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Treatment Of Lipedema Using Cryolipolysis Associated With Microcurrents

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Abstract:
Through a literature review, we present the technique of cryolipolysis with a mobile gauntlet as a treatment for lipedema. Since lipedema is a chronic disease with a high incidence that affects body aesthetics and self-esteem, it needs treatment in order to avoid emotional illnesses. Lipedema is a disease that occurs in adipose tissues through primary lipotrophy characterized by abnormal fat deposition, mainly in the buttocks and legs bilaterally. The mobile gauntlet technique associated with beta adrenergic stimuli promotes the biogenesis of mitochondrial crests, acting on beige adipose tissue as a treatment for obesity and comorbidities due to its thermogenic and neurogenic effect. The described technique is applied using the plates on a movable gauntlet in 4 cycles of 5 minutes in each 30 x 30 cm area associated with the use of microcurrents.
Objective*:The objective of this study was to review the literature on the cryolipolysis technique using a mobile handle and its association with microcurrents in lipedema in order to reduce adipose tissue and tone the dermis, reducing pain and the volume of lipedema, with the presentation of clinical cases.*
Materials and Methods*: In this study, we performed a comprehensive review of all scientific articles available and indexed in PubMed and Web of Science over the last 20 years on this technology and its effects on lipedema. We discussed the scientific evidence available from clinical studies and analyzed the effects and possible mechanisms of action on lipedema by associating microcurrents. The treatments were performed using the mobile plate cryolipolysis handle technique, with intervals for reperfusion. We used 4 series of 5 minutes of freezing and in the intervals 3 minutes for return of circulation, that is, reperfusion without injury. We demonstrated the result after 3 sessions.*
Results*: The association of cold with stimulation of the sympathetic nervous system through electrotherapy promotes activation of the PERK and MICUS systems. The action of freezing and simulating physical activity through microcurrent (release of hormones similar to physical activity) after lipolytic stimuli (electrolipolysis) encounters an environment with many lipid droplets that influence the organization of the ridges; Mitochondria perform β-oxidation of fatty acids, but when stimulated by cold, drastic changes in morphology occur due to activation of PERK; (Gallardo-Montejano, 2021).*
The mobile handle promotes the selective reduction of adipose cells and is effective in the treatment of cellulite and lipedema through the remodeling of dermal collagen (cryodermatringe). Histological analysis confirmed a selective and gradual reduction of adipose tissue by programmed death (apoptosis) triggered by reperfusion. The safety of the method is highlighted by the absence of significant increases in liver enzymes or serum lipids. Molecular studies did not demonstrate changes in peroxisome proliferator-activated receptor (PPAR) transcripts. No changes were evident in the transcripts, which highlights the safety of the technology used (Ferraro, 2012). In our case study, the patients were satisfied with the results, as shown in the photos.
Conclusion: *The literature review presented histological and biochemical aspects of lipedema. Although it is a disease considered primary lipodystrophy, with a high incidence, more studies on treatments are still needed to improve the quality of life and self-esteem of those with the disease.*
Among the treatments presented in the literature, the cryolipolysis technique with a mobile handle is presented as a treatment that reduces adipose tissue, as well as reduces the process of edema and inflammation with the association of microcurrent.
The plates promote reperfusion in adipocytes, generate reactive oxygen species (oxidation) and activate apoptosis. Adipocytes are reactive to thermal shocks. The mobile handle promotes the selective reduction of adipose cells and is effective in the treatment of dermal collagen remodeling.
Concomitant with this effect, there is the activation of PERK, which phosphorylates N-acetylglucosamine transferase (OGT), phosphorylating TOM70 at Ser94, increasing the import of the MIC19 protein into the mitochondria and promoting the formation of ridges and the formation of beige adipose tissue, rich in UCP1, which reinforces our hypothesis that in lipedema we need to inhibit transcription factors, PPRA gamma, and adipocyte typology starting with the mitochondria and their organelles responsible for inhibiting apoptosis (NAIPS).

