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# Efficacy of Cryocavitation in the Noninvasive Management of Lipedema: Preliminary Results of an Integrated Protocol

Ruiz-Silva, C[1]; Bueno, FCP [2] Moleiro, D[3]; Miranda, CE [4]; Siqueira- Silva, LS[5]; Lima-Martins, EE [6]

[1] *(Department, College/ Faculdade Facop, PHd, MSc, PT, Brasil)*
[2] *(Department, College/ Unievangelica, MSc, PT, Brasil).*
[3] *(Department, College/ Faculdade Facop, MSc, PT, Biomedicine Brasil).*
[4]*(Director of Research and Develoment Adoxy, MSc, Physicist, Brasil).*
[5]*(Centro de Estetica Avançada Soraia Lima, Aesthetics and cosmetology, Brasil).*
[6]*(Eloina Lima Estética, Aesthetics and cosmetology, Brasil).*

***Abstract:*** *Lipedema is a chronic and progressive disorder, a primary lipotrophy characterized by abnormal fat deposition, primarily in the buttocks and legs bilaterally. It is symmetrical and disproportionate. It is estimated to affect 10 to 18% of women in Europe and approximately 12.3% of the Brazilian female population.*

*Cytobiological studies suggest that the disorder arises primarily through alterations in the initial stages of cellular differentiation in adipogenesis. Gene expression of leptin and PPAR-gamma increases due to dysregulation of key signaling networks, including Bub1, leading to increased adipocyte proliferation and an alteration in mRNA.*

*Given the complexity of the pathophysiology and the limitations of conventional approaches, innovative therapies that target the cellular and microcirculatory mechanisms involved in lipedema have gained prominence. Among these approaches, cryocavitation stands out, a technology that combines the synergistic action of low-frequency ultrasound with cryotherapy, acting both on selective adipocyte apoptosis and on inflammatory and vascular modulation of the affected tissue.*

*Cryocavitation stimulates beta-adrenergic receptors and promotes mitochondrial cristae biogenesis. Cold stress and beta-adrenergic stimulation activate PERK, which phosphorylates N-acetylglucosamine transferase (OGT). OGT phosphorylates TOM70 at Ser94, increasing the import of the MIC19 protein into mitochondria, promoting cristae formation and respiration. This activates the transformation of white adipose tissue (with high lipids and few mitochondria) into beige adipose tissue (with low lipids and many mitochondria).*

*Conclusion:This study proposed a non-invasive and integrated therapeutic approach for the treatment of lipedema, a strategy called cryocavitation. This technological combination aims to act synergistically on the main pathophysiological targets of lipedema: adipocyte hypertrophy, chronic inflammation, microcirculatory dysfunction, and neuropathic pain.*

*Therapeutic ultrasound, through the phenomenon of unstable cavitation, promotes the separation of hydrogen and hydroxyls in interstitial fluids, generating a peroxidation effect on adipocyte membranes that favors adipocyte breakdown through apoptosis and increased vascular permeability. Furthermore, there is evidence of mitochondrial stimulation and partial conversion of white adipocytes to beige, favoring adaptive thermogenesis and possible modulation of the inflammatory response.*

*Tissue cooling, in turn, induces controlled heat shock with subsequent reactive hyperemia and activation of cellular stress proteins (HSP70), impacting specific apoptotic pathways. This thermal stimulus also contributes to the modulation of mitochondrial metabolism, activation of PERK/OGT, and a possible increase in the expression of UCP1, typical of beige adipose tissue. This conversion may represent a promising path to reducing the lipid-resistant phenotype present in lipedema.*

*The combined action of these technologies appears to contribute to the volumetric reduction of adipose tissue, aesthetic improvement, pain relief, and possible partial reversal of metabolic dysfunctions, while maintaining good tolerability and safety.*

*In a scenario where surgical treatments are still inaccessible to most patients, and pharmacological treatments remain scarce, cryocavitation emerges as a viable, technically sound, and economically sustainable alternative. Larger studies with longer follow-up and histological markers are recommended to further elucidate the physiological effects of this approach on lipedema.*

***Key words****: cryolipolysis, cryotherapy, lipedema, cryotonus, ultrasound, cryocavitation, cryo ultrasound, aesthetics.*

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## I. Introduction

Lipedema is a chronic and progressive disorder, a primary lipotrophy, characterized by abnormal fat deposition, mainly in the buttocks and legs, bilaterally, of subcutaneous adipose tissue, characterized by symmetrical and disproportionate fat deposition in the lower limbs and, in many cases, also in the upper limbs, sparing the hands and feet (RUIZ-SILVA, 2024). First described by Allen and Hines in 1940 at the Mayo Clinic, lipedema was initially confused with obesity and lymphedema, which delayed its recognition as a distinct clinical entity (ALLEN; HINES, 1940 apud KRUZPA et al., 2020). Currently, it is coded in the International Classification of Diseases – ICD-11 (EF02.2) as localized lipodystrophy, but it remains widely underdiagnosed (KRUZPA et al., 2020). The recent publication of the Brazilian Consensus on Lipedema (AMATO et al., 2025), developed by SBACV using the Delphi methodology, highlighted the multifactorial complexity of lipedema and established diagnostic and therapeutic guidelines that reinforce the need for conservative, physiological, and individualized approaches (AMATO et al., 2025).

