

Pharmacological treatment of complications after the use of Cryolipolysis: case series.

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ABSTRACT: The cryolipolysis technique uses selective and controlled cooling based on the principle that lipid-rich tissues are more susceptible to cold damage than water-rich tissues, such as the skin. Cryolipolysis stands out as a non-invasive method for body contouring without damaging subcutaneous tissue, becoming a popular treatment to non-invasively address localized fat accumulation and tone the dermis. However, a large number of complications have occurred and beauticians and aestheticians have no reports in the literature on how to treat these complications with medication. The most reported complication in Pubmed is paradoxical adipose hyperplasia (PAH), but in clinical practice, several complications occur, such as frostbite, panniculitis, PAH and hyperchromia after inflammation.

Objective: This study aims to describe the authors' experience in guiding professionals in the management and treatment of several cases of complications resulting from the application of the Cryolipolysis technique. We guided more than 10,000 complications in 12 years, describing the lesions and the drugs with the greatest effectiveness in the treatment.

Materials and methods: Exploratory research was carried out, presented in a narrative review, to demonstrate the action of the Cryolipolysis technique used in the treatment of aesthetic dysfunctions. The review explored scientific articles published and available in the following databases: MEDLINE (Medical Literature Analysis and Retrieval System Online), PubMed (National Library of Medicine), SCIELO (Scientific Electronic Library Online), LILACS (Latin American and Caribbean Literature in Health Sciences), and Google Scholar. In addition, a series of cases of complications from the use of the

cryolipolysis technique that occurred in a multicentric manner and developed with the use of various commercially available equipment were added to this study.

Results: when using techniques based on scientific studies, respecting time and temperature, in addition to associations with equipment, drugs and techniques that inhibit cellular precursor factors, we will reduce possible interurrences and complications. The most common complications described in this study are neuropathic lesions in sympathetic innervation, paradoxical adipose hyperplasia, frostbite, frostnip and hemosiderin hyperpigmentation, but when an interurrence occurs, we must be able to treat and avoid complications.

Conclusion: The scientific literature demonstrating the lesions and their possible causes with the cryolipolysis technique is robust, but it did not prevent serious complications secondary to the use of Cryolipolysis, which has become common in aesthetics in Brazil and worldwide. Therefore, it deserves full attention for the adoption of appropriate application techniques to minimize such complications, among them: greater temperature control with machines that show the skin temperature on the panel, correct time control, without exaggeration, high-quality antifreeze membrane and mandatory use of the "liner" (plastic) as occurs throughout the world, protection of sympathetic innervation through microcurrent and finishing with drugs that promote the inhibition of factors that lead to cell multiplication such as PPAR gamma and CD 68. In case of injury, the professional must be able to prescribe drugs that prevent the progression of the complication.

KEYWORDS: cryolipolysis, adipose tissue, aesthetic complications, Panniculitis, adipose hyperplasia, frostbite, Frostnip

I. INTRODUCTION

In The cryolipolysis technique uses selective and controlled cooling based on the principle that lipid-rich tissues are more susceptible to cold damage than surrounding water-rich tissues (Ferraro, 2012; Pugliese, 2020). Technological advances have led to several treatments for localized fat, with cryolipolysis standing out as a non-invasive method for body contouring without damaging subcutaneous tissue, and still depending on the technique without generating an inflammatory process (Loap, 2018, Ruiz-Silva, 2024). The use of cryolipolysis has gained popularity as a frequent cosmetic procedure in the United States, according to the Aesthetic Society. In most countries, complications occur due to the wide variety of equipment that is not similar to the North American equipment with FDA, and there are also dozens of techniques and a lack of standardization of the procedure, most of the time, without basis and/or foundations based on scientific literature and the similarity of machines with publications, which has led to the incidence of several post-treatment complications, which have generated thousands of injuries in recent years (Ruiz-Silva, 2023; 2024).

This study aims to describe the authors' experience through several cases of complications resulting from the application of the Freezing technique in Brazil and which gave rise to some important complications after the procedure, as well as a brief review of the world literature on the subject, and how to treat it.

II- METHODOLOGY

This study is characterized by exploratory research, presented through a narrative review, to highlight the action of the Cryolipolysis technique, used in the treatment of aesthetic dysfunctions and its possible adverse effects and/or complications. The review explored scientific articles published between 2008 and 2024, and available in the following databases: MEDLINE (Medical Literature Analysis and Retrieval System Online), PubMed (National Library of Medicine), SCIELO (Scientific Electronic Library Online), LILACS (Literature from Latin America and the Caribbean in Health Sciences), and Google Scholar.

