

A Systematic Review of Paradoxical Adipose Hyperplasia (PAH) Post-Cryolipolysis

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ABSTRACT

Background: Body sculpting, or body contouring, is among the fastest growing areas in cosmetic dermatology. Cryolipolysis, or “fat freezing,” was FDA-cleared (CoolSculpting System, ZELTIQ Aesthetics, Pleasanton, CA) initially in 2010 for fat removal of the flanks, and subsequently received FDA-clearance for other anatomical locations. Over the past several years, there have been increasing published reports and physician discussion regarding paradoxical adipose hyperplasia (PAH) post-cryolipolysis, previously identified as a “rare” adverse effect.

Objective: To review published reports of PAH post-cryolipolysis, expand on previously proposed hypothesis of PAH, and provide recommendations for prevention and treatment of PAH.

Methods and Materials: On July 26, 2016, we systematically searched the computerized medical bibliographic databases PubMed, EMBASE, Web of Science, and CINAHL with the search term “cryolipolysis.”

Results: A total of 314 records were returned from our search terms and 10 records were found to be suitable for our review. We identified a total of 16 cases of PAH post-cryolipolysis in the published literature.

Conclusions: Based upon the published literature, we identified that the current incidence of PAH may be higher than previously reported. Although the pathoetiology of PAH is currently unknown, we hypothesize that some adipocytes may be “naturally selected” for survival due to their inherent tolerance to cryolipolysis. We believe that while cryolipolysis is an effective non-invasive treatment option for body contouring, physicians and patients should be aware of PAH as a potential adverse effect and treatment options.

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INTRODUCTION

Body sculpting, or body contouring, is among the fastest growing areas in cosmetic dermatology. In 2015, dermatologic surgeons performed over 230,000 body sculpting treatments.¹ One survey reported 89% of consumers are concerned with excess weight and 35% of consumers are considering body sculpting treatments.² In addition to the common indication of body sculpting for removal of excess lower abdominal fat for men and women, men are also concerned with pseudogynecomastia (enlarged male breast due to excess fat) and procedures for male breast reduction rose 26% from 2014 to 2015.² Pseudogynecomastia and excess lower abdominal fat may affect patients' quality-of-life, resulting in self-consciousness and psychological distress.³

Liposuction is the most popular and the most effective surgical treatment for focal fat reduction.⁴ However, liposuction is associated with possible adverse effects and downtime. Concerns associated with invasive procedures, such as liposuction, include risks for infection, nerve damage, hematoma, complications with anesthesia, and the high cost associated with surgical treatment. Physicians and consumers alike are seeking minimally invasive, low risk, and cost-effective techniques for focal fat reduction with fast recovery time.

Recently, non-invasive fat reduction techniques have become more widely available and may be associated with fewer adverse effects compared to invasive procedures. Non-invasive fat reduction techniques include using temperature, sound, and light modulation to selectively target adipocytes for fat removal while minimizing the effects on the epidermis and dermis.⁵ Examples include cryolipolysis, high intensity focused ultrasound, and low level and infrared lasers using wavelengths specifically targeted for adipocytes.^{5,6}

A landmark manuscript published in 2008 reported that prolonged, controlled local skin cooling can induce selective damage and removal of fat deposits without injuring local tissue.⁷ This reported phenomenon is based upon historical observations that lipid-rich tissue is more susceptible to cold injury than surrounding water-rich tissue.⁸ Cryolipolysis, or “fat freezing,” was FDA-cleared (CoolSculpting System, ZELTIQ Aesthetics, Pleasanton, CA) for fat removal of the flanks or “love handles” (K080521) in 2010, abdomen (K120023) in 2012, thighs (K133212) in 2014, submental region (K151179) in 2015, and arms (K162050), bra bulge, back, and underneath the buttock or “banana roll” (K160259) in 2016. Cryolipolysis treatment using

the original cryolipolysis applicator requires treatment duration of 60 minutes, during which a fold of adipose tissue is suctioned by a negative pressure applicator consisting of two cooling plates at -10°C .⁹ Newer applicators and updated recommended treatment settings have since been released, achieving lower treatment temperature, reduced treatment time, decreased risk of bruising, one without suction, and greater patient satisfaction (Table 1).^{9,10} Published studies on cryolipolysis reported good safety and efficacy with minimal recovery time and visible effects seen on average at 4 months post-treatment, which makes cryolipolysis an appealing treatment option for patients.¹¹