The exact prevalence of lipedema is still uncertain due to the scarcity of population-based studies and diagnostic difficulties, but it is estimated to affect 10 to 18% of women in Europe (SHIVAT et al., 2020) and approximately 12.3% of the Brazilian female population, according to a recent epidemiological study by Amato et al. (2022), which administered a validated clinical screening questionnaire to a nationally representative sample.

The pathophysiology of lipedema involves multiple mechanisms still under investigation, including dysfunctions in angiogenesis, lymphangiogenesis, and adipogenesis. There is strong evidence of a genetic predisposition, with up to 60% of patients reporting a direct family history of the condition (KRUZPA et al., 2020). Lipedema is known to manifest primarily during periods of hormonal transition, such as puberty, pregnancy, and menopause, which reinforces the hypothesis of an estrogenic influence in its etiology (ISHFAQ et al., 2021).

From a cellular and molecular perspective, the adipose tissue of patients with lipedema presents adipocyte hyperplasia, increased capillary fragility, exacerbated proliferation of mesenchymal stem cells, and chronic inflammation with infiltration of M1 subtype macrophages (ISHFAQ et al., 2021). Transcriptomic studies reveal the dysregulation of more than 4,400 genes in the affected tissue, including alterations in extracellular matrix remodeling pathways, cell cycle, and lipid metabolism. Among the relevant markers, overexpression of the Bub1 gene, associated with cell proliferation and adipocyte differentiation, stands out (ISHFAQ et al., 2021). Corroborating these molecular findings, the Brazilian Lipedema Consensus (2025) recognizes chronic inflammation, extracellular fluid accumulation, and microvascular dysfunction as central processes in the pathophysiology of lipedema, present even in the early stages of the disease. Hormonal influence and genetic inheritance are also recognized as key elements in clinical progression (AMATO et al., 2025).

Cytobiological and protein expression studies in lipoaspirates removed from patients with lipedema suggest that the disorder arises primarily through alterations in the early stages of cellular differentiation in adipogenesis (AL-GHADBAN, 2019). Stromal vascular cells derived from adipose tissue of patients with lipedema are different (PRIGLINGER, 2017), while adipose stem cells from lipedema and control adipose tissue respond differently to adipogenic stimulation in vitro (BAUER, 2019). Therefore, there is increased gene expression of leptin and PPAR-gamma in lipedema adipocytes differentiated in vitro from adipose tissue-derived stem cells (AL-GHADBAN, 2019). Key signaling networks are dysregulated in patients with adipose tissue disorders; The molecular mechanisms of lipedema were identified by analyzing and comparing omics of whole tissue, adipocyte precursors (adipose tissue-derived stem cells – ADSCs), and adipocytes from patients with and without lipedema. 3 Significant differences were also found in gene expression and lipid and metabolic profiles in tissues, ADSCs, and adipocytes from patients with lipedema compared with unaffected controls. Functional assays demonstrated that dysregulated Bub1 signaling leads to increased proliferation of lipedema ADSCs, suggesting a potential mechanism for increased adipogenesis in lipedema. Transcriptional profiling of lipedema and non-lipedema ADSCs revealed significant differential expression of >3,400 genes, including some involved in the extracellular matrix and cell cycle/proliferation signaling pathways. Immunohistochemical analyses indicated degenerative and regenerative changes in lipedema tissue, characterized by crown-like structures (circumscribed necrotizing adipocytes)

supported by infiltrating CD68+ macrophages), a feature commonly seen in obese adipose tissue. These findings suggested increased adipogenesis in lipedema tissue, which may further lead to hypoxia similar to that observed in obesity, resulting in adipocyte necrosis and macrophage recruitment (SUGA, 2009; SHAVIT, 2010).

An important insight into lipedema and cryolipolysis is to consider that Brazilian researchers found these same cells when investigating freezing with suction cryolipolysis for 30 minutes followed by massage (PALAURO, 2024). Preadipocytes that undergo excessive apoptosis as they differentiate acquire relative

resistance to apoptosis (SORISK, 2000). Inhibitors of apoptosis (IAPs) suppress apoptosis by inhibiting caspase activity. Extracellular survival factors inhibit apoptosis in various pathways and bind to cell surface receptors, suppressing apoptosis. They stimulate an increase in the production of antiapoptotic Bcl2 proteins, such as Bcl2 and Bcl-XL. These proteins are activated by multiple adipogenesis pathways, which is the case of lipedema (RUIZ-SILVA, 2023; 2024).