Comparative results in the photodocumentation in the physical evaluation before and after the procedure, followed up in reevaluation, demonstrate promising results with the application methodology in lipedema patients submitted to the protocol presented by the authors.
Keywords: *cryoliolysis, adipose tissue, lipedema.*

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I. Introduction

Lipedema affects 12.3% of Brazilian women and most do not have access to adequate treatments because professionals are not qualified and do not know how to differentiate its diagnosis and it is commonly confused in treatment centers, thus limiting the correct diagnosis and subsequently adequate and effective treatment. Approximately 11 million Brazilian women have Lipedema, a disease that affects millions of people worldwide (Amato, 2022). Because lipedema is a little-known chronic and progressive disease of adipose hyperdeposition, it is often confused with obesity and causes significant impairment of mobility and quality of life (Kruppa, 2020; Ishaq, 2021). It is still unclear whether lipedema should be better defined as a primary lipodystrophy (pathological adipogenesis) or as a primary microangiopathy of small blood and lymphatic vessels. It was first described by Allen and Hines in 1940, and since then, lipedema has been characterized as an abnormal deposition of fat in the buttocks, thighs, hips, and legs bilaterally. This condition results in a disproportionate increase in volume in these areas of the body, creating an appearance of "column legs" or "bell-shaped legs", which may be concomitant with orthostatic edema. (Vyas, 2024) Wold (1951) presents lipedema of the legs as a syndrome characterized by fat legs and edema, however, Bauer in 2019 defines lipedema as the enigmatic disease of peripheral fat. It is important to emphasize that lipedema is not directly related to overweight or obesity, as the accumulated fat is different from common fat. Despite an estimated prevalence of 10% in the general female population, its cause is still unknown. (Kruppa, 2020;) In lipedema, fat is distributed irregularly and symmetrically in the legs, often up to the ankles, creating a characteristic contour.

Inflammatory cells, fibrosis, and edema are consequences of the pathophysiological hypothesis that involves primary microvascular dysfunction in the lymphatic and blood capillaries, due to the hypoxic stimulus caused by the excessive expansion of adipose tissue, which results in endothelial dysfunction leading to a mechanical disorder of lymphatic drainage (Al Ghadbon, 2019). Another characteristic of lipedema is related to pain; increased pain perception has been attributed to dysregulation of locoregional sensory nerve fibers through the inflammatory mechanism and edema. (Al Ghadban, 2020; 2024), injury to the endings of sympathetic innervation.

It is described in the literature that the disorder is the result of a polygenetic alteration mediated in the distribution pattern of estrogen receptors alpha and beta (ER) in the white adipose tissue of the affected areas (ER-α expression ↓, ER-ß expression ↑) (Wiedner, 2018; Suga, 2009). Histologically, adipose hyperdeposition occurs; in lipedema, subcutaneous adipose cells become more numerous (hyperplasia) or just larger (hypertrophy) (Al Ghadban, 2020; 2024). Cytobiological and protein expression studies in lipoaspirates taken from patients with lipedema suggest that the disorder arises mainly through alterations in the initial stages of cellular differentiation in adipogenesis (Al Ghadban, 2020). Stromal vascular cells derived from adipose tissue of patients with lipedema: They are different (Priglinger, 2017), whereas adipose stem cells from lipedema and control adipose tissue respond differently to in vitro adipogenic stimulation (Bauer, 2019). Therefore, there is an increase in gene expression of leptin and PPAR-gamma in lipedema adipocytes differentiated in vitro from adipose tissue-derived stem cells (Al-Ghadban, 2020).

Major 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 or without lipedema. (ISHAQ, 2021); significant differences in gene expression and lipid and metabolic profiles were also found in tissues, ADSCs and adipocytes from lipedema patients 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 ADSCs and non-lipedema ADSCs revealed significant differential expression of >3400 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 (necrotizing adipocytes surrounded 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 seen in obesity, resulting in adipocyte necrosis and macrophage recruitment (Suga, 2009; Shavit, 2018)

Genetic research has not found a specific relationship of dysfunction of a specific transmission gene (Morgan, 2024)

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 (Sorisky, 2000). Inhibitors of apoptosis (IAPs) act to suppress apoptosis by inhibiting caspase activity. Extracellular survival factors inhibit apoptosis in several 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; activated by multiple adipogenesis, which is the case of lipedema. (Ruiz-Silva; Moleiro; Rodrigues et.al, 2024)

