

Paradoxical Adipose Hyperplasia after Cryoadipolysis: A Colombian Observational Study

Reyna Vargas, Gregorio Viera-Mármol, Roberto Sánchez, Jorge Villena,
José Antonio Ferrández, Carmen Cano, Núria Adell, David Rubio
Scientific and Clinical Department Cocoon Medical S.L.U.; 08950 Esplugues de Llobregat, Barcelona, Spain

Abstract— Introduction: Cryoadipolysis is a non-invasive technique for fat reduction based on the application of cold temperatures to skin folds and the underlying adipose tissue. It is based on the principle that adipocytes are more sensitive to cold than other cell types. While its non-invasiveness is an advantage in terms of patient experience, it also has some associated complications which are usually temporary and resolve spontaneously. Paradoxical adipose hyperplasia (PAH) is an infrequent side effect where an increase in adiposity is produced 2–5 months post cryoadipolysis. Its exact mechanism is not completely understood, a fact that causes concern for physicians and patients. The objective of this study is to evaluate the causes of this complication, as well as to try to link these cases to pre-existing clinical conditions or problems related to medical praxis and provide good practice recommendations to prevent PAH from occurring. **Materials and Methods:** 16 patients who underwent cryoadipolysis and presented symptoms compatible with PAH were interviewed by physicians. These 16 patients were among a total of 31 reported cases that occurred following the treatment of 7,588 patients from 2019 to 2020. According to the etiology of the lesions, they were classified as either procedure related, risk factor related or unknown. **Results:** The incidence of PAH among all patients subjected to cryoadipolysis was 0.41%. Nine (56.25%) patients were classified as having a cause that was risk factor related, four (25%) were attributed to a procedure related cause, while three (18.75%) remained in the unknown category. Six (37.5%) patients showed contraindications, there were six (37.5%) cases with suboptimal practice and three (18.75%) patients presented an increase in weight after cryoadipolysis. Twelve (75%) patients underwent liposuction, which in all cases was able to solve the complications. Among the 10 patients with imaging studies, 7 (70%) cases showed previous lesions. **Discussion:** Results in this study reinforce the need to establish stringent patient screening which can contribute to reducing the prevalence of complications such as PAH, as more than 50% of patients with a clinical cause presented risk factors and contraindications. Furthermore, incorrect procedures can contribute to complications such as PAH, which is usually associated with trauma caused by suction. Imaging procedures (MRI) were critical to the diagnosis of PAH, as without them PAH may be confused with other lesions. The treatment option for most patients was liposuction, with some patients first using lipolytic enzymes with no positive results. All in all, little is known about the mechanisms involved in PAH from both a cellular and a histological point of view, which is why the etiology is still unknown. Good practice recommendations, from patient screening to post-treatment care, should facilitate the optimal application of treatments, including the procedure itself. By backing up such recommendations with the available empirical data, much more accurate information could be provided to physicians and patients, which may prevent PAH from occurring or help mitigate it if diagnosed. **Conclusions:** Cryoadipolysis is generally regarded as a safe non-invasive technique for subcutaneous fat reduction. However, further measures are needed to minimize the risk of complications such as PAH, including selective screening, good praxis and appropriate post-treatment care. Therefore, medical training for this technique needs to be intensified.

Keywords— Cryoadipolysis, paradoxical adipose hyperplasia, non invasive fat reduction, side effects, safety, Cooltech.

I. INTRODUCTION

Cryoadipolysis is a non-invasive procedure used to reduce the volume of adipose tissue in different areas of the body for aesthetic purposes. Since its FDA approval for flank contouring in 2010, its use has been expanded to other regions due to high efficacy and a good patient experience compared to classic invasive methods such as liposuction or abdominoplasty [1].

The cryoadipolysis procedure consists of the application of low temperatures to skin folds, including the underlying adipose tissue. To maximize the total surface area of skin that makes contact with the cold surface of the cryoadipolysis applicator, a vacuum is usually generated inside the applicator which sucks the tissue into it [2].