The diagnosis of lipedema is primarily clinical, based on criteria such as disproportionate fat accumulation in the limbs, pain on palpation, orthostatic edema, and a tendency to form spontaneous hematomas. Imaging tests such as ultrasound, magnetic resonance imaging, and bioimpedance can be used to differentiate lipedema from other conditions such as lymphedema, obesity, and cellulitis (KRUZPA et al., 2020; ISHAQ et al., 2021). An important contribution to diagnosis comes from studies such as that by Amato et al. (2021), which established specific ultrasound criteria for lipedema, such as homogeneous thickening of subcutaneous tissue and the presence of hyperechoic fibrous septa.

Furthermore, the Brazilian Consensus on Lipedema (2025) reinforces the importance of a careful clinical diagnosis, with rigorous exclusion of differential diagnoses such as lymphedema, obesity, and chronic venous disease, and recommends the use of complementary methods, such as waist-to-height ratio (WHtR) and bioimpedance, to differentiate lipedema from other lipodystrophies (AMATO et al., 2025). Given the complexity of the pathophysiology and the limitations of conventional approaches, innovative therapies that target the cellular and microcirculatory mechanisms involved in lipedema have gained prominence. Among these approaches, cryocavitation stands out, a technology that combines the synergistic action of low-frequency ultrasound with cryotherapy, acting both on selective adipocyte apoptosis and on inflammatory and vascular modulation of the affected tissue.

The impact of lipedema on patients' quality of life is significant and multifactorial. In addition to chronic pain, hypersensitivity to touch, and a constant feeling of heaviness in the legs, many women suffer from reduced mobility, aesthetic embarrassment, and profound frustration due to lack of results with diet, exercise, or conventional procedures for localized fat. The condition predominantly affects women of working age, impacting their self-esteem, social, emotional, and even professional performance (KRUZPA et al., 2020).

Surgical approaches, such as tumescent liposuction, have been one of the only options with a substantial reduction effect on the affected volume. However, it is an invasive procedure, expensive, with anesthetic risks and requiring multiple sessions—in addition to presenting clinical contraindications in patients with vascular comorbidities, autoimmune diseases, or associated lymphedema (PODDA et al., 2021). Therefore, there is growing interest in conservative therapies with the potential for real physiological action on the affected tissue. This approach is aligned with the position of the Brazilian Consensus on Lipedema, which states that liposuction should be reserved for specific cases with compromised mobility and a joint evaluation between the clinician, surgeon, and patient. Alternatively, the consensus prioritizes evidence-based conservative interventions, such as physical therapies, personalized compression, an anti-inflammatory diet, low-impact exercises, and non-invasive technologies that promote inflammatory modulation and improved microcirculation (AMATO et al., 2025).

In this context, the application of non-invasive technologies such as low-frequency (40 kHz) therapeutic ultrasound and targeted cryotherapy represents an innovative and promising alternative. 40 kHz ultrasound acts primarily through the phenomenon of unstable cavitation—the formation, oscillation, and subsequent collapse of microbubbles in a liquid medium, inducing microjets and shock waves that generate controlled mechanical stress on adipose tissue and endothelial cells. This stress promotes increased vascular permeability, improves interstitial drainage, and stimulates the reabsorption of the chronic edema characteristic of lipedema (Olsson et al. 2008).

Furthermore, the oscillatory motion of ultrasound induces microcirculation and mitochondrial metabolism in adipocytes, promoting lipolysis and the reorganization of subcutaneous tissue. When applied synergistically with low temperatures—as occurs in controlled cryotherapy—the vascular and anti-inflammatory effects are enhanced.