As inclusion criteria, sources that mentioned cryolipolysis treatments for reducing

adipose tissue through apoptosis and lesions resulting from this treatment were selected. Sources that did not present physiology and lesions and journals that were not scientific were discarded.

In addition to the bibliographic review, a survey of several cases of complications after the use of Cryolipolysis that occurred in Brazil in a multicentric manner was added to this study, in order to describe the authors' experience in approaching and managing these adversities after the treatment of localized fat using various commercially available equipment.

III- RESULT AND DISCUSSION

Intercurrences, Complications and Adverse Effects

Intercurrence is the term that defines the occurrence of an unexpected event in a procedure, which could not generally be foreseen or warned to the patient. Any and all procedures, from the simplest to the most complex, are subject to unexpected complications, which do not necessarily incur an error (Oliveira, 2024). Iatrogenesis consists of adverse effects or pathological changes caused by or resulting from correct health treatment carried out within the recommended limits, which are predictable, expected or unexpected, controllable or not, and which can sometimes occur. These are problems that are often predictable and easy to resolve, often avoidable when we know the causes and should not be seen as complications (Oliveira, 2024).

The most serious and difficult to resolve injuries are called complications and we must avoid and know how to treat them (Tafelli, 2017).

Cryolipolysis stands out for being a procedure with a high rate of effectiveness for reducing and modulating adipose tissue, in addition to cryoweight loss (Ruiz-Silva, 2023; 2024).

It is a safe, effective procedure, with a low rate of adverse effects and which offers satisfaction to patients. The greatest fear of professionals who work with Freezing are the dreaded complications and complications. We must know how to avoid them, but it is extremely important to know what to do when they occur.

Post-cryolipolysis injuries have a multifactorial pathophysiology, involving soft tissue damage resulting from prolonged cooling. The peripheral nerves are the most sensitive. The first symptoms are paresthesia of the affected tissues. Initially, the skin is numb, with intense pain after reperfusion and a phase of hyperemia. Edema begins after a few hours, possibly with the

formation of blisters in more severe cases. The literature says that “burns” that are actually frostbite (figure 1) are not common, and usually occur when professionals make technical errors because they are not trained to perform the technique; they handle the device improperly (Ribas, 2021), they do not check how many degrees Celsius the machine is delivering using thermometers or if it is out of calibration.



Figure 1: Frostbite and its evolution with necrosis, hyperchromia and hyperchromia

Panniculitis, Frostbite, Frostbite

Many cases of evident skin chelation have arisen in the clinical practice of Cryolipolysis in Brazil. Given the current situation, our understanding leads us to believe that the lack of control over exposure time in addition to the lack of temperature control has been causing injuries. Most professionals responsible for these cases of Frostbite report that they followed the rules established by the companies that sold the machines or technical training provided by the rental companies. In addition, we see many professionals neglecting to control skin temperature, in addition to not using a good quality antifreeze protective membrane (formula 01) and the lack of the mandatory Liner (plastic) (Zelickson, 2009).

Formula 01: Antifreeze gel or liquid

Vegetable glycerin - 10% - HUMECTANT
Purified water 51.285% - VEHICLE
Hydroxymethyl cellulose - 0.7% - VISCOSITY
REGULATOR
Sorbitol - 14% - MOISTURIZER
Kathon (methylchloroisothiazolinone) 0.015% -
PRESERVATIVE
Propanediol - 4.0% - HUMECTANT
Monoethylene glycol -10.0% - ANTI-
FREEZE/HUMECTANT
Diethylene glycol - 10.0% - SOLVENT

