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Body Contouring

A Multicenter Evaluation of Paradoxical Adipose Hyperplasia Following Cryolipolysis for Fat Reduction and Body Contouring: A Review of 8658 Cycles in 2114 Patients

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Abstract

Background: Paradoxical adipose hyperplasia (PAH) is a rare, moderate-to-severe adverse event associated with cryolipolysis (CoolSculpting, CS).

Objectives: The aim of this study was to describe the incidence, diagnosis, and treatment of PAH occurring after CS for nonsurgical fat reduction.

Methods: A multicenter evaluation of all patients who underwent CS treatment between January 2015 and December 2019 at 8 Canadian medical centers was conducted. Data abstracted included symptoms, management strategy, outcome, operator characteristics, device characteristics, patient characteristics, body region, and CS treatment details. Incidence of PAH was calculated based on the number of treatment cycles.

Results: Our findings revealed incidence rates between 0.05% and 0.39%, which are slightly higher than the manufacturer's quoted rate of 0.025% (1 per 4000 cycles). Incidence rates at all sites were dramatically reduced by over 75% with the implementation of newer models of CS units. Of patients who developed PAH, 55% were male and 77.8% were of European ethnic origin. The majority of cases (76.9%) were associated with older models of CS units.

Conclusions: Development of PAH may be related to a combination of factors, including older models of CS units and applicators, as well as individual characteristics that predispose certain patients.

Level of Evidence: 4

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The Aesthetic Society ranks nonsurgical fat reduction (eg, cryolipolysis) as the fourth most frequent noninvasive cosmetic procedure in the United States, with 129,686 procedures performed in 2019.[1] The growing popularity of these treatments is demonstrated by the 36.81% increase in their frequency since 2013, the first year that The Aesthetic Society reported on these procedures. Allergan plc (Dublin, Ireland) currently manufactures the largest brand of cryolipolysis devices, CoolSculpting (CS). CS is a system that delivers localized cutaneous cooling to reduce fatty layers.[2] According to the manufacturer, CS takes advantage of the observable selective cell death of adipocytes

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following exposure to extremely cold temperatures. Upon cooling, the adipocytes crystallize, undergo apoptosis, and are eventually eliminated by macrophages.[3,4] Although the posttreatment inflammatory process has been described to peak between 2 and 4 weeks following a CS treatment,[5] the excretion process can take up to 3 months to complete.

The safety profile of CS has been evaluated in thousands of research subjects and is generally considered low risk.[6] Common mild-to-moderate adverse events (AEs) include transient erythema, edema, pain, and/or a decrease in sensation at the treatment site.[7] A systematic literature review published in 2015 reported that these common AEs occur in 0.82% of patients treated with CS. Rare mild-to-moderate AEs (including their incidence rates) have been reported to include visible contour irregularities (0.14%), vasovagal reactions (eg, nausea, dizziness [0.07%]), posttreatment anxiety, bloating, and/or pruritis (0.07%).[6] There are no common moderate-to-severe AEs associated with CS. However, a rare and moderate-to-severe AE that has recently been associated with cryolipolysis is paradoxical adipose hyperplasia (PAH).[5,8,9]

PAH has been described as "a delayed increase in adipose tissue at the treatment site" and "a gradual enlargement of the treatment area … a well-demarcated subcutaneous mass, slightly tender to palpation."[5] The first case of PAH following CS reported in the literature was described in 2014,[5] although the manufacturer received its first report of this AE in 2011.[10] Since then, PAH incidence rates of 0.021% to 1.00% have been reported in multiple case series.[2,6,10,11] It should be noted that incidence rates have continued to rise since the original report. The disparity between incidence rates found within the literature indicates that PAH is likely being underreported and misdiagnosed.[12] In support of this belief, a 2017 literature review found only 16 cases of PAH worldwide,[13] whereas the CS device manufacturer had reported 33 by this time.