Adipocytes appear to be particularly sensitive to cold temperatures which allows for the mechanism by which cryoadipolysis reduces fat tissue. Many authors maintain that the principle behind its effectiveness for reducing adipose tissue is that adipocytes have a high content of fatty acids and a very specific cell milieu, the freezing point of which is

higher than water. The application of cold can cause these fatty acids to crystallize, resulting in denaturation or apoptosis [3,4].

These authors argue that cell death releases components to the interstitium, which brings about the recruitment of macrophages to the area of inflammation, which then leads to the recruitment of further immune cells including neutrophils, lymphocytes, and mononuclear cells. All these cells generate an inflammatory process that lasts for about 1 month. Initially, the process is characterized by the presence of pro-inflammatory mediators, but after 2 weeks phagocytosis is the predominant process. Adipocytes are eliminated from the body after 1 to 3 months, resulting in decreased thickness of the fat layer with fibrous septa comprising most of the tissue rather than adipocytes.

Other hypotheses suggest cold-induced thermogenesis and a shift in fat metabolism towards higher catabolism of fatty acids. This hypothesis implies that the reduction in fat tissue volume is produced by a metabolic cause rather than by cell death. Authors defending such hypotheses argue that no indicators of inflammation were found in their studies, a fact

that would rule out membrane damage and subsequent clearance by immune mediators, contrary to the most widely accepted hypothesis [5].

While generally regarded as safe, cryoadipolysis can present some mild complications, including edema, bruising, erythema, and skin discoloration, which usually last for less than a month. Such complications are common, although they do not appear to affect patient experience to a great extent as patient satisfaction is reportedly high for non-invasive techniques and particularly cryoadipolysis.

Most adverse effects do not last beyond a month and resolve spontaneously. Hedayati et al (2020) [6] studied these adverse effects in the most complete systematic review found in the literature, encompassing 53 studies and 3,312 patients. Erythema was found to be the most prevalent adverse effect (n=871), although it did not typically persist. Numbness was next in terms of prevalence (n=301), but was found not to last beyond a month. Bruising (n=124) was the third most common adverse effect but mostly resolved after 2 weeks. Bruising is usually related to higher suction during treatment. Additionally, edema and swelling (n=82) were also reported but did not last beyond a week. Other adverse effects included dysesthesia, pain, paradoxical adipose hyperplasia (PAH), blanching, hyperpigmentation and contour irregularities.

Generally, the adverse effects have three characteristics: they are temporary (lasting no more than 4 weeks), resolve spontaneously and have a mild effect on the patients' quality of life. None of these characteristics apply to PAH, which could cause concern among patients about the safety of cryoadipolysis. Moreover, instances of increased volume following a treatment that aims to reduce adiposity is a major hindrance to cryoadipolysis becoming the go-to technique for body contouring, as it can result in a poor patient experience.

Paradoxical adipose hyperplasia is an infrequent adverse effect from cryoadipolysis treatment, with frequencies below 1% [7–10]. PAH is characterized by an increase in fat tissue volume in the area where cryoadipolysis treatment was applied, hence its classification as a paradoxical phenomenon. Hyperplasia is characterized by an increase in the number of adipocytes, which consequently increases the volume of adipose tissue and is found to occur 2–5 months post cryoadipolysis [10,11]. Such increases are spatially well delimited, mobile and not painful, contrary to tumescent masses of tissue [11].

PAH seems to be more prevalent in areas exposed to higher vacuum pressures, which apply a greater suction force to the tissues. Demographically, it seems to predominantly affect men, which in most studies account for more than half of the PAH cases, despite the majority of patients undergoing cryoadipolysis being women. Besides gender, genetic predisposition appears to play a role, as twins have been reported to both suffer from PAH post cryoadipolysis. Lastly, individuals of Hispanic descent seem to show a higher prevalence than other ethnicities, but this could be a combination of genotypical and environmental factors [12].

Concerning the etiology of this complication, no firm mechanism has been proposed. Some authors argue that upon macrophage uptake of lysed adipocytes, the remaining

adipocytes may present an altered metabolism resulting in hypertrophy. Moreover, given that a vacuum is applied to the treatment area, ischemia and consequent hypoxic injury may trigger hypoxia-inducible factors. This process can lead to angiogenesis, which would then lead to increased nutrient availability as well as the recruitment of preadipocytes or other circulating stem cells [13].

