus suggesting decrease in body circumference in the treated region (9). In addition, mesotherapy, also known as local intradermal therapy, is successfully applied in the treatment of some forms of localized pain syndromes, and it is a valid supportive therapy, when using active components on the extracellular matrix and the lymphatic system, to stimulate the microcirculation and the lymphatic drainage (10,11). The application of kinesio taping for lymphatic drainage (linfotaping) is also useful to relieve pain and improve blood vascular and lymphatic flow by lifting the skin from underlying fascia (12).

Therefore, the aim of this study was to evaluate the effect of a combined conservative treatment with defocused and radial shock wave therapy, mesotherapy, and the application of kinesio taping in patients with lipedema of the lower limbs at the early stages.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the "Sapienza" University of Rome (RS:6491_2021) and was carried out in accordance with National Health Council Resolution No. 196/96. All patients provided their signed informed consent.

Patient Recruitment

Fifteen consecutive patients with diagnosis of lipedema stage II (types 2, 3, and 5) were enrolled from October 2019 through July 2020 and treated as outpatients at the Physical Medicine and Rehabilitation Unit of Sant'Andrea Hospital, University of Rome "Sapienza". The inclusion criteria were as follows: patients older than 18 years, female sex, numeric rating scale (NRS) >3, lipedema at early stages (stage I/II) of the lower limbs (type 2, 3, and 5). Exclusion criteria included presence of pacemaker, coagulation disorders, use of anticoagulant drugs, history of neoplasia, pregnancy, soft tissue wound infection, osteomyelitis and hypersensitivity or allergy to the ingredients used in mesotherapy. Type 1 and 4 were excluded from our criteria as they are uncommon phenotypes, at least in our clinical experience. In addition, type 1 is often difficult to differentiate with localized adiposity of the gynoid type.

Clinical and Functional Outcome Assessments

All outcome measures were taken before treatment (T0), at the end of treatment (T1), and at 1 (T2), and 6 (T3) months after treatment. All assessments were performed by the same examiner and included the self-reported perception of the patient, clinical measures, and instrumental evaluations. The primary outcome measure was pain in the legs quantified using numeric rating scale (NRS) (13). Secondary outcomes consisted in lower limbs circumference assessment using a flexible tape (14), quality of life through the administration of Short Form Survey-12 (SF-12) Questionnaire (15), and the evaluation of the degree of patients' functioning and disability using the International Classification of Functioning, Disability and Health, known more commonly as ICF (16). Subjects were asked to not change diet or exercise during the study period.

<u>Numeric Rating Scale (NRS)</u>

Pain intensity was measured with a segmented numeric version of the visual analog scale. The most common form of the NRS is a horizontal line with an eleven-point numeric range (0-10 mm; 0 means no pain, 10 means severe pain), which is used to quantify the painful sensation before treatment and during follow up (13).

<u>Lower limbs circumference measurements</u>

The circumferential measurements have been standardized and measured using a flexible tape at these points: the proximal third of the thigh, at the thigh root; the distal third of thigh, to the upper edge of patella; and the middle third of thigh, as the middle point of the first two. Leg circumferences were measured at the proximal third of the leg, the bottom edge of patella, the distal third of leg, 4 cm from medial malleolus, and to the middle third of leg, as the middle point of the first two (14).

<u>Short Form Survey-12 Questionnaire (SF-12)</u>

The SF-12 Health Survey is a 12-item subset of the SF-36 that measures the same eight domains of health as the longer scale, concerning in functional health and well-being from the patient's perspective. Like the SF-36, the SF-12 is designed as a general measure of health so can be used with the general population (15).

<u>International Classification of Functioning, Disability and Health (ICF)</u>

The ICF is a classification of health and health-related domains that include body structures and function, activity and participation, and quality of life. Functional assessment of the patients uses 5 categories of B domain, represented by *Body Function and Structure* (b1801: *Body Image*; b280: *Sensation of pain*; b28015: *Pain in lower limb*; b28016: *Pain in Joint*; b2802: *Pain in multiple body* *parts)* and 9 categories of D domain for the evaluation of *Activities and Participation* (d450: *Walking*; d540: *Dressing*; d710: *General interpersonal interactions*; d720: *Complex interpersonal interactions*; d730: *Relating with strangers*; d740: *Formal relationships*; d750: *Informal social relationships*; d760: *Family relationships*; d770: *Intimate relationships*). The qualifiers to quantify the nature of any problems range from 0, indicating no problem, to 4, indicating total problem. For D domain, the qualifiers are used to evaluate both Performance and Capacity. The Performance qualifier describes what an individual does in his or her current environment, improving functioning or reducing disability thanks to Facilitators, which, in lipedema patient, is represented by compression garments (15).