Injury to sympathetic innervation, the lack of axonal nerve transmission generates injury and blockage of the electrical bioconductivity of the SNS, activating hyperplasias, mainly after vacuum compression and massage after cryolipolysis (Jalin, 2020; Strounza, 2018;). We need stimulation of nerve endings of the sympathetic system to generate beige adipose tissue. With the transient decrease in sympathetic neural stimuli, it is possible to activate pre-adipocytes (Seaman, 2016; Ho, 2017). Excessively hypertrophic white adipose tissue, continuously undergoes necrosis, activates transcription factors (PPAR gamma) causing adipocyte hyperplasia, which generates compression of sympathetic innervation, hypoxia, and generates continuous inflammation of the adipose tissue (; Martins; Ruiz-Silva, 2022; Ruiz-Silva, 2022; 2023; 2023).

MICOS deficiency leads to a coarse internal membrane architecture, and these mutations affect MICOS function and are responsible for a diverse spectrum of human diseases (Ruiz-Silva, 2023). The reduction of adipose tissue is energy-dependent and can be achieved by reducing fat stores (lipolysis) or by permanent removal of adipocytes, necrosis and apoptosis. Lipolysis is a metabolic process that degrades triglycerides present in adipose cells into their constituent molecules, glycerol and free fatty acids (FFA), through hydrolysis. (Ruiz-Silva, 2023; 2024).

Mobile gauntlet techniques associated with beta-adrenergic stimuli 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 (Martins; Ruiz-Silva, 2021; Ruiz-Silva, 2023; (Ruiz-Silva; Moleiro; Rodrigues; 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; Moleiro; Rodrigues et.al, 2024)

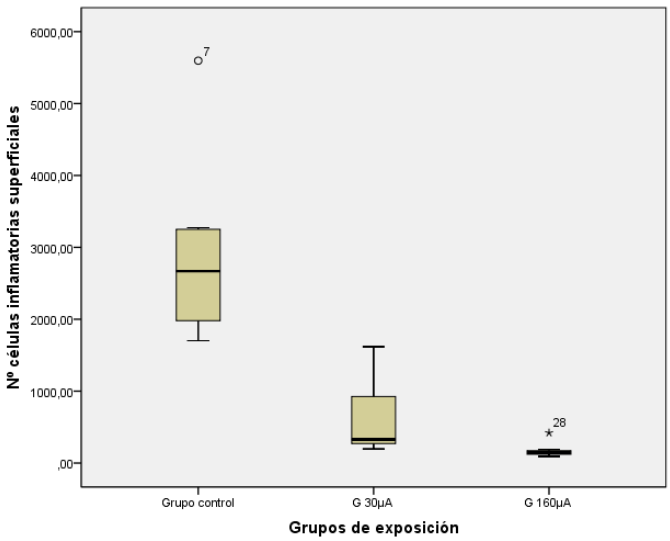
The endoplasmic reticulum (ER) kinase PERK is extremely sensitive to cold stress and sympathetic nervous system (SNS) stimuli, promoting the formation of mitochondrial cristae by increasing TOM70-assisted mitochondrial import of MIC19 (Ruiz-Silva, 2023; 2024). Through cryolipolysis, the multiplication of healthy mitochondria is activated without the predominance of survival factors with anti-apoptosis proteins, through the mobile cryolipolysis handle, generating the activation of the MICOS ridge organization system, through the translocation of MIC19 and outer membrane translocation receptors 70. Beta-adrenergic stimuli also promote the biogenesis of ridges. The big secret is to change this mitochondrial characteristic through fission (Yau, 2020; Martins; Ruiz-Silva, 2021; Ruiz-Silva, 2023; 2023). The association of cold with the stimulation of the sympathetic nervous system through electrotherapy promotes activation of the PERK and Micos systems. The action of freezing and simulating physical activity through micro-current (release of hormones similar to physical activity) after lipolytic stimuli (electrolipolysis) 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-Montejano, 2021)

Cristal density increased dramatically after cold exposure, forcing the overexpression of perilipin 5 (PLIN(5). This increase in ridge density may be driven by PERK-dependent ER stress (Latorre-Muro et al., 2021). Microcurrents or TCM, Cellular Microtherapy consists of the application of low-intensity (μA) and low-frequency currents similar to the endogenous electric fields generated during tissue repair systems (Ruiz-Silva, 2006; 2016; Xu, 2021; Lee, 2024).