While the shift in the market trend from liposuction to non-invasive methods is well documented, the scientific literature is yet to describe the mechanism by which cryoadipolysis treatment can cause PAH. Therefore, most manufacturers recommend a thorough screening before the cryoadipolysis procedure to minimize risks. In the present study we analyze the clinical story of 16 patients who suffered from PAH after receiving cryoadipolysis treatment. This study aims to determine the etiology of this complication, as well as to try to link these cases to preexisting clinical conditions or problems related to medical praxis.

II. MATERIALS AND METHODS

This study was conducted between September and October 2020 at the Clinical Department of Cocoon Medical, Spain. 10 Colombian physicians were interviewed, who had reported 16 cases of lesions compatible with PAH between 2019 and 2020. During this period of time, a total of 7,588 patients underwent a cryoadipolysis session with Cooltech® in Colombia. A total of 31 patients presented a voluminous swelling in the treated area, of which 16 are studied here.

The cryoadipolysis procedures were carried out with the Cooltech® device (Cocoon Medical, Esplugues de Llobregat, Spain). In all cases, treatment time was 70 minutes at a cooling temperature of -8°C and with a suction pressure ranging from 230 mbar to 180 mbar. The Double, Straight, and Curved applicators were used. The areas treated included the flanks, abdomen and back. All other parameters were maintained according to the benchmarks stated in the Cooltech® user manual.

The patients included in this study initially visited physicians seeking to reduce their adiposity in different areas. 1 to 12 months after receiving cryoadipolysis, they returned to the physicians reporting enlargement of the areas where the cryoadipolysis procedures were applied.

Each patient had their clinical history and information about the cryoadipolysis procedure recorded. The physicians were further interviewed regarding each case to complete the information with data from the medical studies (ultrasonography and magnetic resonance imaging) performed to assess the lesion and the treatment offered to the patient to resolve it.

This information has been used to determine the type of lesion (PAH or another type of lesion with a similar external appearance) and to evaluate the potential causes, which may include contraindications, potential risk factors and clinical practice. Causes have been classified as procedure related (potentially caused by suboptimal praxis), risk factor related (potentially correlated with the presence of contraindications), or unknown (cases whose etiology could not be associated with the prior categories).

Permission to evaluate their clinical data as well as the treatment outcomes was obtained from all patients in accordance with the Declaration of Helsinki.

III. RESULTS

From 2019 to 2020, a grand total of 7,588 cryoadipolysis cycles were performed with Cooltech® on patients in Colombia. These cycles resulted in a total of 31 cases with

symptoms compatible with PAH (incidence: 0.41%), of which 16 have been analyzed in this study.

These 16 individuals (10 women and 6 men) were all of Hispanic descent. Their treatment involved various areas (flanks, abdomen and back) as well as 3 different applicators (Double, Straight, and Curved). Relevant data about the treatments are summarized in *Table I*.

TABLE I. Procedural, diagnostic and treatment details of 16 cryoadipolysis patients who later suffered from PAH.