Over the past several years, there have been increasing published reports and physician discussion regarding paradoxical adipose hyperplasia (PAH) post-cryolipolysis, previously identified as a “rare” adverse effect. PAH often clinically presents as a painless, firm, well-demarcated, visually appreciable enlarged tissue growth in the treatment area 3 to 9 months post-cryolipolysis. Herein, we review published reports of PAH post-cryolipolysis, expand on previously proposed hypothesis of PAH, and provide recommendations for prevention and treatment of PAH.

METHODS

We employed the following literature review search strategy: on July 26, 2016, we systematically searched the computerized medical bibliographic databases PubMed, EMBASE, Web of Science, and CINAHL with the search term “cryolipolysis” (see Figure 1 for schematic of literature search strategy based upon the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines).¹² The relevant records that met the following criteria were selected for inclusion: clinical reports of PAH post-cryolipolysis. Information on patient characteristics, anatomic locations, treatment settings, number of treatment sessions, time of PAH onset, histology or radiology assessments, and management of PAH of published reports were extracted

from reviewed articles. Exclusion criteria included non-English articles. A Grade of Recommendation is not included in this systematic review as PAH is an adverse effect post-cryolipolysis.

RESULTS

A total of 314 records were returned from our search terms. After removal of duplicates, 138 records were screened for titles, abstracts, and/or full-texts, and 10 records were found to be suitable for our review. These 10 records include 7 case series and/or case reports and 3 conference abstracts and are summarized in Table 2.^{3,13-21} We identified a total of 16 cases of PAH post-cryolipolysis in the published literature.

DISCUSSION AND FUTURE DIRECTIONS

Based upon the published literature, there is strong clinical evidence indicating PAH is an adverse effect associated with cryolipolysis as the adipose hyperplasia occurs at the treatment site, with a timeline of 3 to 9 months post-cryolipolysis, and no reports of any significant dietary or weight changes per patients with PAH. To date, there have been over 2 million cryolipolysis procedures performed worldwide.²² Based upon manufacturer’s post-market consumer data and limited published reports, the incidence of PAH has been on the rise from 2013, 2014, and the second quarter of 2015 (0.0032%, 0.021-0.026%, and 0.025%, respectively).^{21,23} The most recent post-market consumer data provided by the device manufacturer for 2016 shows the PAH incidence rate remains consistent with the previously published incidence rate of approximately 0.025%, or 1 in 4,000 treatment cycles.²¹ Post-market consumer data indicated that PAH has occurred in areas including the abdomen, flanks, back, thighs, and chest, and may be associated with high vacuum settings and greater force on tissue.²¹

Based upon the published medical literature, although only a small percentage of cryolipolysis procedures resulted in PAH,

TABLE 1.

Current Cryolipolysis Applicators Commercially Available (CoolSculpting System, ZELTIQ Aesthetics, Pleasanton, CA)

Name	Suction	Temperature	Treatment Time	Indicated Area
CoolAdvantage™ Applicator with interchangeable contours	Yes	-11°C	35 minutes	3 interchangeable contours • CoolCurve+ Advantage™: Flanks • CoolCore Advantage™: Abdomen • CoolFit Advantage™: Inner thighs
CoolCurve+™ Applicator	Yes	-10°C	60 minutes	Flanks
CoolMax™ Applicator	Yes	-10°C	60 minutes	Flanks (Twice the size as CoolCurve+™ Applicator for large volume reduction)
CoolCore™ Applicator	Yes	-10°C	60 minutes	Abdomen
CoolFit™ Applicator	Yes	-10°C	60 minutes	Inner thighs
CoolMini™ Applicator	Yes	-10°C	45 minutes	Submental region
CoolSmooth PRO™ Applicator	No	-13°C	75 minutes	Outer thighs