Ultrasound and Elastosonography Assessment

All patients underwent conventional B-mode ultrasonographic evaluation with a high-resolution 4-15 MHz linear-array transducer (MyLab 70 XvG system; Esaote, Genoa, Italy) before treatment (T0), at the end of treatment (T1), and at 6 months after treatment (T3). The images were recorded by the same experienced examiner placing the probe on the skin and trying not to apply pressure.

The points of scanning were the following:

Trochanteric region: the examination of this region was performed by asking the patient to lie on the opposite hip assuming an oblique lateral or true lateral position. The hyperechoic curvilinear line of the greater trochanter was used as a landmark.

Proximal, middle, and distal thighs and legs: at the same point of the circumference's measurement; in particular, for distal thigh ultrasound evaluation was measured at 2.5 cm from superior patella border and for the distal leg at 4 cm from medial malleolus.

For the examination of the thighs, patients were placed in a supine position, while they were evaluated in a prone position for the assessment of legs. Field size and gain were adjusted as necessary to optimize image quality.

The following parameters were assessed to investigate subcutaneous adipose tissue (SAT):

SAT thickness was measured, perpendicular to the surface, as the distance between the posterior echogenic border of the dermis and the anterior echogenic border of the muscular fascia. Tissue thickness measurement was measured with an electronic caliper.

SAT echogenicity: Images were recorded and assessed only for trochanteric region, distal thigh and leg.

According to Suehiro et al (17), SAT echogenicity grade was defined as follows:

Grade 0: no increase in echogenicity. The SAT was observed as black.

Grade I: diffuse increase in echogenicity but identifiable horizontal or obliquely oriented echogenic lines caused by connective tissue bundles.

Grade II: diffuse increase of echogenicity. Echogenic lines are not identifiable.

SAT elasticity: SAT elasticity measurements were performed using sonoelastography. This assessment was performed only on the trochanteric region. Gentle external compressions were applied with transducer perpendicular to the skin tissue. Following acquisition of all the images, each elastogram was subsequently processed with the ElaXTo software to quantitatively measure the percentage of hardness (Elx-% HRD) as an index of tissue fibrosis. Same size windows with the same area (0.30 cm^2) were identified as two regions of interest (ROIs) at trochanteric region, the superficial subcutaneous ROI (ElxZ1) and deep subcutaneous ROI (ElxZ2).

Intervention

Administration of shock wave therapy

An electromagnetic generator (DUOLITH SD1, Storz Medical, Tagerwilen, Switzerland) delivering defocused and radial

ESWT was used. The protocol consisted of a course of eight sessions, twice a week. The treatment was carried out in an outpatient setting, without anesthesia or topical drugs. Defocused shock waves were delivered first on thighs, moving the probe slowly in the anterior region from the thigh root to the knee, then on the lateral thigh, with focus on the trochanteric region. Finally in the posterior thigh, from the gluteal fold to the popliteal fossa. Then posterior leg region was treated, with particular attention to the ankles. It utilized an energy flux density from 0.45 mJ/mm^2 to 1.24 mJ/mm^2, as tolerated by the patient; a frequency of 3-5 Hz for a total number of 3400 s/m (2400 for each thigh and 1000 for each leg). Radial shock waves subsequently have been performed in the same region treated with defocused shock wave, with an energy of 3 Bar and a frequency of 20 Hz, for a total of 5000 s/m (3500 for each thigh and 1500 for each leg).