In inflamed adipose tissue, a low concentration of endogenous electric current in the tissues reduces the oxygen supply, decreasing the arrival of growth factors, oxygen generating hypoxia and inhibiting collagen synthesis (Ruiz-Silva, 2006; 2016; Xu, 2021; Coy, 2022). Microcurrent compensates for the bioelectricity that is decreased in hypoxic and inflamed tissue (Ruiz-Silva, 2006; 2016; Xu, 2021; Coy, 2022) generating ATP and Mitogenesis. The presence of microcurrent generates a constant intensity current, increased electrical flow, dissociating the water molecule, hydrogen and hydroxyl ions are formed around both electrodes. The hydrogen that leads to the creation of ATP, it follows that, as a residual effect after the microcurrent stimulator is turned off, the production of ATP continues at the site. This ATP formation can be explained through Mitchell's chemiosmotic theory (Cheng, 1985, Ruiz-Silva, 2016).

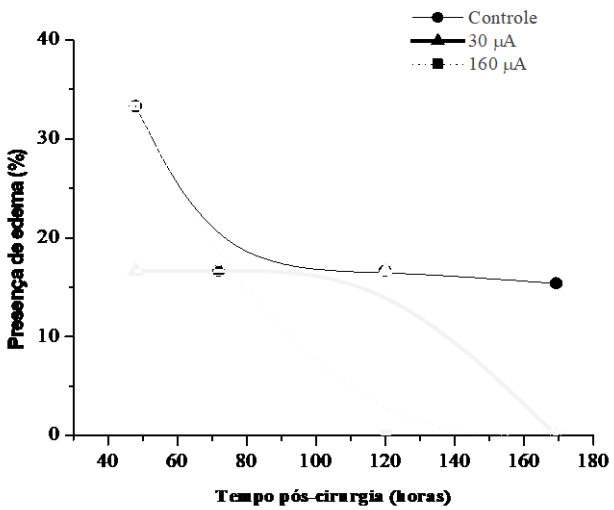
Ruiz-Silva in two theses prescribes 0.1 to 0.5 Hz with an intensity of 150 uA, from 40 minutes to 1 hour of application, current with an intensity of 150 μA, with a biphasic, symmetrical, balanced square waveform. (Ruiz-Silva, 2006; 2016), promotes anti-inflammatory effects, oxygenates, increases collagen, toning the tissue

and increases the number of mitochondria. Ruiz-Silva demonstrated that the number of superficial inflammatory cells decreased as the intensity of the applied low-frequency microcurrent increased, finding a statistically significant difference in the number of superficial inflammatory cells between the three groups (p=0.0001)



Graph 1: Superficial Inflammatory Cell Count In The Control Group And In The Groups Exposed To 30 µa And 160 µa Of Low-Frequency Current (Ruiz-Silva, 2016)

In another experiment with Ruiz-Silva animals, a decrease in edema was demonstrated with microcurrents. In the first 48 hours, only 16.65% (n=1) of the animals in the G30 group presented edema, compared to 33.3% (n=2) in the GC and G160 groups. At the end of 120 hours, none of the animals in the treated group presented edema. At the end of 7 days, the animals in the group treated with 160 µA did not present edema, while the control group presented 16.65% of the specimens with edema.



Graph 2: Edema dynamics between 48 and 168 hours post-surgery in animals treated with microcurrent therapy compared to control animals.

The main purpose of the SNS is to stimulate the body's fight-or-flight response, while remaining constantly active to maintain homeostasis (Motiejunaite et al. 2021), microcurrent stimulation exerts "hormone-like effects", secretion of norepinephrine in the postganglionic sympathetic neuron of the nervous system and G-protein of the cell membrane (Al-Tubaikh 2018). Norepinephrine secretion increases, binding to the β3-adrenoreceptor (β3-AR), which in turn converts ATP to cAMP in adipocytes (Noites, 2017), therefore MCT

induces lipolysis throughout the stimulation of the postganglionic sympathetic neuron (Vilarinho et al. 2022; Couto; Ruiz-Silva; 2010).