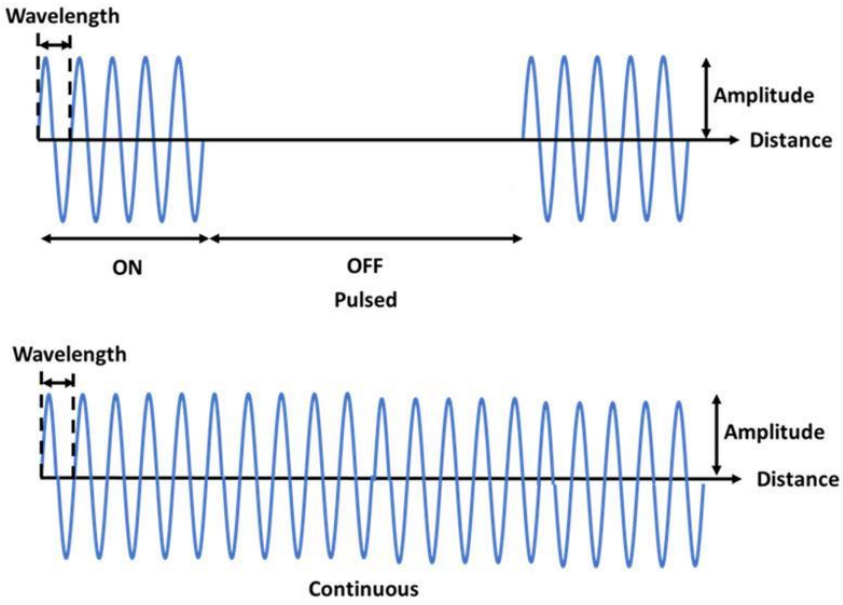
Cryotherapy, by exposing adipose and vascular tissue to temperatures between -5°C and -15°C, triggers a cascade of cellular events, including initial vasoconstriction, followed by reflex vasodilation, increased tissue oxygenation, and stimulation of the anti-inflammatory polarization of M2 macrophages (IKEDA et al., 2020). This immunological modulation is especially relevant in lipedema, where the chronic inflammatory component is directly associated with pain and adipose tissue fibrosis. Reinforcing this therapeutic proposal, the national consensus argues that physiological approaches that impact the inflammatory and vascular microenvironment are preferable in the early and intermediate stages of the disease. Interventions that induce macrophage polarization toward the M2 profile and reduce interstitial edema are especially indicated in the conservative management of symptomatic lipedema (AMATO et al., 2025).

Mobile gauntlet techniques combined with ultrasound-generated beta-adrenergic stimulation promote mitochondrial cristae biogenesis. Beige adipose tissue is a game-changer in the treatment of obesity and comorbidities due to its thermogenic and neurogenic effects (RUIZ-SILVA, 2023; RUIZ-SILVA, 2024). Cold stress or beta-adrenergic stimulation activate PERK, which phosphorylates N-acetylglucosamine transferase

(OGT). OGT phosphorylates TOM70 at Ser94, increasing the import of the MIC19 protein into mitochondria, promoting cristae formation and respiration. This activates the transformation of white adipose tissue (with many lipids and few mitochondria) into beige adipose tissue (with few lipids and many mitochondria) (RUIZ-SILVA, 2023; RUIZ-SILVA, 2024). The endoplasmic reticulum (ER) kinase PERK is extremely sensitive to cold stress and sympathetic nervous system (SNS) stimuli, promoting mitochondrial cristae formation by increasing TOM70-assisted mitochondrial import of MIC19 (RUIZ-SILVA, 2023; RUIZ-SILVA, 2024). Through cryolipolysis, the multiplication of healthy mitochondria is activated without the predominance of survival factors with anti-apoptosis proteins, through the mobile cryolipolysis gauntlet, generating the activation of the MICOS cristae organization system, through the translocation of MIC19 and outer membrane translocation receptors 70. Beta-adrenergic stimuli also promote the ridge biogenesis. The big secret is to change this mitochondrial characteristic through fission ((RUIZ-SILVA, 2023; MARTINS, RUIZ-SILVA, 2021; RUIZ-SILVA, 2024; YAU, 2020). The association of cold with the stimulation of the endings of the sympathetic nervous system through 40 kHz ultrasound in a LICUS (Low Intensity Continuous Ultrasound) system promotes activation of the PERK and Micos systems. The action of freezing and simulating physical activity through ultrasound (release of hormones similar to physical activity) after lipolytic stimuli (lipolysis) finds an environment with many lipid droplets that influence the organization of the cristae; Mitochondria perform β-oxidation of fatty acids, however, when stimulated by cold, drastic changes in morphology occur due to activation of PERK (GALLARDO, 2021). The density of the cristae increased dramatically after exposure to cold, forcing the Overexpression of perilipin 5 (PLIN5). This increase in cristae density may be driven by PERK-dependent ER stress (LATORRE-MURO, 2021).

Ultrasound with the LICUS technique – Low-Intensity Continuous Ultrasound

consists of using 40 kHz ultrasound at an intensity of 0.3 watts/cm² in continuous mode. The human body is extremely sensitive to mechanical impulses and minimal vibrations from ultrasound in LICUS, especially when transmitted at long-wave frequencies. It has central and peripheral neuromodulatory effects and plays a significant role in activity, suppression, and proliferation at low intensities (Uddin, 2021).




It increases NO (nitric oxide), activates molecular and cellular pathways that lead to cell differentiation and transcription factors, increases macrophage migration and the Ca gradient in the membrane, activates fibroblasts and healing, at low intensities (Lucas, 2020; Draper, 2020).