The exact mechanisms underlying the development of PAH following CS are unknown.[11] Although PAH poses no known health risks due to its benign nature, it is cosmetically unflattering and can be psychologically distressing to patients. As there have been no reported cases of its spontaneous resolution, treatments to date have relied on corrective liposuction[14] or direct excision.[15] These solutions are often disconcerting to patients who originally sought out CS due to its noninvasive nature. Possible risk factors for developing PAH have been identified and may shed light on its possible etiology. For example, investigators have reported that 42% to 71% of PAH cases occur in men.[2,10,12] Given that only 15% of males comprise the CS population, there is a clear overrepresentation of PAH in males, suggesting male sex as a possible risk factor.[10] Additional risk factors have included the use of a large hand-piece, treatment of the abdominal region, Hispanic origin, history of cryolipolysis, and certain genetic factors.[10] However, it has been difficult to establish correlations between PAH and possible risk factors because the collection of data parameters has not been consistent between sources. Furthermore, given that PAH has been reported in all treatment areas (eg, abdomen, thigh, bra fat, submental, flanks, upper arms) and with varying patient, user, and model parameters (eg, unit, applicator, vacuum settings), definite causative factors have not been established.

Although PAH is a rare complication of adipose tissue injury, there is growing interest in further describing its incidence, diagnosis, and treatment, as well as discussing aspects of its possible etiology and methods to avoid it, due to its notable aesthetic consequences.

The objectives of this study are to describe the incidence, diagnosis, and treatment of PAH occurring after CS for nonsurgical fat reduction.

METHODS

In compliance with normative documents governing research with humans, the following study received unconditional approval from the independent review board (IRB) Veritas IRB.

Procedures

A multicentered retrospective chart review of all patients who underwent CS treatment between January 2015 and December 2019 was conducted. Data were collected from 8 Canadian medical centers. Sites offered an array of medical and surgical aesthetic treatments by a combination of plastic surgeons, dermatologists, and nurse practitioners. Each site was overseen by a local director with extensive experience in aesthetics, under the leadership of a general medical director.

Data Extraction

Medical charts of all patients who underwent CS were reviewed following a posttreatment diagnosis of PAH. Aside from a PAH diagnosis, no other inclusion/exclusion criteria were utilized. System logs were taken from CS devices associated with PAH and consulted by the device manufacturer, to ensure that the devices were functioning properly at the time of the treatment(s). The following data were extracted from each chart and transcribed to the abstraction instrument:

- Symptoms, including onset and duration;
- Treatment/management strategy;
- Outcome (eg, resolved, recovered with sequelae, ongoing, unknown);

- Operator characteristics (ie, clinical profession [technician, nurse, physician]);
- Device characteristics (eg, model, unit, UPM********** number);
- Patient characteristics (eg, body mass index, age, sex);
- Affected body areas;
- Number of treatment cycles and sessions per patient and area before PAH diagnosis;
- CS treatment details (eg, methods of use [on label versus any site-specific changes to manufacturer's directives]).

Data were abstracted by healthcare professionals and chosen based on the number of charts and sites needing to undergo review and to ensure interrater reliability.[16] The same abstractors were used across all sites. The principal investigator resolved any conflicts or ambiguous data.

Analyses

Descriptive analyses of patient charts fulfilling the eligibility criteria were performed. Given the manufacturer's suggestion that a more accurate incidence rate of PAH may be delineated by reporting its occurrence based on the number of treatment cycles, rather than the number of patients, the current investigators employed this method of calculation.[10] This decision was based on the understanding that a single patient may receive multiple treatment cycles to either the same or different areas of the body and that this may be implicated in the risk of developing PAH.

RESULTS

As per the participating clinics' standard-of-care guidelines, all post-CS patients who presented at follow-up with a voluminous mass in the treatment area(s) were sent for evaluation by a physician, as this may have been indicative of PAH. All CS treatments were performed by technicians who completed the relevant CS training and were subsequently certified by the device manufacturer. Users performed all treatments according to the on-label user guidelines and clinical best practices.[2,15] Chart notes did not reveal the occurrence of any unexpected events or system errors during treatments. Before and after color photographs were available for all patients. Most charts included photographs that captured views of the front, back, left, right, 45° right, and 45° left angles. Baseline and posttreatment photographs were taken with the same positioning (Figures 1, 2). All diagnoses of PAH were made by board-certified plastic surgeons. When determining a diagnosis, the following criteria were further assessed:

- Change in weight following the procedure.
- Presence of a visibly enlarged tissue volume over the treatment area.
- Presence of firmness on palpation of the enlarged zone when compared with that of surrounding untreated tissues.
- Date of onset of the tissue growth, in relation to the CS treatment(s).