Mesotherapy (Local Intradermal Therapy)

During each session, patients received intradermal microinjections of pre-constituted homeopathic compound (Lymdiaral®, produced by Pascoe and contains: Conium D3 2.5 mg, Hydratis D3 2.5 mg, Viscum album D2 2.5 mg, Phytolacca D4 2.0 mg, Scilla D1 2.0 mg, and sodium chloride) to improve vasoactive and draining function of the microcirculation. Intradermal injections of 2 vials of 2 ml each were applied in the posterior region of legs using a 4mm x 32G needle in 0.2 ml doses at each injection site with a depth of 1-3 mm.

Kinesio Taping Lymphatic application (Lymph taping)

Kinesio tape was applied in each leg in a proximal-to-distal direction on the trochanteric region, posterior region of the thigh and calf. For this application the skin was stretched, and the tape placed without additional stretch in the draining area. It was retained for three days and reapplied in the following visit. The tape used is made from 100% cotton and it is water resistant, hypoallergenic, thermoadhesive, and stretchable longitudinally. Upon its removal, the patients were instructed to wear 20-25 mmHg medical class 1 compression stockings, until next visit.

Statistical Analysis

Data are reported as mean ± standard deviation, or median with first and third quartiles, or in terms of absolute frequencies of cases according to the type of variables. Because the Kolgomorov-Smirnov test results, most of variables were not normally distributed and non-parametric statistics were used, such as Friedman's analysis of variance and chi squared test, to assess within subject effects. One-tail correlations were assessed using Pearson coefficient (R) for normally distributed data and Spearman coefficient (Rho) for not gaussian data according to Kolgomorov-Smirnov test. For all the analyses, the alpha level of significance for rejecting null hypothesis was set at 5%. All the statistical calculations were performed using IBM SPSS version 23.

RESULTS

All 15 participants completed the treatment and were included in the analyses. Mean patient age was 38.0±10.6 years and mean body mass index was 26.1±3.3. Twelve patients had already undergone other conservative treatments, but not in the six months before this study.

Clinical and functional results

The analysis revealed a decrease in NRS score (*Table 1*) and in lower limbs circumference measurements (*Table 2*) at each follow up. SF-12 questionnaire statistically significantly increased both in physical and mental composite scores (*Table 3*). The ICF analysis showed an improvement of "body function" (B domain) and "activities and participation" (D domain) (*Table 4*).

Ultrasound and Elastosonography Results

When compared with the baseline (T0), a

TABLE 1
Differences in NRS at baseline (T0), at the end of the Treatment (T1), 1 Month after the Treatment (T2), and after 6 Months (T3) of Follow up*

Outcome	Baseline T0	Post- treatment T1	T2	T3	P Value ⸸
NRS-Pain	6.9 ± 1.0	1.5 ± 1.2	1.5 ± 1.1	1.8 ± 1.1	< 0.001

NRS = Numeric Rating Scale
*Values are expressed as the mean ± standard deviation.
⸸ Friedman's Analysis of variance.

TABLE 2
Lower Limbs mean Circumference (cm) at Baseline (T0), at the end of the Treatment (T1), 1 month after the Treatment (T2), and after 6 Months (T3) of Follow up *

	Baseline	Post-treatment			
	T0	T1	T2	T3	P Value ⸸
proximal thigh	66.6±5.3	63.9±5.0	63.9±5.0	64.0±5.1	< 0.001
mid-thigh	56.6±4.6	54.0±4.3	53.9±4.2	54.1±4.3	< 0.001
distal thigh	46.3±3.5	44.3±3.6	44.2±3.6	44.4±3.7	< 0.001
proximal leg	39.0±2.0	37.1±1.9	37.1±1.9	37.2±1.9	< 0.001
Mid-leg	36.6±2.3	34.8±2.2	34.6±2.1	34.8±2.4	< 0.001
distal leg	24.9±1.1	23.2±1.2	23.1±1.2	23.2±1.3	< 0.001

*Values are expressed as the mean ± standard deviation.
⸸ Friedman's Analysis of variance.

TABLE 3
Mean Score in SF-12 Questionnaire at Baseline (T0). at the end of the Treatment (T1). 1 Month after the Treatment (T2), and after 6 Months (T3) of Follow up *

	Baseline	Post-Treatment			
	T0	T1	T2	T3	P Value ⸸
SF-12 MCS	40.4 ± 3.8	52.7 ± 2.4	53.8 ± 2.3	54.1 ± 1.9	< 0.001
SF-12 PCS	41.8±7.8	50.5±5.4	51.3±5.1	51.3±4.3	< 0.001

SF-12 = 12-Item Short Form Survey; MCS = Mental Score, PCS= Physical Score
*Values are expressed as the mean ± standard deviation.
⸸ Friedman's Analysis of variance.