The properties of cavitation and microtransmission always occur in continuous cycles of compression and reflation of microbubbles within inert fluids, leading to localized stress and loosening of the matrix and cell membrane (Uddin, 2021). In the 2021 systematic review, we demonstrated increased cellular nutrition and oxygenation, anti-inflammatory effects, angiogenesis, increased NO at 0.25 w/cm², sonophoresis at 0.3 w/cm², healing at 0.3 w/cm², capillarization and myofiber formation, and pain reduction at 0.4 w/cm² (Uddin, 2021).

Increased mitogenic factor C ERK/MARK (Lucas, 2020).

In a study by Liu et al. (2023), a model of secondary lymphedema was established in the tail of rats through surgical ligation of the lymphatic vessels. LICUS treatment was administered 3 days after model creation, with a total treatment period of 28 days. After 28 days of treatment, compared with the lymphedema group, the tail circumference and subcutaneous tissue thickness of the rats in the LICUS group decreased by 30%, the

proportion of collagen fibers and the cross-sectional area of the lymphatic vessel decreased, and blood flow in the tail increased significantly (LIU, 2023).

**Cryolipolysis using the Mobile Handle**

Mobile handle techniques associated with beta-adrenergic stimulation promote mitochondrial cristae biogenesis (Martins; Ruiz-Silva, 2021; Ruiz-Silva, 2023; (Ruiz-Silva, 2024; Ruiz-Silva, 2024). Cold stress or beta-adrenergic stimulation activate PERK, which phosphorylates N-acetylglucosamine transferase (OGT). OGT phosphorylates TOM70 at Ser94, increasing the import of the MIC19 protein into mitochondria, promoting cristae formation and respiration. This activates the transformation of white adipose tissue (with high lipids and few mitochondria) into beige adipose tissue (with low lipids and many mitochondria) (Ruiz-Silva, 2024).

Ultrasound in The LICUS system promotes anti-inflammatory effects, oxygenation, increased collagen production, toning tissue, and an increase in the number of mitochondria. The main purpose of the SNS is to stimulate the body's fight-or-flight response while remaining constantly active to maintain homeostasis (MOTIEJUNAITE, 2021). Microcurrent stimulation exerts "hormone-like effects," including the secretion of norepinephrine in the postganglionic sympathetic neuron of the nervous system and the G-protein in the cell membrane (AL-TUBAIKH, 2018). Norepinephrine secretion increases by binding to the β3-adrenoreceptor (β3-AR), which in turn converts ATP to cAMP in adipocytes (NOITES, 2016). Therefore, MCT induces lipolysis through stimulation of the postganglionic sympathetic neuron (MIWA, 2002; Poot, 2007).

**Physics of Cryocavitation (Fusion)**

The synergistic interaction between tissue cooling (cryotherapy) and the application of low-frequency ultrasound at 40 kHz (LICUS) is defined in this study by the concept of "Fusion," represented by the equation:

$$F = \sum (Cryo + LICUS) + S$$

Where:

- F is the final therapeutic effect of the combined technique;
- Cryo represents the thermal and physiological effects induced by cryotherapy;
- LICUS refers to Low Intensity Continuous Ultrasound;
- S represents the synergistic component resulting from the interaction of the two physical stimuli.

First, it is important to understand that ultrasound is a mechanical wave that propagates through a medium and can cause various effects on tissue, such as heating, mechanical stress, and cavitation. Cavitation is the formation and collapse of bubbles in a liquid medium, which can create microjets and shock waves that induce mechanical stress in the tissue.

Physically, cavitation is a key phenomenon in this approach, being intensified by cryogenic conditions. Unstable cavitation occurs when gas or vapor bubbles, initially formed in regions of low pressure induced by ultrasound, violently collapse, generating microjets and shock waves capable of inducing profound mechanical effects on adipose tissue and the interstitial medium.

The propensity for unstable cavitation increases significantly with decreasing temperature. The explanation is rooted in three physical fundamentals:

Reduction in vapor pressure with cooling, according to the equation:

$$Pv(T) \propto exp\left(-\frac{L}{RT}\right)$$

Vapor pressure reduction with cooling, according to the equation:

$$Pv(T) \propto exp\ (-\ L/RT)$$

Cavitation nucleation criterion, which is facilitated when the local pressure drops below the vapor pressure reduced by cooling:

$$P < Pv(T)$$

Rayleigh-Plesset equation, which describes the dynamics of bubble growth and collapse:

$$\rho = \left(\boldsymbol{R\ddot{R}} + \frac{\mathbf{3}}{\mathbf{2}}\boldsymbol{\dot{R}}^{\mathbf{2}}\right) = Pb - P\infty - \frac{\mathbf{2}\boldsymbol{\sigma}}{R} - \mathbf{4}\boldsymbol{\mu}\frac{\boldsymbol{\dot{R}}}{\boldsymbol{R}}$$

In this context, cooling the interstitial fluid:
• Decreases viscosity and vapor pressure;
• Increases the pressure gradient between the bubble interior and the liquid medium;
• Promotes unstable collapse, generating beneficial biophysical effects such as adipocyte lysis and extracellular matrix reorganization.