II. Material And Methods

Twenty female patients, aged between 25 and 50 years, were treated. They were diagnosed with lipedema, with pain, fatigue and aesthetic complaints of increased adipocyte volume and sagging in the lower limbs, with clinical indication for cryolipolysis using a mobile handle and microcurrent. All patients were duly informed with the Free and Informed Consent Form, in addition to having signed an authorization for the use of their images, completed for diagnostic, scientific and educational purposes. The equipment used in this study was plate cryolipolysis of different brands, including Gelox (plastic ice gel bag).

The clinical sequence of the technique followed the following protocol:
1. Cleaning the area to be treated with 2% aqueous chlorhexidine.
2. Use of CrioHD brand antifreeze gel to protect the epidermis and dermis (CrioHD, São Paulo, Brazil).
3. Use of plates in a mobile handle in 4 cycles of 5 minutes in each area of 30 x 30 cm.
4. Use of microcurrents.

The treatments were performed using the mobile plate cryolipolysis handle technique, with intervals for reperfusion. We used 4 series of 5 minutes of freezing and in the intervals of 3 minutes for the return of circulation, that is, reperfusion without injury.

III. Result

Figures 1 to 5 show clinical cases treated with the protocol described above.

Figure 1a, B And C. Patient L.M.F 38 Years Old. Source:Dra.Janaina Jardim Rodrigues.(2024).

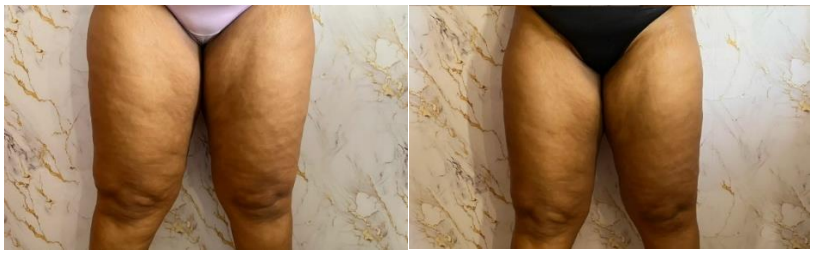


Figure 2. Patient R.O.T 34 Years Old. Source:Dra. Monara Margon - Estética Avançada (2024)

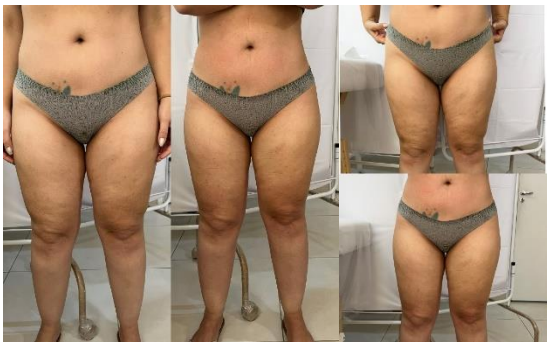


Figure 3a, B, C And D. Patient L.T 40 Years Old. Source: Dra. Monara Margon -Estética Avançada (2024).

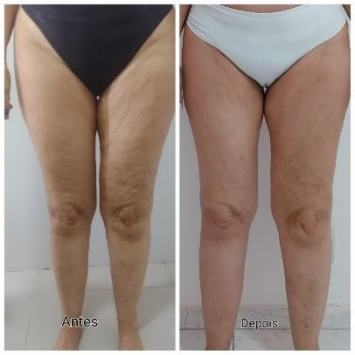


Figure 4. Patient W.M 62 Years Old. Source:Dra.Maira Erba (2024).

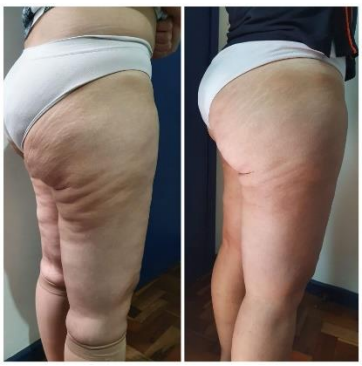


Figure 5. Patient L.M.J. 47 Years Old. Source: Dra. Janaina Jardim Rodrigues (2024).