TABLE 4
Median Score in ICF Function Domains at Baseline (T0), at the end of Treatment (T1), after 1 Month (T2), and after 6 Months (T3) of Follow up*

	Baseline	Post- treatment			
	T0	**T1**	**T2**	**T3**	**P Value ǂ**
B DOMAIN	10 (12; 14)	4 (3; 5)	3 (2; 4)	4 (2; 5)	< 0.001
D DOMAIN (Capacity)	16 (9; 18)	8 (5; 10)	8 (4; 9)	8 (4; 9)	< 0.001
D DOMAIN (Performance)	10 (7; 14)	5 (3; 7)	5 (3; 6)	5 (3; 7)	< 0.001

ICF = International Classification of Functioning; B DOMAIN = Body function, D DOMAIN = activities and participation for capacity and performance qualifiers.
*Values are expressed as the Median (first quartile; third quartile).
ǂ Friedman's Analysis of variance.

Table 5
Lower Limbs Mean Thickness (mm) at Baseline (T0), at the End of the Treatment (T1), and 6 Months after Treatment (T3)*

		Post – treatment		
	Baseline T0	**T1**	**T3**	**P Value ǂ**
Trochanteric region	33.0±9.4	26.3±7.9	26.3±7.9	< 0.001
Proximal thigh	21.8±4.9	15.6±4.6	15.7±4.4	< 0.001
middle thigh	17.8±4.4	13.1±2.9	13.2±2.9	< 0.001
distal thigh	18.5±3.5	14.0±2.7	14.0±2.8	< 0.001
proximal leg	10.2±2.7	7.6±2.3	7.6±2.3	< 0.001
middle leg	15.9±2.6	11.5±2.7	11.5±2.7	< 0.001
distal leg	17.2±3.1	11.0±1.6	11.1±1.6	< 0.001

*Values are expressed as the mean ± standard deviation.
ǂ Friedman's Analysis of variance.

statistically significant reduction in subcutaneous fat thickness was observed in each of the 7 measurement points at the end of treatment (T1) and at 6 months after treatment (T2) (all p<0.001) (*Table 5*). SAT assessment showed a reduction of subcutaneous echogenicity, and a better organization and visualization of connective tissue bundles at each follow up (p<0.001) for the three region examined (trochanteric region, distal thigh, and leg) (*Table 6*; *Fig. 1*). Moreover, a significant reduction in percentage of hardness was observed in the two regions of interest (ROIs) at trochanteric region, the superficial subcutaneous ROI (ElxZ1) and deep subcutaneous ROI (ElxZ2) that results in an increase in SAT elasticity (p<0.001) (*Table 7; Fig. 2*). Both ElxZ1 and ElxZ2 results significantly correlated with NRS-pain at T0 (R=0.482, p=0.034 and R=0.497, p=0.030, respectively), but neither at T1 (p>0.2) nor at T3 (p>0.09).

Side Effects

During the entire study period, there were no treatment-related side effects reported

TABLE 6
Distribution Cases for Grade (0-I-II) of Echostructural SAT Changes of the Lower Limbs at Baseline (T0), at the end of Treatment (T1), and after 6 Months of Follow up (T2) *

	Baseline			Post-Treatment						
	T0			T1			T2			P Value ⸸
	0	I	II	0	I	II	0	I	II	
Trochanteric region	2	12	16	4	24	2	4	24	2	<0.001
Distal thigh	0	16	14	4	24	2	4	24	2	<0.001
Distal leg	0	16	14	4	26	0	4	26	0	<0.001

*Values are expressed as the number of cases for each grade.
⸸ Chi squared test.