Previous studies (Matsumoto et al., 1998; Mulvana et al., 2010) have demonstrated that reduced temperatures increase the cavitation activity of ultrasound. These physical effects, amplified by the cooled environment, represent the scientific basis for the combined use of ultrasound and cryotherapy in the noninvasive management of lipodystrophies such as lipedema.

There are two types of cavitation: stable and unstable. Stable cavitation occurs when small bubbles oscillate in response to the ultrasound wave, without collapsing. Unstable cavitation, on the other hand, occurs when bubbles grow in size and eventually collapse violently, producing high-speed jets and shock waves.

One of the main factors affecting the behavior of ultrasound waves is temperature. Specifically, as temperature decreases, the likelihood of unstable cavitation bubble formation increases.

Several studies demonstrate that reducing temperature can significantly intensify the occurrence of unstable cavitation. Matsumoto et al. (1998), in a study published in Ultrasonics Sonochemistry, investigated the influence of temperature on cavitation activity induced by low-frequency (20 kHz) ultrasound in water. The authors observed that as the temperature was reduced from 25°C to 10°C, there was a significant increase in cavitation activity, measured by sonochemiluminescence and sonoluminescence. They proposed the following equation to describe the relationship between the cavitation threshold and temperature:

$$th = P0 \cdot exp\left(-\frac{\boldsymbol{Ea}}{kT}\right)$$

Where:
Pth is the threshold pressure for cavitation,
P0 is an empirical constant,
Ea is the activation energy of the process,
k is the Boltzmann constant,
T is the absolute temperature.
Additionally, Mulvana et al. (2010) evaluated the thermal effects on cavitation induced by high-frequency ultrasound (1.1 MHz) in water. They found that bubble collapse was more intense at lower temperatures, generating greater local release of thermal energy. To express the influence of temperature on bubble growth, the authors proposed the equation:

$$Rmax = R0 \cdot exp(aT)$$

Where:
Rmax: the maximum radius reached by the bubble before collapse,
R0: an initial constant,
a: a coefficient dependent on the medium and experimental conditions,
T: the temperature.

These findings reinforce that environments with reduced temperatures favor the formation and violent collapse of bubbles—central characteristics of unstable cavitation—thus increasing the therapeutic efficacy of approaches that integrate ultrasound and cryotherapy.

Researchers have demonstrated that cooling the piezoelectric crystal used in ultrasound equipment can significantly influence the intensification of unstable cavitation. Specifically, cooling promotes a decrease in the vapor pressure of the surrounding liquid, increasing the pressure difference between the bubble interior and the external environment, which favors the nucleation and collapse of cavitational bubbles.

The dynamic behavior of these bubbles—especially in unstable regimes—can be described by the Rayleigh-Plesset equation, which models the temporal variation of the bubble radius (R(t)) as a function of the physical properties of the medium:

$$R\,\frac{d2R}{dt^2} + \frac{3}{2} + \left(\frac{dR}{dt}\right)^2 + \frac{4\nu L}{R}\,\frac{dR}{dt} + \frac{2\gamma}{\rho L R} + \frac{\Delta P(t)}{\rho L} = 0$$

Where:
R(t) is the bubble radius;
ρLé: the liquid density;
νL: the kinematic viscosity of the liquid medium;
γ: represents the surface tension between the bubble and the liquid;
ΔP(t) = P∞(t) - Pb(t), where Pb(t) is the internal pressure of the bubble and P∞(t) is the pressure in the fluid distant from the bubble.

The equation shows that factors such as viscosity, surface tension, and density directly influence bubble growth and collapse. Reducing the temperature, by decreasing the viscosity and vapor pressure of the medium, enhances accelerated bubble growth and makes collapse more violent. These are typical characteristics of unstable cavitation.

Thus, the use of cryo-ultrasound in the Fusion system, in which the crystal is actively cooled, optimizes the generation of unstable bubbles in subcutaneous adipose tissue. This physical effect is crucial for amplifying the mechanical and biophysical mechanisms of adipocyte disruption, extracellular matrix reorganization, and increased vascular permeability.
Based on these principles, the present study proposes a therapeutic approach based on solid physiological evidence, with the potential to directly address the pathophysiological pillars of lipedema: disproportionate fat accumulation, chronic inflammation, and microcirculatory impairment. Next, we investigate the clinical effects of the combined application of cryotherapy and ultrasound in the non-invasive management of this condition.