Patient ID	Procedure (applicator, area, pressure, laxity, fat fold)	Patient (gender, age, BMI)	# of months reporting adverse effect	Diagnostic procedure	Type of lesion	Potential cause	Treatment	Observations
1	Double, flanks, 230 mbar, moderate, 56 cm	Male, n/a, n/a	n/a	Physical examination	Unknown	Procedure related	Lipolytic enzymes + liposuction	Pressure exceeded the benchmarks: 230 vs 180 mbar
2	Straight, infraumbilical, 220 mbar, moderate, 52 cm	Male, n/a, n/a	3	Physical examination	Unknown	Unknown	Lipolytic enzymes + liposuction	Incomplete patient information
3	Straight, supraumbilical and back, 230 mbar, moderate, 50 cm	Female, n/a, n/a	8	MRI	PAH or other lipodystrophy	Risk factor related	n/a	Invasive meningioma or adenoma
4	Straight, infraumbilical, 220 mbar, mild, 50 cm	Male, n/a, n/a	12	MRI	No PAH Skin tissue lesion	Unknown	Liposuction	Incomplete patient information Weight gain
5	Double, infraumbilical, 180 mbar, mild, 23 cm	Female, 51, n/a	3	MRI	PAH or other lipodystrophy	Risk factor related	Liposuction	C-section (contraindication)
6	Straight, infraumbilical, 220 mbar, mild, 38 cm	Female, 51, n/a	6	USG + MRI	PAH or other lipodystrophy	Risk factor related	Liposuction	Gestational hypothyroidism, hernia in the treatment area, C-section (contraindication)
7	Straight, infraumbilical, 220 mbar, moderate, 50 cm	Female, n/a, n/a	6	MRI	PAH or other lipodystrophy	Procedure related	Liposuction	Verificatory suction test was not performed prior to procedure Insufficient skin fold to perform treatment
8	Straight, infraumbilical, 220 mbar, moderate, 38 cm	Female, n/a, 24.2	4	Physical examination	PAH or other lipodystrophy	Procedure related	Liposuction	Insufficient skin fold
9	Straight, infraumbilical, 220 mbar, mild, 38 cm	Female, 35, 24.98	5	Physical examination		Unknown	n/a	n/a
10	Straight, infraumbilical, 220 mbar, mild, 36 cm	Male, 37, 26.94	4	MRI	No PAH Skin tissue lesion	Procedure related	Lipolytic enzymes + liposuction	Rectal diastasis Trauma caused by suction
11	Straight, infraumbilical, 180 mbar, mild, 34 cm	Female, 56, n/a	2	MRI	PAH or other lipodystrophy	Risk factor related	Liposuction	Benign hemangioma Metabolic disorder
12	Curved, infrascapular, n/a, moderate, 47 cm	Female, 38, 31.1	1	Physical examination		Risk factor related	Liposuction	Obesity, BMI>30 (contraindication)
13	Double, infraumbilical, 220 mbar, moderate, 36 cm	Female, 47, n/a	3	MRI	PAH or other lipodystrophy	Risk factor related	Liposuction	Previous surgical procedure (contraindication) Pressure exceeded the benchmarks: 230 vs 180 mbar
14	Straight, infraumbilical, 230 mbar, mild, 50 cm	Female, 32, 21.36	4	MRI	PAH or other lipodystrophy	Risk factor related	n/a	Hernia in the treatment area (contraindication) Reduced skin fold Trauma caused by suction
15	Double, infraumbilical, 180 mbar, moderate, 47 cm	Male, 56, n/a	5	Physical examination		Risk factor related	n/a	Incomplete patient information Weight gain
16	Straight, infraumbilical, 220 mbar, mild, 47 cm	Male, 44, 25.63	6	MRI	PAH or other lipodystrophy	Risk factor related	Liposuction	Umbilical hernia (contraindication) Weight gain

These patients received cryoadipolysis and, after an average of 4.8 months (SE 2.7), all reported damage compatible with PAH to their physicians. Upon visiting the physicians, patients were subjected to an interview which attempted to assess potential risk factors or contraindications. Only 6 patients had their complete clinical history recorded, while not all information was found to be available for the remaining 10 patients.

In order to confirm a diagnosis, the patients were subjected to a medical examination, and in 10 (62.5%) cases an imaging study was performed (ultrasonography and magnetic resonance imaging). The remaining 6 (37.5%) patients were not subjected to imaging procedures, and their diagnoses were based on the medical examinations.

Imaging showed that 7 patients (70% of the 10 patients who underwent imaging studies) had prior lesions, including hernias (3), hemangioma (1), meningioma (1), rectal diastasis (1) and scarring from a previous surgery (1). In 8 (80%) cases, imaging procedures were able to identify subcutaneous tissue lesions compatible with PAH or another lipodystrophy, while in 2 (20%) cases, damage to the skin tissues was observed.

After interviewing the physicians and analyzing all available data, 9 (56.25%) patients were found to show the etiology of the complications linked to risk factors of the cryoadipolysis technique, 4 (25%) to procedure-related causes (suboptimal practice), while the remaining 3 (18.75%) patients could not be classified under the aforementioned categories and were thus classified as unknown. Among the 9 patients who did present risk factors, 6 (37.5%) patients showed contraindications, such as obesity, hypothyroidism or hernias, and 3 (18.75%) patients showed metabolic disorders. Notably, 2 of the 9 patients with risk factors were also found to have been subjected to suboptimal practice yet were included in the former category. Moreover, 3 (18.75%) patients reported weight gain after the cryoadipolysis technique.