Fig. 1. Longitudinal ultrasonographic scan of the distal third of leg, at 4 cm from medial malleolus, (a) before treatment (T0), (b) at the end of treatment (T1), and (c) at 6 months after treatment (T3). Note that compared to the baseline (a) there is a reduction in SAT thickness (from 17.2 to 10.0 mm) and an improvement in the ultrasonographic pattern at T1 (b) and T2 (c).

by the patients. The only observation was the occasional appearance of small hematomas at the injection points of mesotherapy, which disappeared within 24-72 hours.

DISCUSSION

There are few studies in the available literature on the use of shock waves, mesotherapy, and kinesio taping in the treatment of lipedema. This pilot study showed that a multidisciplinary therapeutic approach could be helpful in addressing different pathological aspects of lipedema, such as pain, inflammation, lymphatic drainage, disability, and body image. Statistically significant changes mainly occurred after treatment and results were maintained at follow-up.

The increased perception of pain that typifies lipedema has been attributed to dysregulation of locoregional sensory nerve fibers through an inflammatory mechanism (5). There are several studies in the literature that report the analgesic and anti-inflammatory effects of shock wave therapy. These effects are due to increase of local perfusion with consequent stimulation of the formation of new blood vessels (neoangiogenesis) with greater local influx of blood and new cells, resulting in local oxygenation, improved tissue trophism and drainage of metabolic wastes (8). Moreover, ESWT plays a role as desensitization with a double mechanism: producing transient dysfunction of nerve excitability at the

TABLE 7
Percent Hardness (ELX% HDR) Mean of the Two Regions of Interest (ROIs) at Trochanteric Region, the Superficial Subcutaneous ROI (Z1), and Deep Subcutaneous ROI (Z2) at Baseline (T0), at the end of the Treatment (T1), and 6 Months after Treatment (T2) *

	Baseline	Post - Treatment		
	T0	**T1**	**T2**	**P Value ǂ**
ELX% HRD Z1	51.7±16.5	38.4±5.0	38.7±5.3	< 0.001
ELX% HRD Z2	66.6±14.5	41.8±5.7	41.9±5.9	< 0.001

ELX%HDR = SAT percentage of hard; Z1= superficial subcutaneous ROI, Z2= deep subcutaneous ROI
*Values are expressed as the mean ± standard deviation.
ǂ Friedman's analysis of variance.

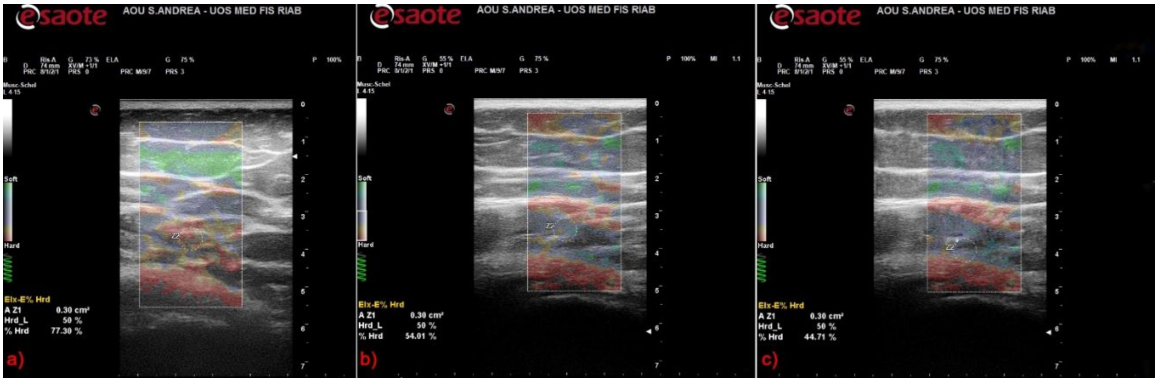

Fig. 2. Elastosonographic scan of the trochanteric region (a) before treatment (T0), (b) at the end of treatment (T1), and (c) at 6 months after treatment (T3). Note that compared to the baseline (a), there is a reduction in percentage of hardness from 77.3% to 44.71% (also depicted in red color) of the deep subcutaneous ROI (dotted circle) at T1 (b) and T2 (c).

neuromuscular junction by bringing about the degeneration of Acetylcholine receptor (AChR) and diminishing transmission of signals to the brainstem (19).