Cryolipolysis promotes apoptosis (Ruiz-Silva, 2024), time and temperature of current articles do not exceed -11 degrees for a maximum of 35 minutes (Kania, 2024; Michon, 2021; Azab, 2021; Jain, 2020; Pugliese, 2020; Kilmer, 2020; Abdel, 2020; Few, 2020; Putra, 2019; Palauro, 2025), but many professionals neglect the time by doing more than 60 minutes of freezing per area. To generate apoptosis via hypoxia, the intracellular lipid enters a solid state around 10°C (Stevens 2013) and the adipocytes around 3°C to 10°C, this is the key to the results (Pinto, 2013; Jane, 2014; Sasaki, 2014). However, cell death by necrosis at -2°, 0° and 2°C; excessive times at low temperatures generate necrosis in addition to apoptosis. Cold-induced panniculitis is a common injury in cold regions, and was extensively studied by Harvard University in the United States in the 1970s and 1980s. They studied Popsicle Panniculitis, Equestrian Panniculitis, and Trench Foot (Hong, 2022; Manstein, 2008; Zelickson, 2009), and defined it as hardened red nodules followed by transient necrosis. In 1970, the term “popsicle panniculitis” emerged after the presence of a hardened red nodule followed by transient necrosis of adipose tissue on the face of a child who had sucked on a popsicle, which evolved to generate a dimple on the face. The buttocks of children exposed to ice cubes after vaccination also had the same lesions (Jalian, 2013).

Cold panniculitis is a form of panniculitis with an idiosyncratic response to exposure to cold. It affects people who have spent prolonged periods in the cold, affecting areas of the skin that have been exposed to the environment.

The histological aspects of cold panniculitis are similar to those of panniculitis caused by Lupus erythematosus and dermatomyositis (which are contraindications for Cryolipolysis), remembering that they are inflammatory diseases.

In some cases, cold panniculitis is characterized by particularly dense chronic inflammation at the interface of the subcuticular dermis (Rivitti, 2014). Also called hypodermatitis, panniculitis is an inflammatory process of the hypodermis (adipose tissue). There is no universally accepted classification of panniculitis, many pathologists classify it by dividing panniculitis into septal and lobular forms (Delgado 2009; Rivitti, 2014) "septal" meaning inflammation confined predominantly to the septa, was classically associated with erythema nodosum (EN)

"lobular" indicating inflammation predominantly involving the fat lobule itself, similar to most other types of panniculitis (Lupus)

Supportive care

- Anti-inflammatory drugs
- Avoid any excess that can generate Panniculitis.
- There is no specific definitive treatment.
- Several strategies are used with moderate results, including NSAIDs and antimalarials: Diclofenac, Ibuprofen, Naproxen, Nimesulide, Indomethacin, Ketoprofen, Mefenamic acid, Piroxicam, ASA (acetylsalicylic acid)

For local application, I suggest topical ointment and cream containing 0.64 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone)

Diprogenta Cream is the most indicated; each gram of DIPROGENTA Cream and 1 mg of gentamicin, in the form of sulfate, has a rapid onset of action and is indicated for the relief of inflammatory manifestations sensitive to corticosteroids. It has anti-inflammatory, antipruritic and vasoconstrictive action, and has a prolonged duration of action, allowing application twice a day.

Gentamicin, a broad-spectrum bactericidal antibiotic, is effective against a broad spectrum of common skin pathogens.



Figure 4 and 5: Panniculitis after double freezing technique with two massage maneuvers in region that has compartment



Figure 6 and 7: Panniculitis after double freezing technique with two massage maneuvers in region that has compartment

Subcutaneous edema

Subcutaneous edema consists of the accumulation of clear liquid in the subcutaneous tissue, which appears gelatinous. Edema occurs when there is an accumulation of liquid under the skin, which normally appears due to inflammation and hypoxia (Kumar, 2005).

In clinical practice, we have seen that it frequently occurs when professionals use techniques that heat the dermal tissue before cryolipolysis, for example, the contrast technique that heats before freezing, the use of high-frequency ultrasound of 1 and 3 MHz, where the thermal effect predominates.

The big mistake, widely publicized by internet influencers, is to use radiofrequency or cryofrequency before freezing, in addition to using a thermal blanket.

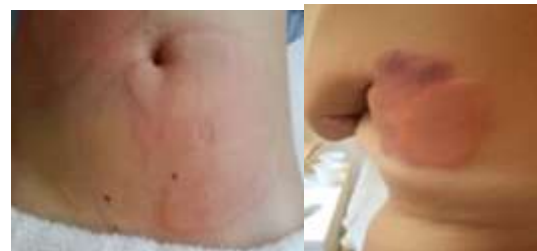


Figure 8 and 9: subcutaneous edema after previous use of Radiofrequency and after cryolipolysis

Treatment: Local application, I suggest topical ointment and cream containing 0.64 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone)

Diprogenta Cream is the most indicated; each gram of DIPROGENTA Cream and 1 mg of gentamicin, in the form of sulfate, has a rapid onset of action and is indicated for the relief of inflammatory manifestations sensitive to corticosteroids. It has anti-inflammatory, antipruritic and vasoconstrictive action, and has a prolonged duration of action, allowing application twice a day.