## II. Methodology

To ensure sample homogeneity and internal validity of the study, strict eligibility criteria were defined. Participants were selected through detailed clinical screening, conducted by a specialized team, using a validated lipedema diagnostic protocol, complemented by a physical examination.
Inclusion Criteria
Patients who met the following criteria were included in the study:
• Female, aged between 25 and 55 years;
• Confirmed clinical diagnosis of grade II or III lipedema, according to the Schingale classification (2011);
• Distribution of lipedema in the lower limbs, with a history of lipodystrophic accumulation resistant to diet, exercise, and lymphatic drainage;
• Body Mass Index (BMI) between 20 and 34.9 kg/m², excluding grade II or higher obesity;
• Ability to understand and agree to the procedures, including signing the Informed Consent Form (ICF);
• Absence of previous invasive procedures in the treated area (liposuction, cryolipolysis, etc.) in the last 12 months;
• Availability to attend all sessions and evaluations specified in the research protocol.
Exclusion Criteria
Patients who presented one or more of the following conditions were excluded:
• Diagnosis of primary or secondary lymphedema, confirmed by lymphoscintigraphy or clinical criteria;
• Use of medications that may interfere with the inflammatory or metabolic response (e.g., corticosteroids, beta-blockers, anticonvulsants);
• Presence of active autoimmune diseases or severe peripheral vascular disorders;
• Pregnant or lactating women, or women suspected of being pregnant;
• History of hypersensitivity to cold (e.g., cold urticaria, Raynaud's disease, cryoglobulinemia);
• Metal implants, pacemakers, or electronic devices in the treated area;
• Participation in another clinical study in the last 90 days. Protocol Parameters
The suggested standardized clinical sequence follows these steps for each session:
1. Cleansing the treated area with a 2% chlorhexidine aqueous solution, ensuring adequate asepsis of the epidermis.
2. Application of CrioTech® protective gel (ANVISA registration: 81151320014), specifically for cryotherapy procedures, to protect the superficial layers of the skin against possible thermal damage.
3. Application of cryocavitation (continuous mode, 50W) for 8 minutes per 10x15 cm area, at a temperature of -5°C, with continuous and controlled movement of the applicator over the treated quadrant.

Fusion, the new applicator, can be called Technological Mutualism, as it is a benefit resulting from the combination of two Adoxy devices, the Asgard and the Hybrius, to create a new product category for aesthetics: cryocavitation:


## III. -Results

Figures 1 to 5 demonstrate the results of the proposed protocol.