The 6 (37.5%) patients who were subjected to suboptimal practice either received excessive suction pressure (2) or their treatment was applied with an unsuitable applicator (4).

To resolve the associated complications, 12 (75%) patients were offered liposuction, while 4 (25%) did not qualify to receive any treatment. 3 of them showed clinical complications while the remaining patient is still being monitored in order to provide a safe solution, as the cause of the complication was unknown.

Of the patients who received liposuction, 3 (25%) patients were first subjected to treatment with lipolytic enzymes which provided no significant improvement. All patients who received liposuction had their lesions suitably resolved.

IV. DISCUSSION

Hyperplasia is an increase in the number of cells in an organ or tissue. The process is cellular and is characterized by an irreversible modification of the DNA which causes the alteration of the morphology and cellular function. There are two types of hyperplasia: physiological and pathological. Physiological hyperplasia can be classified as hormonal hyperplasia or compensatory hyperplasia, which involve an

increase in tissue mass after injury. Pathological hyperplasia is caused by excess hormones or growth factors in the cells, as a consequence of the proliferation regulated by growth factors and the subsequent formation of new cells.

Little is known about the pathophysiology of PAH after a cryoadipolysis procedure, as its exact mechanism has yet to be described. 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 [7]. These preadipocytes will then be able to proliferate afterwards, leading to an increase in tissue volume. Other hypotheses include hypertrophy of adipocytes, changes in the expression of receptors associated with adipocyte metabolism, reduction in sympathetic innervation or hypoxia. Another explanation is that, upon cooling, hypoxia may trigger a response that includes hypertrophy, fibrous cells and vasculature.

In this study, we report a PAH incidence of 0.41% with a total of 31 cases in 7,588 cycles. This value is well above the initial values provided by other manufacturers (0.0051%) [11], which were subsequently corrected to 0.025% [14,15]. However, the value found in this study is in the range reported by other authors. Singh et al (2015) [7] reported a 0.47% incidence in a trial that included 422 cycles and 2 patients affected by PAH. Kelly et al (2016) [8] reported a 0.72% incidence in a study of 2,073 over a 36-month period. Of note, at least 11 of these were of Hispanic descent [16].

Since cryoadipolysis is a relatively recent technique, little information is available about its infrequent adverse effects, as analysis of such events requires a high number of patients to be observed. Although little literature is available on this issue, risk factors for PAH include obesity (BMI>30), reduced skin folds, scars in nearby tissues, recent surgeries, autoimmune diseases, altered circulation, high calorie diets including fatty acids and/or animal proteins, sedentarism and malignant pathologies [6].

While physicians and manufacturers are constantly gathering information about adverse effects, PAH seems to be underreported [6]. The time PAH takes to appear after cryoadipolysis, combined with the reluctance of patients suffering from such complications to return to the physicians where they received treatment, might be contributing to the underreporting of this event [7].

In data gathered in this study, most patients (10) underwent magnetic resonance imaging (MRI) that was suitable for an accurate diagnosis, yet 6 were only subjected to a medical examination. While medical criteria are always important, in the absence of proper imaging procedures, a physical diagnosis is not conclusive. This is particularly true with complications such as PAH that can be easily confused with other types of lesions.

The results of PAH diagnosis by MRI should be thoroughly analyzed as they can be confused with other causes of increased volume. Additionally, histopathologic analysis may also be necessary since it allows for a much more accurate diagnosis of the damaged tissue. However, such analysis is more invasive as it requires collecting live samples

from patients. Given that one of the advantages of cryoadipolysis is its non-invasiveness, both patients and physicians might be reluctant to opt for such a diagnosis technique. Knowledge of cellular and histological changes in adipose tissue after cryoadipolysis would contribute to assessing the pathogenesis of PAH.