Frostnip superficial cold injuries

Frostnip occurs when the top layer of your skin is slightly injured due to exposure to cold. When your body is exposed to cold, blood vessels constrict, diverting blood away from the skin to maintain core body temperature. After prolonged exposure to cold temperatures, we have superficial hypoxia. If we do not have antifreeze blankets or excessive exposure, dermal injury may occur in the cooled areas, presenting numbness, edema and

redness. (Valente, 2018; Dow, 2024).

With reperfusion, the region may hurt or burn intensely. Remember that we will usually have injury to nerve endings of the sympathetic system due to freezing of the myelin sheath. No permanent damage occurs, although the area sometimes remains particularly sensitive to cold for a few months (Starink, 2024; Dow, 2024). It can generate hemosiderin hyperchromia



Figure 10 and 11: Frostnip with improvement after use of Betamethasone

Frostbite

Frostbite is the destruction of tissue by direct action of cold and the development of reperfusion injury. Injuries occur when the skin temperature is $<0^{\circ}\text{C}$ for a long period. It is important to note that the risk of burns increases from 5% to 95% when the temperature on the skin surface decreases from -4.8°C to -7.8°C . (Essien, 2024)

After exposure to temperatures below zero, ice crystals are formed in the extracellular medium and, if freezing is rapid, this can even occur in the intracellular medium. The fluxes of ions such as sodium and potassium cause damage to cell membranes and, subsequently, apoptosis. An endothelial inflammatory process mediated by the arachidonic acid cascade may occur with release of thromboxane A₂, prostaglandins, bradykinins and histamine vasoconstriction, platelet aggregation, leukocyte adhesion and erythrocytosis, which results in venous and arterial thrombosis and subsequent tissue ischemia, necrosis and dry gangrene (Wibbenmeyer, 2024).



Figure 12 and 13: Frostbite subcutaneous tissue in a solid state, with ice formation where subcutaneous edema was generated.

Frostbite (“geladura” in Portuguese)

“Heat burns and ice or cold freezes”. It is an injury resulting from the freezing of tissues. Initial presentations may be deceptively benign, the skin appears white or blistered and numb; rewarming causes severe pain and may result in the development of gangrene.

Ice crystals form within or between tissue cells, freezing them and causing their death. Adjacent non-frozen regions are at risk, as vasoconstriction and local thrombosis can cause ischemic damage due to reperfusion during rewarming, inflammatory cytokines are released (e.g., thromboxanes, prostaglandins), exacerbating tissue injury.

The depth of tissue loss depends on the duration and depth of freezing (Dow, 2019; 2024).

The affected area is cold, hard, white and numb. When warmed, the area acquires erythematous patches and becomes edematous and painful. Blisters form within 4 to 6 hours, but the full extent of the lesion may not be apparent for several days. Blisters filled with clear serum indicate superficial injury; this heals without residual tissue loss.

Blisters with blood proximal to the lesion indicate deep injury and probably tissue loss. Freezing of the deep tissues causes dry gangrene with a hard black carapace over the healthy tissue; wet gangrene, gray, edematous and soft, is less common (Dow, 2019; 2024).

Wet gangrene can become infected, but dry gangrene probably does not.



Figure 14 and 15: Frostbite of subcutaneous tissue in a solid state, with ice formation where subcutaneous edema was generated, do not massage or force reperfusion.

Local action of cold Injuries very similar to burns and classified into degrees:

- 1) First degree, injury characterized by local pallor or redness and anserine appearance of the skin (erythema)
- 2) Second degree, erythema and formation of blisters or blisters with clear, hemorrhagic content;
- 3) Third degree, necrosis of soft tissues with formation of blackened, adherent and thick crusts;
- 4) Fourth degree, by gangrene or disarticulation.