In 2005, Siemes et al first evaluated anti-fibrosclerotic effects of shock wave therapy in lipedema. They demonstrated that oxidative stress parameters in blood serum decreased and biomechanical skin properties leading to smoothening of dermis and hypodermis surface improved after serial shock wave application (20). There is also growing evidence that ESWT is able to improve skin properties both in terms of appearance as well as in terms of ultrasound improvement of the subcutaneous fat (21,22). In vivo and clinical studies showed that ESWT induces neocollagenesis and neoangiogenesis and upregulates the basic fibroblastic growth factor (FGF2) expression, leading to a reduction in thickness of subcutaneous fat tissue and changes in the skin structure with respect to depressions, elevations, roughness and elasticity (23-25). Angehrn and coworkers demonstrated that low-energy defocused ESWT causes remodeling of the collagen within the dermis, stimulates lipid mobilization, and improves lipolysis in areas with edema (26).

Previous research on patients with lipedema has reported enhanced adipose stem cell proliferation, which is likely responsible for the massive adipose tissue enlargement typically found in this condition (27). Adipocyte hyperproliferation because of hypoxia may lead to adipocyte necrosis, production of inflammatory cytokines, and macrophage infiltration (28). ESWT studies with humans and animals have verified effectiveness of shock waves on adipose tissue. On microscopic examination, the fat cell with its membranes were destroyed after shock wave treatment by two mechanisms: compression and cavitation (29,30). Furthermore, in vitro tests have shown that the application of acoustic pulses leads to increased short-term cell permeability; this cell permeability may stimulate the exchange of substances of fat cells and activate fat-splitting enzymes (phospholipases) through the beta-receptors on the fat cell membranes (22). A recent study evaluated the effects of shockwaves on adipogenesis. The authors demonstrated that low-energy shockwaves suppressed adipocyte differentiation by decreasing peroxisome proliferator-activated receptor γ (PPARγ) (31).

Although not pathognomonic, microangiopathy has been considered a typical histological feature of lipedema. This vascular alteration may be a consequence of the primary endothelial dysfunction through hypoxia mechanism (32). Several studies have demonstrated that the ESWT causes the release of mediators, such as vascular endothelial growth factor (VEGF) and nitrous oxide, which significantly increase angiogenesis and local blood circulation (8,33,34).

The rationale for the use of ESWT in lipedema of the lower limbs may be described as follows: reduce pain and inflammation, act on adipose tissue, and improve skin and body contour, as emerged from the analysis of the above studies. The choice of defocused shock wave as the first step of the treatment depends on the need to reach deep layers of subcutaneous tissue, up to 40mm from the skin, and to treat an enough large area respect to focused shock wave probe. The subsequent application of radial shock wave aims to stimulate the lymphatic drainage. The fatty acids and metabolic scores released by adipose tissue must be removed from the interstitial space where they would cause inflammation (35). In this regard, radial shockwave therapy (RSWT) has proven effective in improving lymphatic drainage and blood flow, and they are used afterwards for the treatment of lymphedema (36). RSWT enhances the expression of VEGF-C and VEGFR3, increases the formation of lymphatic vessels, and induces lymphangiogenesis (37).

Valid help was found in the use of mesotherapy to enhance the activity of the shock waves. Currently, this microinvasive therapeutic technique is widely used in the treatment of painful loco-regional conditions, as well as in the management of chronic venous insufficiency, edematous fibrosclerotic panniculopathy, and aging facial skin (38). A recent Italian study evaluated the efficacy of Lymdiaral® on patients affected by primary and secondary lymphedema. The results demonstrated the effectiveness of the therapeutic principle both in the reduction of limb circumferences and in the improvement of the parameters related to quality of life. Moreover, in literature it is widely demonstrated the analgesic effect of mesotherapy due to the action of the needle (10). Our protocol provides use of the complex phyto-homeopathic drug, Lymdiaral®, whose active components can selectively act on the extracellular matrix, the lymphatic system, and indirectly on the microcirculation with anti-inflammatory and draining result. Therefore, the use of mesotherapy, in association to RSWT, is helpful to determine a further analgesic, anti-inflammatory, and draining stimulus.