Concerning the etiology of the PAH in our patients, more than 50% of the patients showed risk factors and contraindications for receiving cryoadipolysis. These mostly involved lesions in the areas in which treatments were applied (hernias, C-sections, and cysts). All these complications increase the risk of prolonged inflammation, a process that needs to be resolved for cryoadipolysis to be effective [17]. Moreover, some patients also presented metabolic complications, such as hypothyroidism or those caused by obesity, which are exclusion criteria for the application of cryoadipolysis. Furthermore, three of these patients were also ineligible for receiving liposuction.

The bibliography suggests that Hispanic patients seem to be at a higher risk of PAH following cryoadipolysis [16]. In this regard, our study cannot contribute to such affirmations as it was carried out in Colombia, yet incidence is in accordance with similar studies conducted in areas with low populations of individuals of Hispanic descent. Moreover, such studies are merely observational and do not present any solid hypotheses on why the Hispanic population could be at a higher risk. In addition, during the 2019 to 2020 period, only one case of lipodystrophy was reported in Spain. It is therefore possible to understand this risk factor at a territorial level, taking into account the eating habits of certain countries that predispose the population to metabolic pathologies and chronic degenerative diseases. All these pathologies are known to produce a state of chronic inflammation in subjects as well as an altered metabolism compared to healthy patients. Some countries in the Americas are known to have diets that are richer in red meat, saturated fatty acids and processed foods, as well as a higher frequency of obesity, an important contraindication for the cryoadipolysis procedure.

All these data reinforce the need to establish thorough patient screening prior to the application of cryoadipolysis, as not doing so may lead to complications which can exacerbate the self-image problem that compels most patients to choose body contouring technologies in the first place. For such reasons it remains of critical importance to provide accurate information to patients, so it is not only physicians who are aware of the complications and possible risks.

In order to generate exclusion criteria, it is of critical importance to establish thorough patient screening prior to the application of procedures. While patients might see cryoadipolysis as a solution for their self-image issues, it is critical not to apply such procedures to patients who present risk factors as this may cause complications such as PAH. Data presented in this study demonstrate that there is a proportion of physicians who are not aware of the risk factors, exclusion criteria and possible complications, as more than 50% of patients showed some contraindications or risk factors.

Nowadays, manufacturers are dedicating their efforts towards generating reliable clinical data to assess

complications and their prevalence. Moreover, medical education is also a priority for these companies, as it is prudent to avoid adverse effects as much as possible. However, the lack of reliable data on most complications, including PAH, as well as the economic incentives to perform surgeries on patients who suffered from PAH, may lead to medical indications that are not as conservative as they should be.

In this regard, it is also highly relevant that the lesions of 6 (37.5%) patients were potentially related to suboptimal clinical practice. The use of an incorrect cold applicator, in particular, is suspected to be the leading cause of this complication, as it can cause increased tissular damage. This damage could in turn exacerbate the inflammatory process, a fact that has been associated with less favorable prognoses. In line with this, several authors have reported that consecutive (within a period of less than 3 months) cryoadipolysis treatments seem to increase the risk of PAH [6].

Several treatments can be applied to reverse PAH, which can cause an image problem for patients aiming to reduce adipose tissue. Among these technologies, the most common are mesotherapy, radiofrequency, ultrasound, shock waves, deoxycholate, lymphatic drainage, and lastly, liposuction. While the latter is the most invasive alternative treatment, it has also proven to be the most effective for eliminating PAH. This generates a conflict in patients, as one of the major advantages of cryoadipolysis is a lack of complications thanks to its non-invasiveness. For this reason, screening patients prior to cryoadipolysis is of enormous importance, as risk factors increase the probability of PAH after cryoadipolysis. Moreover, PAH cannot always be resolved with liposuction, since PAH has been shown to persist after surgery [7].

It is worth mentioning that lipolytic enzymes were the initial treatment for 3 of the patients but did not have any effect on reducing the enlargement of the fat tissue. All 3 patients underwent liposuction afterwards, which resolved the issue positively. Moreover, 9 other patients received liposuction with no prior lipolytic treatment and the PAH was resolved correctly. While physicians might have favored lipolytic enzymes over direct liposuction due to its non-invasiveness, these results suggest that it is not effective for resolving PAH.

Few studies have addressed the infrequent adverse effects of cryoadipolysis. Further studies need to be carried out to assess all risk factors and exclusion criteria, that way both manufacturers and physicians can make data-driven decisions to enable better outcomes for patients.