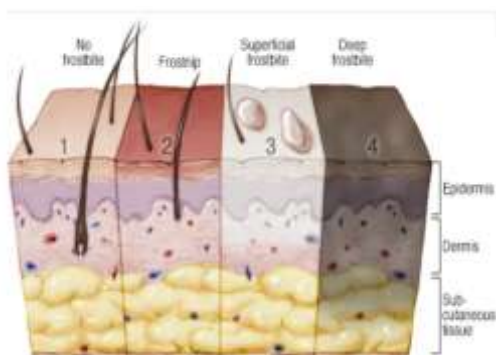


Figure 17: representation of injuries due to exposure to cold (<https://www.mayoclinic.org>)



Figure 18: 4th degree frostbite after 60 minutes of suction cryolipolysis at -11 degrees and maximum vacuum

Chilblains

Chilblains are characterized by inflammatory skin lesions caused by prolonged exposure to cold. Symptoms are precipitated by acute exposure to cold. The first symptoms are paresthesias of the affected tissues that may progress to itching and burning pain.

Painful bluish nodules may form, which may persist for several days. Skin manifestations, which appear up to 12 to 24 hours after acute exposure, include localized edema, erythema, cyanosis, plaques, nodules and, in rare cases, ulcerations, vesicles and blisters. The best treatment is the use of topical corticosteroids (0.1% triamcinolone cream) (Dow, 2019; 2024).



Figure 19, 20, 21 and 22: 2nd degree frostbite, evolution occurred as chilblains.

Flictena

Flictena is an elevation covered by epithelium containing liquid and measuring more than 1 cm, it is synonymous with a blister. When a frostbite occurs, our lymphatic system sends a liquid to help the body contain the burn, thus preventing the loss of mineral salts and water.



Figure 23 and 24: 4th degree frostbite with Flictena

Cold Allergy

Cold allergy is a condition that can cause very uncomfortable injuries and have serious consequences for those affected if they are exposed

to extreme temperatures. It is very important to diagnose it in order to avoid these damages and to know why the body reacts when it comes into contact with cold (de Albuquerque, 2024).

Cold allergy is the popular name for a condition known scientifically as cold urticaria. Its episodes are more common in the coldest periods of the year, autumn and winter, and usually involve the appearance of red patches, swelling and itching in areas exposed to cold temperatures. These situations occur due to hypersensitivity of the dermis when receiving this type of stimulus, the so-called induced urticaria, which causes hypersensitivity crises and, consequently, the manifestation of the symptoms of the condition, is the excessive release of histamine by the body when receiving the stimulus of exposure to cold.



Figure 25 and 26: Cold allergy after cryolipolysis and improvement with the use of Prednisone

Cold-associated urticaria

Cold-associated urticaria is part of the so-called cholinergic urticaria, representing a characteristic example of hypersensitivity to cold. Most cases are idiopathic, but it can also be associated with increased affinity of immunoglobulin E for mast cells. The diagnosis can be confirmed by exposing the patient to cold.

The greatest danger, however, is the risk of anaphylaxis. This generalized reaction is normally caused by intense exposure to cold, such as when entering the sea or a cold pool, and can cause a drop in blood pressure, loss of consciousness, nausea, vomiting, and swelling of the throat and tongue, impairing breathing (Geller, 2013).

Cold-associated urticaria is treated in a similar way to urticarial lesions.

Antihistamines are recommended for acute cases. We recommend Fernegam, Histamim, Loratadine, 10 mg, Clarintin or Prednisone, 20 mg.



Figure 27 and 28: Cold allergy caused by freezing with Gelox and improvement with the use of Prednisone

Bruises and Ecchymosis

After suction with excessive pressure, it is common for a purple spot to appear, probably an ecchymosis, but often mistakenly called a hematoma.

Both ecchymosis and hematoma can appear after cryolipolysis. Ecchymosis is formed when superficial blood vessels are damaged and a small hemorrhage occurs. It appears after the rupture of the blood vessel and over time, its color changes from greenish to yellowish before disappearing naturally. It appears in irregular, diffuse and flat spots, without causing elevations in the area (Silva, 2021; Mota, 2024).

The treatment for ecchymosis and hematoma are also different.

While ecchymosis is a rupture of the most superficial blood vessel, hematoma is a deeper rupture that can cause elevations in the skin and dark spots.

Treatment for bruises resulting from injuries and contusions usually disappears spontaneously within days or weeks. To relieve pain in the affected area, you can apply 500 mg of mucopolysaccharide polysulfate in a 40-gram ointment; gel with 100 grams of escin with diethylamine salicylate, and use anti-inflammatories such as ibuprofen.