*Information based upon manufacturer brochure and website, and Kilmer 2016.⁹

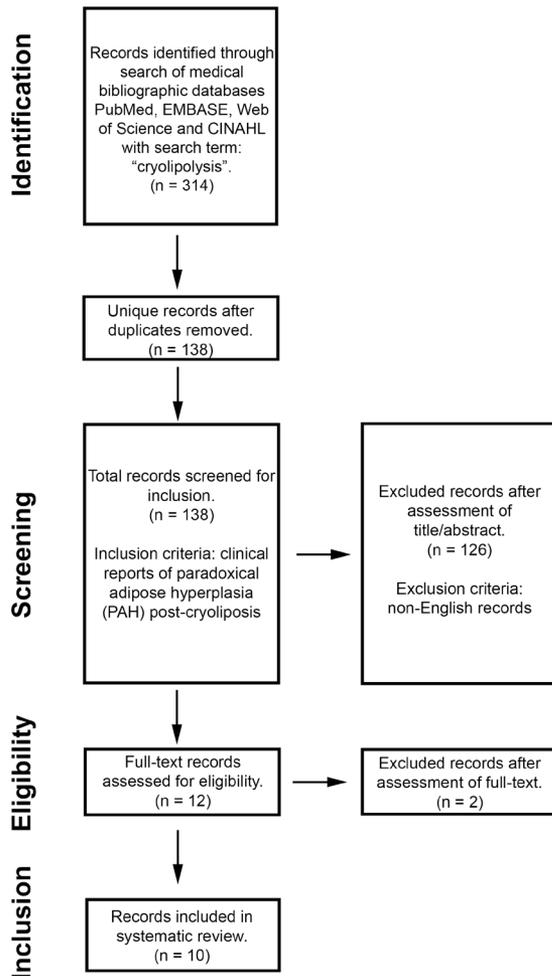
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FIGURE 1. Schematic of literature search strategy based upon the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines.



the continuing popularity and high volume of cryolipolysis procedures performed may suggest that PAH may not be a “rare” adverse effect. In addition, we propose that the number of confirmed cases of PAH may be underreported due to a lack of published cases in the medical literature, and/or patients possibly feeling more self-conscious after “unintentional fat gain” post-cryolipolysis or other reasons, resulting in loss to follow-up or delays in PAH diagnosis.

According to published evidence, PAH may impact certain demographics disproportionately. Interestingly, review of the published literature may indicate that men may have a predisposition to PAH post-cryolipolysis as we identified 10/16 cases with male patients. However, this may not be true as the manufacturer’s data reported that 55% of patients with PAH were men.²⁴ Furthermore, as only 15% of reported total patients who received cryolipolysis were men, the relative number of PAH cases is much higher for men compared to women. In addition

to a sex predisposition, genetic predisposition is a possibility. We identified 2 sets of twins who all developed PAH post-cryolipolysis.^{16,19} Of note, PAH occurred more frequently in patients of Hispanic and Latino descent compared to other ethnicities, which poses the question if PAH may be multifactorial as it may be associated with sex, genetics, lifestyle, and/or environmental factors.²¹

The exact pathoetiology of PAH remains to be elucidated, but researchers have proposed several mechanisms of PAH development.¹³ We hypothesize that not all adipocytes are affected by fat freezing and are phagocytized by macrophages, which may result in hyperplasia of remaining adipocytes as these adipocytes may be “naturally selected” for survival. These “naturally selected” adipocytes may have changes in their receptor expression and signaling factors associated with adipocyte metabolism resulting in adipose hyperplasia.