Despite the limited medical information and studies, efforts should be aimed at educating physicians on performing optimal treatments, which can in turn minimize procedural risks and even eliminate the occurrence of PAH (Figure 1).

The first things to address to prevent any possible complications before applying the treatment are identifying risk factors and contraindications, informing clients about the expected results and side effects, and giving recommendations and guidelines to the patient on obtaining the best possible results, preventing adverse effects, and understanding the risks should these recommendations not be followed.

Prevention (Pre-treatment)	Caution (During treatment)	Care (Post-treatment)	Medical action
<ul style="list-style-type: none"> • Risk management • Identify contraindications <ul style="list-style-type: none"> ○ Detect ○ Inform ○ Recommend 	<ul style="list-style-type: none"> • Optimal procedure <ul style="list-style-type: none"> ○ Handpiece ○ Pressure ○ Preparation of the area 	<ul style="list-style-type: none"> • Healthy lifestyle • Diet • Exercise • Communication with clinicians 	<ul style="list-style-type: none"> • Control the evolution • Imaging studies • Inform manufacturers

Fig. 1. Good practice recommendations to minimize the risk of PAH.

Secondly, clinical practice should be improved to enable the provision of optimal procedures. This would include the correct selection of the cold applicator and its usage parameters, as well as the correct performance of the cryoadipolysis treatment, since repeated treatments on the same area or the overlapping of treatments can cause adverse effects in the fatty tissue.

Thirdly, it should be emphasized that physicians must inform patients about post-treatment care, this involves following a diet that is low in saturated fat and calories combined with gentle exercise and massaging the treatment area to promote the fat reduction process. Patients should understand the expected evolution of the treated area, which may include mild pain, loss of skin sensitivity, and inflammation during the first 4 weeks, followed by a gradual loss of volume between 1 and 3 months after treatment. Changes other than those expected may be a sign of hyperplasia or another lipodystrophy or tissue injury.

Finally, early medical intervention could be essential to avoiding the occurrence of PAH. In the event of an unexpected evolution, physicians should analyse patients with a blood test and follow preventive treatments with lipolytic enzymes, non-invasive equipment, diet and exercise, and medication if necessary. Physicians should also contact the manufacturer for clinical support and medical recommendations. If no improvement is seen, an imaging study should be performed to obtain a correct diagnosis of the lesion.

V. CONCLUSIONS

As such a recent technology, the effectiveness of cryoadipolysis has been demonstrated in terms of fat reduction, but most of its associated complications have not been well documented due to the limitations in the literature. The heterogeneity of the patient selection in each study as well as the abundance of case reports rather than longitudinal studies hinders the process of drawing significant and steady conclusions on the prevalence of PAH among cryoadipolysis patients. Furthermore, the clinical evaluation of complications following such treatments is a cumulative effort; as more studies are carried out, more information is gathered, and more reliable incidences can be determined. Efforts should be directed towards establishing consistent inclusion criteria, with the participation of several centers and physicians to ensure reliable results are generated.

Further education of physicians on the risk factors of PAH and consequent documentation of such contraindications to allow for more adequate patient screening is no trivial matter. This would in turn minimize the incidence of such high-risk

patients and all the complications derived from PAH. Ultimately, physicians should be educated on the correct usage of the medical device to minimize the risk of complications from suboptimal praxis. On the other hand, patients should notify physicians of any deviations from what is expected while also maintaining a healthy lifestyle to minimize the risk of complications such as PAH.

Globally, cryoadipolysis is a safe technique for body contouring which typically only results in milder and more temporary adverse effects. Further studies need to be carried out to assess its long-term effects, including PAH, which if not properly addressed can result in aesthetic concerns for patients. However, improving clinical protocols with best practice recommendations and better training for physicians has been shown to be an excellent solution for PAH.

CONFLICTS OF INTEREST

All authors are employed by Cocoon Medical S.L.U., the company that manufactures and commercializes Cooltech®. However, this publication strictly adheres to the objectivity and ethics of independent research.