Incidence Rate

In total, 2114 patients were treated with 8658 cycles of CS between January 2015 and December 2019. The mean number of cycles per patient was 4.09. The number of cycles performed by year are presented in Table 1. Nine patients (PAH incidence by patient = 9/2114 or 0.43%) developed PAH in 13 distinct anatomic regions. These 9 patients underwent a combined total of 28 cycles (PAH incidence by cycle = 13/8658 or 0.15%; Table 2). A cycle was defined as 1 applicator, to 1 area, per visit. A patient may have undergone multiple cycles during the same visit, if different applicators were used at the same time. Sequential cycles to the same area were never employed during the same visit. Clinically, PAH developed after a single cycle in 8 out of 13 cases (61.54%); 3 out of 13 (23%) developed PAH after 2 cycles, and 2 out of 13 (15%) developed PAH after 3 cycles. Patients who developed PAH underwent a total bodily mean [standard deviation] of 4.78 [2.53] (range, 2-10; median, 4) and 3.31 [1.49] (range, 2-6; median, 3) cycles per anatomic area, including the left and right sides.

Affected Areas

The CS cycle frequencies by body area are presented in Table 3. PAH-affected anatomic sites included the upper and lower abdomen (n = 8/13; 61.54%), flanks (n = 2/13; 15.38%), bra fat (n = 2/13; 15.38%), and inner thighs (n = 1/13; 7.70%) (Table 4). Five of 9 (55%) of patients received treatment in a single anatomic area, and 4 of 9 (44%) received treatment in 2 different anatomic areas (ie, bra fat and thighs). In patients who developed PAH, they developed it in all anatomic areas treated with CS.

Sample Demographics

The sample of 9 patients who developed PAH consisted of 5 (55%) males and 4 (45%) females (Table 4). The mean age of males was 54.40 [9.23] years (range, 45-68 years) and the mean age of females was 51.50 [3.10] years (range, 48-55 years). Fitzpatrick skin types ranged from II to IV, with the majority of patients being of European ethnic origin (7/9; 77.77%). Of the remaining

