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 pathoetiolog 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.


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 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.\(^3\) 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).5,10 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 30 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 2.5,10 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).21,22 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,
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.24 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 if this proposed phenomenon stems from the -10°C cooling effects or from the physical injury due to negative suction requires further investigation.

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<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patient Characteristics</th>
<th>Anatomic Locations</th>
<th>Treatment settings</th>
<th># of Treatment sessions</th>
<th>Time of PAH onset</th>
<th>Histology or radiology assessments</th>
<th>Management</th>
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</thead>
<tbody>
<tr>
<td>Singh et al(^1)</td>
<td>2015</td>
<td>Male Age: 44</td>
<td>Pectoral (Bilateral)</td>
<td>Zeltiq EZ 6.3</td>
<td>Total of 3 sessions</td>
<td>4 months post-1st treatment</td>
<td>No</td>
<td>Tissue growth was present 6 months post-1st treatment and patient elected for liposuction.</td>
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<td></td>
<td></td>
<td>Fitzpatrick skin type IV</td>
<td></td>
<td>applicator</td>
<td>1 session at Time 0.</td>
<td>2 months post-second treatment</td>
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<td></td>
<td>Standard setting according to manufacturer guidelines</td>
<td>2 additional sessions at 4 months post-initial treatment</td>
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<td></td>
<td></td>
<td>Author’s clinical practice: 2/422 patients; Reported incidence of 0.47%</td>
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<td>Stefani et al(^2)</td>
<td>2015</td>
<td>Male Age: 52</td>
<td>Lower abdomen</td>
<td>Zeltiq EZ 8</td>
<td>1 session</td>
<td>6 months post-treatment</td>
<td>Histology: increased number of adipocytes, fibrosis, and scar tissue</td>
<td>Tissue growth was present at 1 year post-treatment and patient elected for liposuction.</td>
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<td></td>
<td></td>
<td>Fitzpatrick skin type III</td>
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<td>applicator</td>
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<td>Standard setting according to manufacturer guidelines</td>
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<tr>
<td>Kelly et al(^3)</td>
<td>2016</td>
<td>Male (4 patients)</td>
<td>Lower abdomen</td>
<td>Zeltiq EZ 8</td>
<td>3 sessions over a 2-year period.</td>
<td>3 months post-3rd treatment (2 years post-initial treatment)</td>
<td>Histology: normal adipose and fibrous tissue, no change in the fibrous or adipose cellularity and structure except for hypertrophy MRI: normal fatty infiltration.</td>
<td>Tumescent liposuction.</td>
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<td>Mean age: 50, (range 38 to 57)</td>
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<td>applicator</td>
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<td>BMI: Mean – 26.2 kg/m² (range 24 to 28 kg/m²)</td>
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<td>Hispanic (All 4 patients)</td>
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<td>Author’s clinical practice: 4/510 patients over 20 months with 1 set of twins; Reported incidence of 0.78%</td>
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<td>Seaman et al(^4)</td>
<td>2016</td>
<td>Female Age: 48</td>
<td>Abdomen, posterior trunk, and bilateral flanks</td>
<td>Standard setting according to manufacturer guidelines</td>
<td>2 sessions one month apart</td>
<td>3 months post-2nd treatment (4 months post-initial treatment)</td>
<td>Histology Multiple assays evaluating interstitial cells, adipocytes, and endothelial cells.</td>
<td>Tissue growth remained unchanged at 6 months post-2nd treatment and patient elected for suction lipectomy at 7 months.</td>
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<tr>
<td>Sasaki(^5)</td>
<td>2016</td>
<td>Female Age: 48</td>
<td>Left upper inner thigh</td>
<td>“Flat plate applicator” CIF – 42</td>
<td>1 session</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
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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 patient 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.

**REFERENCES**


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