Hematomas are also caused by ruptured blood vessels, but blood accumulates in the tissue, causing a raised bump. Depending on the size and location, the hematoma may require surgical intervention to drain the blood. Initially, we must reduce inflammation by using anticoagulant ointments based on heparin, which are indicated and reduce inflammation, relieve pain and reduce swelling and purple spots in the injured areas. Thrombofob 200 u gel with 40 grams of sodium heparin

Paradoxical adipocyte hyperplasia (HAP)

Adipogenesis is the hyperplasia of adipose tissue (increase in localized fat) and can be activated after cryolipolysis by activation of transcription factors, in addition to increased fibroplasty with generation of fibrosis, adhesions and nodules.

PPARGama is the main receptor of the adipocyte nucleus responsible for cell division and differentiation. They are potent activators of adipogenesis, which convert fibroblasts into adipocytes (Silva, 2016). Blocking this receptor combats adipose tissue hyperplasia. PPARgama and C/EBP are responsible for adipose tissue hyperplasia (Sorisky, 2000).

Block: Reduction of adipocyte hypertrophy and recurrence of adipose tissue (Ruiz-Silva, 2024)

There is an increase in hyperplasias worldwide 100 times more than reported in articles or underreported (Ho, 2017; Khan, 2019; Michon, 2021), due to the difficulty of diagnosis (Vogel, 2018) generating a worldwide underreporting (Ho, 2017), however most machines do not require notification.



Figure 29 and 30: case of post-freezing hyperplasia that lasted 8 hours, Brazilian single-session method

Increase in the rate from 0.0051% (Jalin, 2014) to 1% (Jain, 2020; Strounza, 2018)

Michon, 2021; reports that it is predominant in suction machines that do not freeze the center, they suck excessively, especially in those who used the excessive time of 60 minutes.

Vacuum Cryolipolysis causes a series of injuries, which led most companies to modify the vacuum system to Minimum Vacuum Cryolipolysis and Central Freezing, thus avoiding areas of poor contact without freezing and without apoptotic effect, compartment injuries in upper and lower limbs, in addition to injuries in nerve endings (Nikolis, 2021; Khouri; 2015; Stefny, 2015)

Nikolis, 2021; reduction in the incidence of 75% with central freezing.

Negative pressure may be a factor (Stefany, 2015). The possible cause is the transient decrease in sympathetic neural stimuli that can activate preadipocytes (Ho, 2017), understanding that the paradoxical response is part of the natural selection of adipocytes for survival (MC Keown, 2021; Ho, 2017; Wang, 2018; Khan, 2018; Franzoni, 2024).

The non-injured generate a rebound and multiplication effect, a survival effect (Stefany; 2015; Ho, 2017).

Massage with the tissue still “SOLID” Frozen, generates injury.

Another hypothesis is that the massage performed at the end of the cryolipolysis session, with the aim of increasing lipolysis, causes trauma to the adipocyte membranes, resulting in inflammatory adipocytolysis. Cookson described this phenomenon as pyroptosis and reported that it resembles apoptosis, but is inflammatory (Strounza, 2018)

The inflammatory adipocytolysis process is dependent on caspase-3 and leads to the formation of holes in the adipocyte membranes, leading to an inflammatory repair process; However, some holes are irreparable and, thus, the adipocytes become necrotic (Seaman, 2016).

The region presents a large, painless swelling in the treated area, post-mild abdominal nodular panniculitis with spontaneous regression in one month, paresthesia in the treated area for a few weeks, and may present hematoma after abdominal cryolipolysis.

In the tomodesitometry, we have the presence of a non-necrotic parietal pseudomass, with a fatty appearance, without signs of necrotizing fasciitis or fluid effusion (seroma or hematoma). Abdominal magnetic resonance imaging (MRI) confirmed these findings and revealed hypertrophy of the superficial abdominal adipose tissue, above the superficial fascia (Strounza, 2018).

Histological analysis of the pathological adipose tissue performed after surgery revealed nonspecific lobular panniculitis, septal thickening, interstitial infiltration of foamy macrophages and foci of adiponecrosis. In addition, adipocytes of variable size were present.

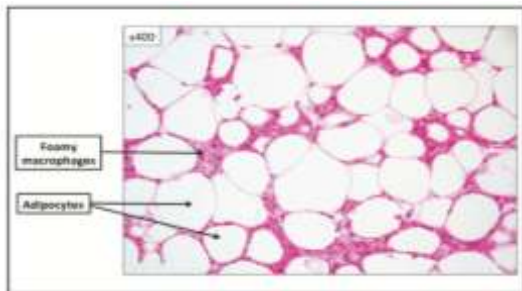


Figure 31: Foamy macrophages, adiponecrosis and replication of new adipocytes, characteristics of suction freezing followed by vigorous massage.