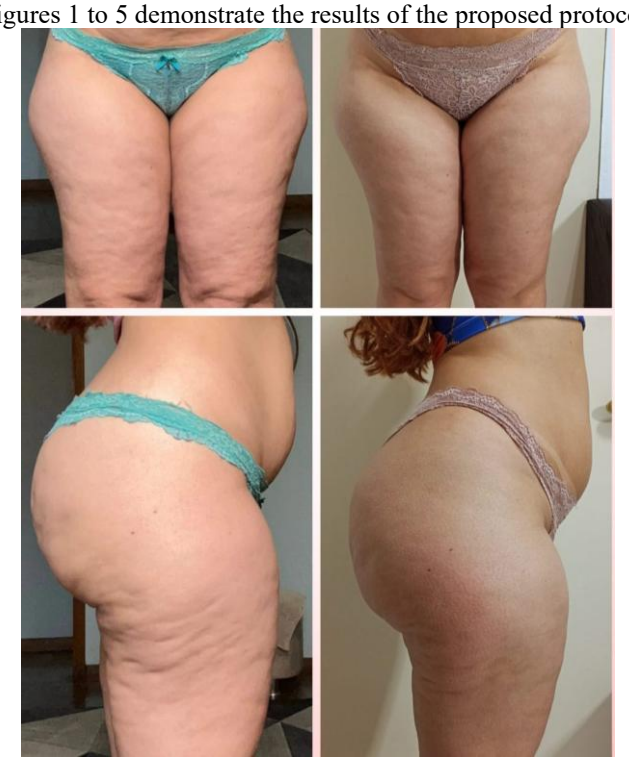


Photo 1: Patient LMM, 48 years old, Dr. Soraia Lima

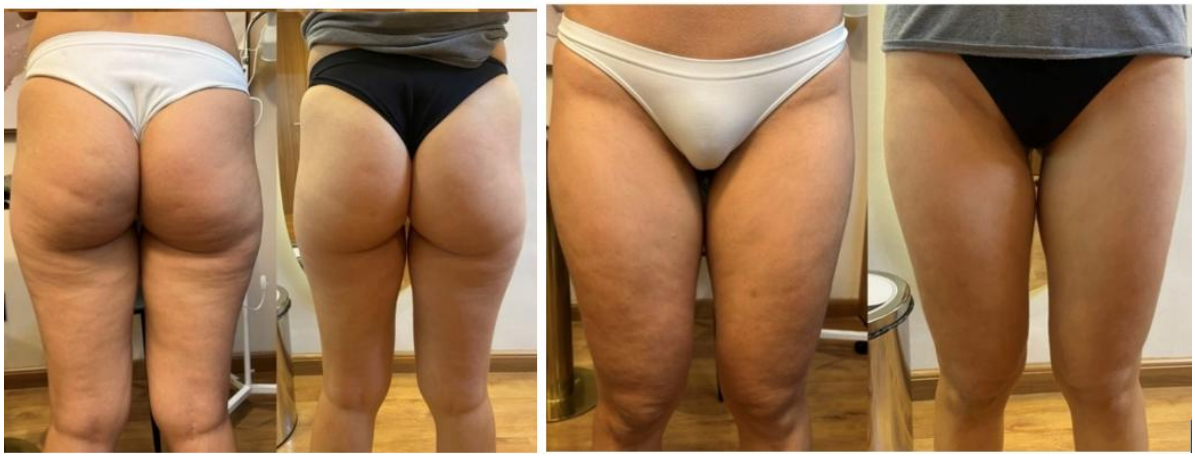


Photo 2: Patient AE, 37 years old, Eloina Lima

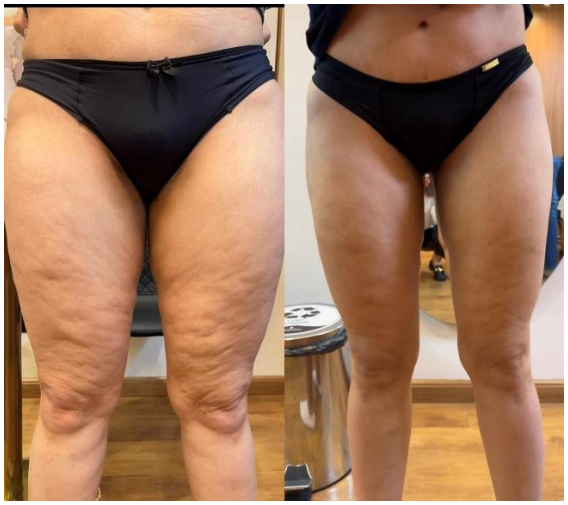


Photo 3: Patient MA, 44 years old, Eloina Lima

Photo 4: Patient DA, 37 years old, Eloina Lima

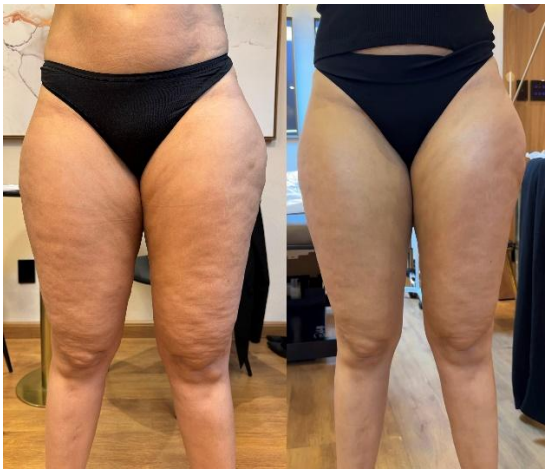


Photo 5: Patient LF, 39 years old, Eloina Lima

## IV. Conclusion

The present study proposed a non-invasive and integrated therapeutic approach for the treatment of lipedema, a strategy called cryocavitation. This technological combination aims to act synergistically on the main pathophysiological targets of lipedema: adipocyte hypertrophy, chronic inflammation, microcirculatory dysfunction, and neuropathic pain.

Therapeutic ultrasound, through the phenomenon of unstable cavitation, promotes the separation of hydrogen and hydroxyls in interstitial fluids, generating a peroxidation effect on adipocyte membranes that favors adipocyte breakdown through apoptosis and increased lymphatic vascular permeability (ZOU, 2021; Ruiz-Silva, 2025). Furthermore, there is evidence of mitochondrial stimulation and partial conversion of white adipocytes to beige adipocytes, favoring adaptive thermogenesis and possible modulation of the inflammatory response (FISCHER et al., 2020). Tissue cooling, in turn, induces controlled heat shock with subsequent reactive hyperemia and activation of cellular stress proteins (HSP70), impacting specific apoptotic pathways. This thermal stimulus also contributes to the modulation of mitochondrial metabolism, activation of PERK/OGT, and a possible increase in the expression of UCP1, typical of beige adipose tissue (JIANG et al., 2017). This conversion may represent a promising path to reducing the lipid-resistant phenotype present in lipedema.

The combined action of these technologies appears to contribute to the volumetric reduction of adipose tissue, aesthetic improvement, pain relief, and possible partial reversal of metabolic dysfunctions, while maintaining good tolerability and safety.

In a scenario where surgical treatments are still inaccessible to most patients, and pharmacological treatments remain scarce, cryocavitation emerges as a viable, technically sound, and economically sustainable alternative. Larger studies, with longer follow-up and histological markers, are recommended to further elucidate the physiological effects of this approach on lipedema.

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