It is known that hypoxic injury to adipocytes may increase vascularity by release of hypoxia-inducible factors (HIFs), which initiates a signaling cascade toward angiogenesis and potentially adipose hypertrophy and hyperplasia.²⁵ Additionally, cooling of the adipocytes without cell rupture may lead to hypoxic injury and result in rebound hypertrophy and hyperplasia of adipocytes.¹⁸ Histopathology of PAH demonstrates septal thickening, which may be a result of reactive fibrosis stemming from hypoxic injury in adipocytes.¹³ The result of hypoxic and physical injury may increase blood flow and stimulate adipocyte proliferation, which may support the theory of survival of “naturally selected” adipocytes. Cryolipolysis may also have effects on the recruitment of resident or circulating pre-adipocyte or stem cell population, which has previously been reported to result in adipose hypertrophy.²⁶

Instances of transient decreased sensation at the treatment area has been reported post-cryolipolysis, and studies have shown that sympathetic denervation of adipose tissues can induce pre-adipocyte and adipocyte proliferation in animal models.²⁷ There is currently a paucity of published evidence supporting this theory in clinical studies. We believe it is possible that sympathetic denervation of adipose tissues could occur intra- or post-cryolipolysis, however future studies may perform additional histology staining or molecular assays for confirmation.

A different hypothesis is that the negative pressure suction from cryolipolysis may have a stimulatory effect on adipocytes.¹⁸ This hypothesis is based upon the observed effects from the BRAVA system (Brava, LLC, Miami, FL), which is a negative pressure vacuum-based external breast expander to stimulate the body to generate a vascularized scaffold that is later suitable for fat grafting.²⁸ As previously stated above, we hypothesize that cryolipolysis may have a stimulatory effect on the “naturally selected” adipocytes for survival. However,

whether this proposed phenomenon stems from the -10°C cooling effects or from the physical injury due to negative suction requires further investigation.

Currently, the treatment of choice for PAH is liposuction. Other treatments of cryolipolysis are not recommended for PAH as this may worsen the condition.¹⁷ We recommend the use of small applicators (with a smaller surface area treated per treatment) as many instances of PAH have been associated with

large applicators, particularly in patients who may be predisposed to developing PAH (male sex and of Hispanic or Latino descent). We encourage patients to consult body contouring experts, such as dermatologic surgeons who are experienced with cryolipolysis, as they are trained in non-invasive procedures and have made the largest clinical and scientific research contributions to cryolipolysis.²⁹ We believe that all patients should be fully informed of the potential adverse effects from cryolipolysis, and realistic expectations should be discussed

TABLE 2.**Published Clinical Cases of Paradoxical Adipose Hyperplasia (PAH) Post-Cryolipolysis**

Authors	Year	Patient Characteristics	Anatomic Locations	Treatment Settings	# of Treatment Sessions	Time of PAH Onset	Histology or Radiology Assessments	Management
Jalian et al ¹³	2014	Male Age: 40s	Lower abdomen	Zeltiq EZ 8 applicator Standard preset cooling factor Large applicator (27.7 x 3.8 cm rectangle) Manufacturer recommended vacuum settings	1 session	3 months post-treatment	MRI: increased adipose tissue with normal signal intensity.	Tissue growth stabilized in size by approximately 5 months. Patient did not elect corrective treatment.
	2014	Female Age: 50s	3 separate areas on the abdomen	"Large and small applicator" Manufacturer recommended vacuum settings	1 session	9 months post-treatment	Histology: disorganized adipocytes varying in shape and size; increased septal thickening around fat lobules; increased vascularity within adipose tissue; normal appearing epidermis and dermis.	Abdominoplasty was performed at 9 months.
Macedo et al ¹⁴	2014	Male Age: 40 Weight: 80 kg	Lower abdomen	N/A	N/A	3 months post-treatment	No	Tissue growth continued until 5 months post-treatment. Patient received liposuction for management.
Raphael et al ¹⁵	2014	Female Age: 75 Caucasian	Abdomen	N/A	2 sessions (1 month apart)	4 months post-2nd treatment (5 months post-initial treatment)	Histology: no apparent underlying pathology for adipose hyperplasia.	Pannectomy.
Munavalli et al ³	2015	Male Age: N/A BMI: less than 35 kg/m ² Author's clinical practice: 1/21 patients; Reported incidence of 4.7%	Pectoral (Unilateral)	Cooling intensity factor of 41.6 Average energy extraction rate of 72.9 mW/cm ²	3 sessions (2 sessions on same day then 3rd session 60 days later)	N/A	No	Tumescent liposuction.
Rai et al ¹⁶	2015	Identical twins Age: 40s	Lower abdomen and flanks	N/A	N/A	N/A	No	Tumescent liposuction.