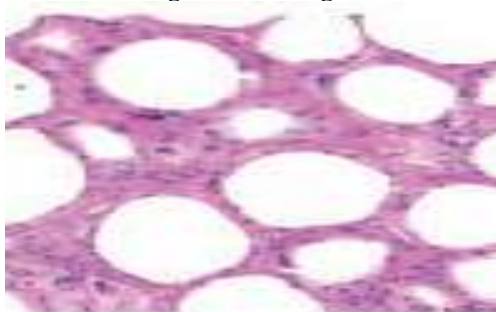


Figure 32: Note that in 2008 Masten already demonstrated the presence of interstitial infiltration of foamy macrophages and foci of adiponecrosis. Presence of new adipocytes replicating

It is worth noting that in lipedema and in post-cryolipolysis followed by solid tissue massage, there is an increase in the CD68+ differentiation cluster (Ruiz-Silva, 2024).

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 observed in obesity, resulting in adipocyte necrosis and macrophage recruitment (Wiedner, 2028; Morgan, 2024).

Genetic research has not found a specific relationship to dysfunction of a specific transmission gene (Sousky, 2000). 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; 2025). Preadipocytes that undergo excessive apoptosis as they differentiate acquire

relative resistance to apoptosis (Jain, 2020). Inhibitors of apoptosis (IAPs) act to suppress apoptosis via inhibition of caspase activity, extracellular survival factors inhibit apoptosis in several pathways and bind to cell surface receptors, and suppress apoptosis; 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 (Seaman, 2016).



Figure 33 and 34: Classical paradoxical adipose hyperplasia

Some authors suggest that the increase in volume is due to the fact that preadipocytes, whose fat content is lower, will not be lysed by the application of cold, unlike mature adipocytes. These preadipocytes will then be able to proliferate later, leading to an increase in tissue volume.

Other hypotheses include adipocyte hypertrophy, changes in the expression of receptors associated with adipocyte metabolism, reduced sympathetic innervation or hypoxia (Cox, 2022).

Another explanation is that, after cooling, hypoxia can trigger a response that includes hypertrophy and fibrous cells (Vargas, 2021; Gonzalez, 2025)

Apoptosis is non-inflammatory, in cryoexposure, in cryothermogenesis we avoid inflammation we can prescribe the following supplements and drugs.

- Propolis 15 drops
- Omega 3 – 3000 mg daily
- Magnesium chloride – 500 mg
- Vitamin C – 1 to 2 grams daily
- Vitamin D – 4000 IU
- Zinc – 30 mg
- Indole-3-Carbinol (I3C) – 400 mg daily

Drugs that prevent lesions by inhibiting PPAR gamma and C/EBP

Morosil (Citrus sinensis (L) Osbeck). 300 to 500 mg per day

Dry extract of Moro red oranges, this orange is grown exclusively in the area around the Etna volcano in eastern Sicily (Italy). Morosil acts

on the metabolism of adipose tissue, thermogenesis inhibits phosphodiesterase, acts on inflammatory tissue and hypoxia, has C3G anthocyanins that reduce lipogenesis, and polyphenols have high antioxidant power and act to reduce events related to inflammation and oxidative stress (Pagliacil, 2005; Cardile, 2015).

DIMPLESS (Cucumis melo L) prevents PAH, 40 mg - 1 capsule per day

Freeze-drying concentrate of the French variety of Cantaloupe melon, SOD concentration 20 times higher than any other melon specie, Rich in Superoxide Dismutase (SOD), approximately 85% to 90%,

Also formed by other enzymatic antioxidants such as Catalase, Glutathione Peroxidase and non-enzymatic ones such as Coenzyme Q10, Lipoic Acid, Carotenoids, Vitamin A, E and C. Reduces fat accumulation by reducing the activity of LPL(lipoprotein lipase), Stimulates lipolysis, Reduces adipogenesis by inhibiting transcriptional factors (PPARy, C/EBPα)

Powerful antioxidant action (prevents the formation and neutralizes free radicals), Anti-inflammatory action, Properties anti-fibrotic by modulating TGF-β to 70% regression of fibrous tissue.

Subcutaneous drugs after cryolipolysis PPAR inhibitors.

Tripeptide 41.... 1.2% -Transforming Growth Factor B, - (Ducan, 2006).