IV. Discussions

Lipedema is a chronic disease characterized by adipose hyperproliferation, with subcutaneous adipose cells becoming more numerous (hyperplasia) or just larger (hypertrophy) (Al Ghadban, 2020). The tissue has inflammatory cells, fibrosis, and edema, with primary microvascular dysfunction in the lymphatic and blood capillaries. Excessive expansion of adipose tissue generates hypoxic stimulation and compression of sympathetic nerve endings, leading to pain and further activation of adipocyte transcription factors (Shavit, 2018; ISHAQ, 2021; Ruiz-Silva; Moleiro; Rodrigues et.al, 2024).

One of the main goals of treatment should involve mitogenesis, which is the increase in the number of mitochondria by activating crystalline formation, global disinflammation of the affected limb, inhibition of PPAR gamma transcription factors, and activation of adipocyte darkening. Mitochondrial inner membrane complex system (MICOS) deficiency leads to a coarse inner membrane architecture, and these mutations affect MICOS function and are responsible for a diverse spectrum of human diseases. The cure comes from mitochondrial fission and multiplication of cristae (Ruiz-Silva; Moleiro; Rodrigues; 2024).

We must restore the electrical conductivity of locoregional sensory nerve fibers by regenerating the fiber of the sympathetic innervation endings. The lack of axonal nerve transmission generates injury and blockage of the electrical bioconductivity of the SNS, activating hyperplasia. For this, we use microcurrents with a frequency of 0.1 Hz to 0.5 Hz and a constant intensity of 150 uA. We use square, bipolar, biphasic, symmetrical and balanced current (Jalin, 2020; Strounza, 2018;).

We need stimulation of nerve endings of the sympathetic system to generate beige adipose tissue.

Due to the increased gene expression of leptin and PPAR-gamma in lipedema adipocytes differentiated in vitro from adipose tissue-derived stem cells (Al-Ghadban, 2020; 2024), we must inhibit the inflammatory PPAR-gamma.

We activate the multiplication of healthy mitochondria without predominance of survival factors with anti-apoptosis proteins, through the mobile cryolipolysis handle, generating the activation of the MICOS ridge organization system, through the translocation of MIC19 and outer membrane translocation receptors 70. Beta-adrenergic stimuli also promote ridge biogenesis. (Yau, 2020; Martins; Ruiz-Silva, 2021; Ruiz-Silva, 2023; 2023).

The association of cold with the stimulation of the sympathetic nervous system through electrotherapy promotes activation of the PERK and MICUS systems. The action of freezing and simulating physical activity through microcurrent (release of hormones similar to physical activity) after lipolytic stimuli (electrolipolysis) encounters an environment with many lipid droplets that influence the organization of the ridges; Mitochondria perform β-oxidation of fatty acids, but when stimulated by cold, drastic changes in morphology occur due to activation of PERK; (Gallardo-Montejano, 2021).

The mobile handle promotes the selective reduction of adipose cells and is effective in the treatment of cellulite and lipedema through the remodeling of dermal collagen (cryodermatringe). Histological analysis confirmed a selective and gradual reduction of adipose tissue by programmed death (apoptosis) triggered by reperfusion. The safety of the method is highlighted by the absence of a significant increase in liver enzymes or serum lipids; molecular studies demonstrated no changes in the transcripts of the peroxisome proliferator-activated receptor (PPAR). No changes were evident in the transcription, which highlights the safety of the technology used (Ferraro, 2012).

There was also neoangiogenesis, improved oxygen and nutrient flow, and a marked increase in lymphatic drainage (Ferraro, 2012).

V. Conclusion

The literature review presented histological and biochemical aspects of lipedema. Although it is a disease considered primary lipodystrophy, with a high incidence, more studies on treatments are still needed to improve the quality of life and self-esteem of those with the disease.

Among the treatments presented in the literature, the cryolipolysis technique with a mobile handle is presented as a treatment that reduces adipose tissue, as well as reduces the process of edema and inflammation with the association of microcurrent.

The plates promote reperfusion in adipocytes, generate reactive oxygen species (oxidation) and activate apoptosis. Adipocytes are reactive to thermal shocks. The mobile handle promotes the selective reduction of adipose cells and is effective in the treatment of dermal collagen remodeling.

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