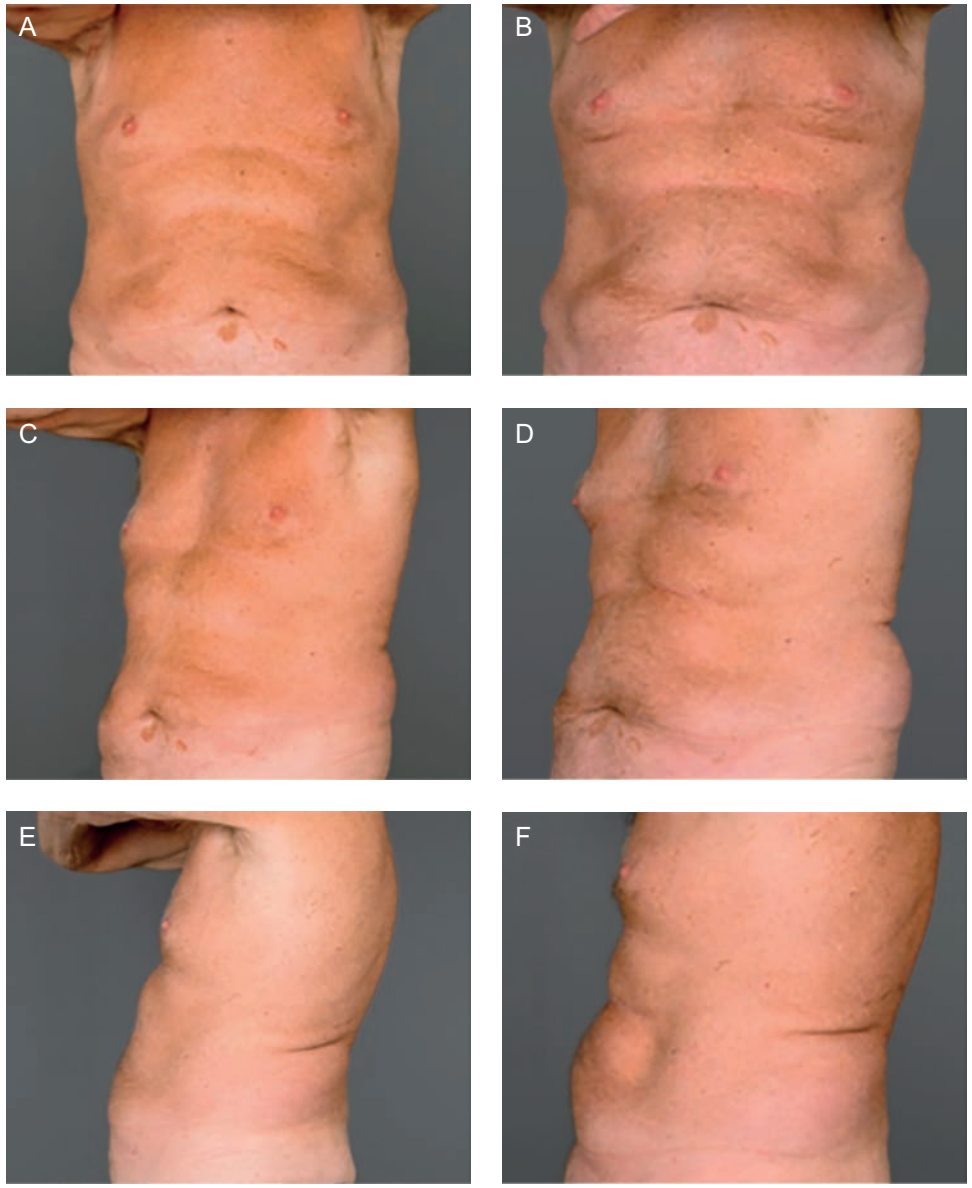

Figure 1. Case 1. (A, C, E, G, I, K) Baseline images of a 68-year-old male, pre-CS (weight, 172 lb). Note the presence of bilateral mild hypertrophy (anterior abdomen), as well as lateral flanks. (B, D, F, H, J, L) After 4 cycles of CS (2 cycles in the lower abdomen and 2 in the flanks). Time point: month 12. Note a significant increase from baseline in volumization of all 4 quadrants of the abdomen, as well as lateral flanks. Physical exam revealed significant hardness of tissue upon palpation (weight, 171.55 lb). CS, CoolSculpting.

patients, 2 were of Middle Eastern background. The average weight at first treatment of males was 188.66 [21.29] lb (range, 167.30-218.20 lb) and the average weight of females was 155.54 [23.44] lb (range, 128.44-183.00 lb). Patients lost an average of 0.83 lb by last follow-up. As height information was missing for 6 of the 9 charts, body mass index was not calculated. At the time of PAH diagnosis, the mean time that had elapsed since the patient's first CS treatment was 489.71 [321.40] days (range, 160-1041 days).

Device Information

Ten different CS units were in use during the review period; 3 of which were associated with PAH (ie, UPMXXXXX15001, UPMXXXXX18001, and UPMXXXXX86004). Of the 10 applicator models available from the manufacturer during the review period, sites possessed the following 8: CoolCore, CoolMax, CoolCurve, CoolMini, CoolAdvantage (contours: CoolCurve, CoolFit, CoolPlus), CoolAdvantage Plus, CoolAdvantage Petite, and CoolSmoothPro. Models