Hyperchromia due to hemosiderin

One of the most common causes of cold panniculitis, which is accompanied by an inflammatory process that generates hyperchromia, is the use of the double or triple reperfusion technique, which consists of double freezing followed by massage. When performed in regions that have a compartment, they generate an increase in hemosiderin due to the Fenton reaction, causing iron stains. Remembering that the abrupt increase in O₂ and Ca, activates Superoxide with lipid peroxidation, a large amount of Hydroxyl is generated (Bitu-Moreno, 2020). Superoxides undergo dismutation by SOD, receive another hydrogen and become a Hydroxyl radical that influences the membrane and Nucleic Acid (Pinho, 2014), promotes the increase in the concentration of Malondialdehyde, Myeloperoxidase (presence of H₂O₂) (Costa, 2022) generated lipid peroxidation and oxidative stress.

Hemosiderin is a pigment resulting from the destruction of hemoglobin, being a

consequence of the excess deposit of iron. Red blood cells are rich in hemoglobin, which is rich in iron ions that give the blood its red color. When death occurs by extravasation, hemoglobin is retained in this space, releasing iron. The iron then undergoes oxidation when it receives heat, giving rise to a pigment called hemosiderin, which is responsible for the rust-colored stains.

Suggested treatment is to use a hemosiderin depigmenting serum gel with Hemaline 2% and Haloxyl 2%

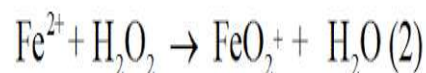
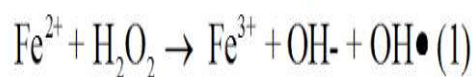


Figure 35: Fenton reaction



Figure 36 and 37: Hemosiderin hyperchromia

hypopigmentation

Loss of pigment after a skin injury. The skin may lose its pigment after recovering from frostbite. In this case, it is not as white as in vitiligo and, over time, it may return to its normal pigmentation.

We suggest using a skin repigmentation cream, Pigmerise" represents a major advance over the current first-choice treatments for Vitiligo, such as psoralens and chelin. It is a natural phytocomplex, derived from black pepper extract (Piper nigrum L.), in resin oil, standardized with a high concentration of alkaloids and volatile oils. Pigmerise" does not contain alcohol in its composition and can be applied to sensitive areas, such as the mouth, eye area and genital region, thus increasing patient adherence to treatment.

Pigmerise" stimulates the proliferation of melanocytes that are located deep in the epidermis and increases melanogenesis. Pigmerise" protects cellular DNA and, therefore, does not trigger the risk of developing melanoma. Pigmerise" is safe and effective with or without exposure to UV

radiation. The formulation of Pigmerise" in Fitalite" favors a deeper absorption of the phytocomplex, actively reaching the melanocyte. Suggested formulation is Pigmerise™ 20%, Fitalite™ qsp 50 g

Another option is to use the formula with

- Quelina 3%
- Tacrolimus 0.1%

Quelina, also known as Quelynah, is the best solution and aesthetic option for those who want to repigment the spots caused by Vitiligo and Psoriasis. As it is a photochemotherapeutic agent, it is activated when applied and exposed to light.

Patients who have sensitivity in the areas affected by skin problems can use Quelina due to its lower possibility of side effects.

Tacrolimus is used topically to treat inflammatory skin diseases.

In studies where tacrolimus and topical quelina were used as treatment in combination, rapid results were observed, repigmentation of the lesions mainly in the face region and no adverse reactions were reported. In addition, the combination of these formulations is a therapeutic option for the treatment of vitiligo in children, as it does not cause adverse effects related to the use of corticosteroids.



Figure 37, 38, 39 and 40: hyperchromia followed by hypochromia

IV- CONCLUSION

The scientific literature demonstrating the lesions and their possible causes with the cryolipolysis technique is robust, but it did not prevent serious complications secondary to the use of Cryolipolysis, which has become common in aesthetics in Brazil and worldwide. Therefore, it deserves full attention for the adoption of appropriate application techniques to minimize such complications, among them: greater temperature control with machines that show the

skin temperature on the panel, correct time control, without exaggeration, high-quality antifreeze membrane and mandatory use of the "liner" (plastic) as occurs throughout the world, protection of sympathetic innervation through microcurrent and finishing with drugs that promote the inhibition of factors that lead to cell multiplication such as PPAR gamma and CD 68. In case of lesion, the professional must be able to prescribe drugs that prevent the progression of the complication.

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