TABLE 2. Continued

Published Clinical Cases of Paradoxical Adipose Hyperplasia (PAH) Post-Cryolipolysis								
Authors	Year	Patient Characteristics	Anatomic Locations	Treatment settings	# of Treatment sessions	Time of PAH onset	Histology or radiology assessments	Management
Singh et al ¹⁷	2015	Male Age: 44 Fitzpatrick skin type IV Author's clinical practice: 2/422 patients; Reported incidence of 0.47%	Pectoral (Bilateral)	Zeltiq EZ 6.3 applicator Standard setting according to manufacturer guidelines	Total of 3 sessions. 1 session at Time 0. 2 additional sessions at 4 months post-initial treatment.	4 months post-1st treatment, and under went two additional treatments of cryolipolysis. Additional tissue growth was present 2 months post-second treatment.	No	Tissue growth was present 6 months post-1st treatment and patient elected for liposuction.
		Male Age: 52 Fitzpatrick skin type III	Lower abdomen	Zeltiq EZ 8 applicator Standard setting according to manufacturer guidelines	1 session	6 months post-treatment	Histology: increased number of adipocytes, fibrosis, and scar tissue.	Tissue growth was present at 1 year post-treatment and patient elected for liposuction.
Stefani et al ¹⁸	2015	Male Age: 29 Weight: 164 lbs	Lower abdomen	Zeltiq EZ 8 applicator Standard setting according to manufacturer guidelines	3 sessions over a 2-year period.	3 months post-3rd treatment (2 years post-initial treatment)	Histology: normal adipose and fibrous tissue, no change in the fibrous or adipose cellularity and structure except for hypertrophy MRI: normal fatty infiltration.	Tumescent liposuction.
Kelly et al ¹⁹	2016	Male (4 patients) Mean age: 50, (range 38 to 57) BMI: Mean – 26.2 kg/m ² (range 24 to 28 kg/m ²) Hispanic (All 4 patients) Author's clinical practice: 4/510 patients over 20 months with 1 set of twins; Reported incidence of 0.78%	Lower abdomen	"Large applicator"	N/A	N/A	No	N/A
Seaman et al ²⁰	2016	Female Age: 48	Abdomen, posterior trunk, and bilateral flanks	Standard setting according to manufacturer guidelines	2 sessions one month apart	3 months post-2nd treatment (4 months post-initial treatment)	Histology Multiple assays evaluating interstitial cells, adipocytes, and endothelial cells.	Tissue growth remained unchanged at 6 months post-2nd treatment and patient elected for suction lipectomy at 7 months.
Sasaki ²¹	2016	Female Age: 48 BMI: 28.4 kg/m ²	Left upper inner thigh	"Flat plate applicator" CIF – 42 Vacuum pressure – 50 mm Hg	1 session	N/A	No	N/A

prior to treatment. Regular follow-up visits are important as patients may be self-conscious, however timely diagnosis and surgical management of PAH may yield excellent outcomes.

Limitations of this systematic review include lack of published specifications of applicator size and treatment settings regarding whether suction was applied. Faster (35 minutes), colder (-11°C) applicators and updated recommended treatment settings have been released that function with or without suction.

Based upon the published literature, we believe that the current incidence of PAH may be higher than reported. This may be due to a combination of factors: PAH was previously underrecognized or underreported and cryolipolysis is among the fastest growing non-invasive body sculpting procedure employed today. Although the pathoetiology of PAH is currently unknown, we hypothesize that some adipocytes may be “naturally selected” for survival due to their inherent tolerance to cryolipolysis. We envision future studies may utilize molecular assays and genomic evaluations to characterize involvement of key pathways responsible for PAH. PAH is significant as cryolipolysis is becoming more widely available and performed by physicians and non-physician technicians in outpatient clinics, med spas, and aesthetic offices. We believe that while cryolipolysis is an effective non-invasive treatment option for body contouring, physicians and patients should be aware of PAH as a potential adverse effect and treatment options.

DISCLOSURES

DH has no conflicts of interest to disclose. Dr. Jagdeo is a scientific consultant for Zeltiq. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

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