At the end of the treatment, patients underwent kinesio taping lymph application to improve and extend therapeutic outcomes. Kinesio taping is a technique that consists of applying neurofunctional elastic bandages for orthopedic dysfunctions. It has been adopted in clinical practice for dysfunctions in other systems, including the lymphatic system (39). Multiple theories have been proposed to explain the mechanisms of taping, including enhance cutaneous mechanoreceptors, improved blood and lymphatic circulation, reduced pain severity, realignment of joints, assisting postural alignment, and relaxing overused muscles (40). Kinesio taping improves vascular and lymphatic flow by lifting the skin from underlying fascia and therefore increasing the space between the dermis and epidermis. As a result, a pressure reduction at that point is generated and a displacement of lymph according to the pressure gradient is favored. It also is enhanced by body movements and muscle contraction (39). In this way, the lymphatic drainage system is stimulated 24 hours a day (41). In addition, the elasticity of the tape relieves compression of painful cutaneous mechanoreceptors, relieving pain (42). To consolidate the effects of the treatment, the use of class I - II compression garments was recommended as appropriate, because able to reduce the pain and discomfort of affected limbs (43).

The literature contains few studies focusing on the use of US in patients with lipedema. The characteristic increase in subcutaneous fat tissue seen in lipedema may be due to adipocyte hypertrophy and/or hyperplasia. In addition, there is evidence of an increase in the rate of adipocyte death, possibly due to hypoxia induced by excessive tissue enlargement, and infiltration of fat tissue by scavenger inflammatory cells (macrophages and mast cells) that produce scar tissue in an attempt to repair itself creating fibrosis and abnormal elastic fibers (26,44). These alterations result as increase of SAT thickness and echogenicity, disorganization of connective tissue bundles, and decrease tissue elasticity on ultrasound examination. We have found ultrasonography and sonoelastography useful for monitoring response to treatment in observing a reduction of SAT thickness and echogenicity with an improvement of structural pattern and elasticity. The positive correlation found between circumference measurements and SAT ultrasound thickness confirm the effects of the combined treatment on the adipose tissue. Moreover, the correlation between the reduction of pain and the improvement of SAT elasticity confirms the analgesic, anti-inflammatory, and anti-fibrosclerotic effects of shock wave treatment.

Shock wave application is a new approach for the treatment of lipedema, and it may represent an easy to handle, non-invasive, side effect free, conservative option therapy in this pathology. However, it is necessary to underline the importance of a personalized and multidisciplinary therapeutic approach that aims to educate to a proper lifestyle by dietary modification and adequate physical activity and to provide psychological support when necessary. It is also important considerer that lipedema is a chronic condition, and it is necessary to re-evaluate the choice of treatment based on its clinical evolution.

This study has several limitations: the small number of patients (due also to COVID-19 restrictions), long time of treatment performance where average time for each session was 45-50 minutes, and high number of sessions. Another limitation of the study is the lack of a control group due to ethical reasons of not treating patients, the rarity of the condition, and the treatment difficulties in the pandemic period. Another limitation is also the inability to be able to determine which of the individual treatments carried out was most effective in determining the results obtained. Considering that the last follow up was at 6 months from the end of treatment, it should be interesting to observe the effect of the combined therapy for a longer follow up. This is a pilot study that only describes our data and results, which confirm that the combined treatment used produces a wide variety of positive results, including reduction of pain and lower limb circumferences, and improvement in quality of life and disability in treated patients. Further investigations and clinical trials are required to confirm the efficiency of this combined therapy, potentially comparing with other possible interventions. Our specified application parameters could be useful for a future well designed, randomized clinical trial in a broader population including other morbidities (45).

CONCLUSIONS

This pilot study revealed positive effects of combined conservative treatment of defocused and radial shock wave therapy, mesotherapy, and kinesio taping lymph application in early-stage lipedema of the lower limbs. Results show a significant reduction of pain and leg circumference with consecutive improvement of quality of life, involving both physical and mental health. A reduction of disability was also observed, especially in the ICF categories of the *Body Image* (b1801) and *Sensation of Pain* (b280). The present study demonstrates for the first time, at the best to our knowledge, that the combination of defocused and radial shock wave therapy, mesotherapy and kinesio taping is a novel and promising noninvasive, feasible, safe strategy for the treatment of lipedema.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare no competing financial interests exist.

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