REFERENCES

- [1] Mármol, G. V., Llanos, M. D. L., Oliva, J., and Giménez, C. Efficacy and Safety of Subcutaneous Fat Reduction by Cryoadipolysis. *International Research Journal of Pharmacy and Medical Science (IRJPMS)*. 2019;2(3):38–43.
- [2] Manstein, D., Laubach, H., Watanabe, K., Farinelli, W., Zurakowski, D., and Anderson, R. R. Selective cryolysis: A novel method of non-invasive fat removal. *Lasers in Surgery and Medicine*. 2008;40(9):595–604.
- [3] Avram, M.M., and Harry, R.S. Cryolipolysis for subcutaneous fat layer reduction. *Lasers Surg Med*. 2009;41(10):703–8.
- [4] Krueger, N., Mai, S. V., Luebberding, S., and Sadick, N. S. Cryolipolysis for noninvasive body contouring: Clinical efficacy and patient satisfaction. *Clinical, Cosmetic and Investigational Dermatology*. 2014;7:201–205.
- [5] Loap, S., and Lathe, R. Mechanism Underlying Tissue Cryotherapy to Combat Obesity/Overweight: Triggering Thermogenesis. *Journal of Obesity*. 2018;1–10.
- [6] Hedayati, B., Juhász, M., Chu, S., and Mesinkovska, N. A. Adverse Events Associated With Cryolipolysis: A Systematic Review of the Literature. *Dermatologic Surgery*. 2020;46:S8–S13.
- [7] Singh, S. M., Geddes, E. R. C., Boutros, S. G., Galiano, R. D., and Friedman, P. M. Paradoxical adipose hyperplasia secondary to cryolipolysis: An underreported entity? *Lasers in Surgery and Medicine*. 2015;47(6):476–478.
- [8] Kelly, E., Rodriguez-Feliz, J., and Kelly, M. E. Paradoxical Adipose Hyperplasia after Cryolipolysis: A Report on Incidence and Common Factors Identified in 510 Patients. *Plast Reconstr Surg*. 2016;137(3):639e–40e.
- [9] Karcher, C., Katz, B., and Sadick, N. Paradoxical Hyperplasia Post Cryolipolysis and Management. *Dermatol Surg*. 2017;43(3):467–470.
- [10] Stroumza, N., Gauthier, N., Senet, P., Moguelet, P., Nail Barthelemy, R., and Atlan, M. Paradoxical Adipose Hypertrophy (PAH) After Cryolipolysis. *Aesthet Surg J*. 2018;38(4):411–417.
- [11] Jalian, H. R., Avram, M. M., Garibyan, L., Mihm, M. C., and Anderson, R. R. Paradoxical adipose hyperplasia after cryolipolysis. *JAMA Dermatology*. 2014;150(3):317–319.
- [12] Ho, D., and Jagdeo, J. A systematic review of paradoxical adipose hyperplasia (PAH) post-cryolipolysis. *Journal of Drugs in Dermatology*. 2017;6(1):62–67.
- [13] Fong, G. H. Regulation of angiogenesis by oxygen sensing mechanisms. *Journal of Molecular Medicine*. 2009;87(6):549–560.
- [14] CoolSculpting post-market consumer data, ZELTIQ Aesthetics, quarterly report for Q2 2015.



- [15] Sasaki G. H. Reply: Cryolipolysis for Fat Reduction and Body Contouring: Safety and Efficacy of Current Treatment Paradigms. *Plastic and Reconstructive Surgery*. 2016;137(3):640e–641e.
- [16] Kelly, M. E., Rodriguez-Feliz, J., Kelly, E., and Torres, C. Paradoxical Adipose Hyperplasia: A Report on Increased Incidence, Clinical Management, and Outcomes. *Plastic and Reconstructive Surgery*. 2017;5(9S):53–54.
- [17] Ingargiola, M. J., Motakef, S., Chung, M. T., Vasconez, H. C., and Sasaki, G. H. Cryolipolysis for Fat Reduction and Body Contouring: Safety and Efficacy of Current Treatment Paradigms. *Plastic and Reconstructive Surgery*. 2015;135(6):1581–1590.
- Chaim, B., and Ot, C. Case report of a rare side effect associated with cryolipolysis. *Journal of the American Academy of Dermatology*. 2014;70(5):AB195