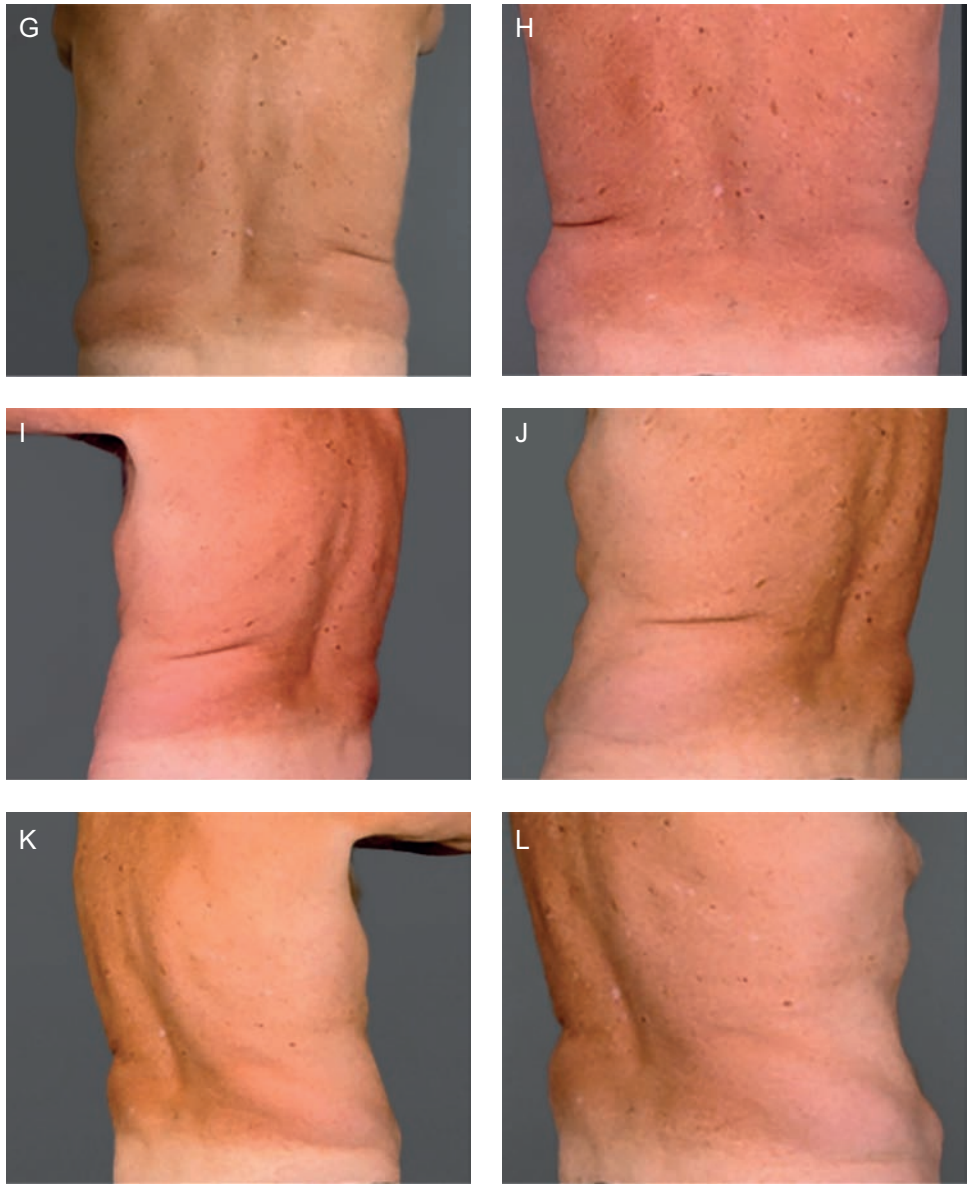

Figure 1. Continued.

associated with PAH included: CoolCore, CoolMax, CoolCurve, CoreAdvantage, CoolAdvantageCurve, and CoolAdvantageFit. The significant majority of PAH cases (ie, 10/13 cases; 76.9%) were associated with older models (ie, UPMXXXXX15001 and UPMXXXXX18001), which were eventually replaced in 2016. Only 3 PAH cases in 2 patients have been observed since implementing the use of newer models.

Corrective Treatment and Outcome

Of the 9 patients diagnosed with PAH, 6 underwent corrective liposuction (resolved); 1 attempted treatment with subsequent CS cycles (unresolved); 1 refused surgical intervention; and 1 patient was undecided as to treatment strategy. It should be noted that only those who underwent corrective liposuction had complete resolution of their PAH. In the 1 patient who attempted additional CS treatments as a management strategy, the severity of their PAH improved but aesthetic results failed to return to baseline. This patient continues to have an increased amount of firm fat in the treatment area, in comparison to pretreatment.

DISCUSSION

To the authors' knowledge, this is the largest study to report incidence rates of PAH following CS and the first to report rates based on the number of cycles instead of patients.

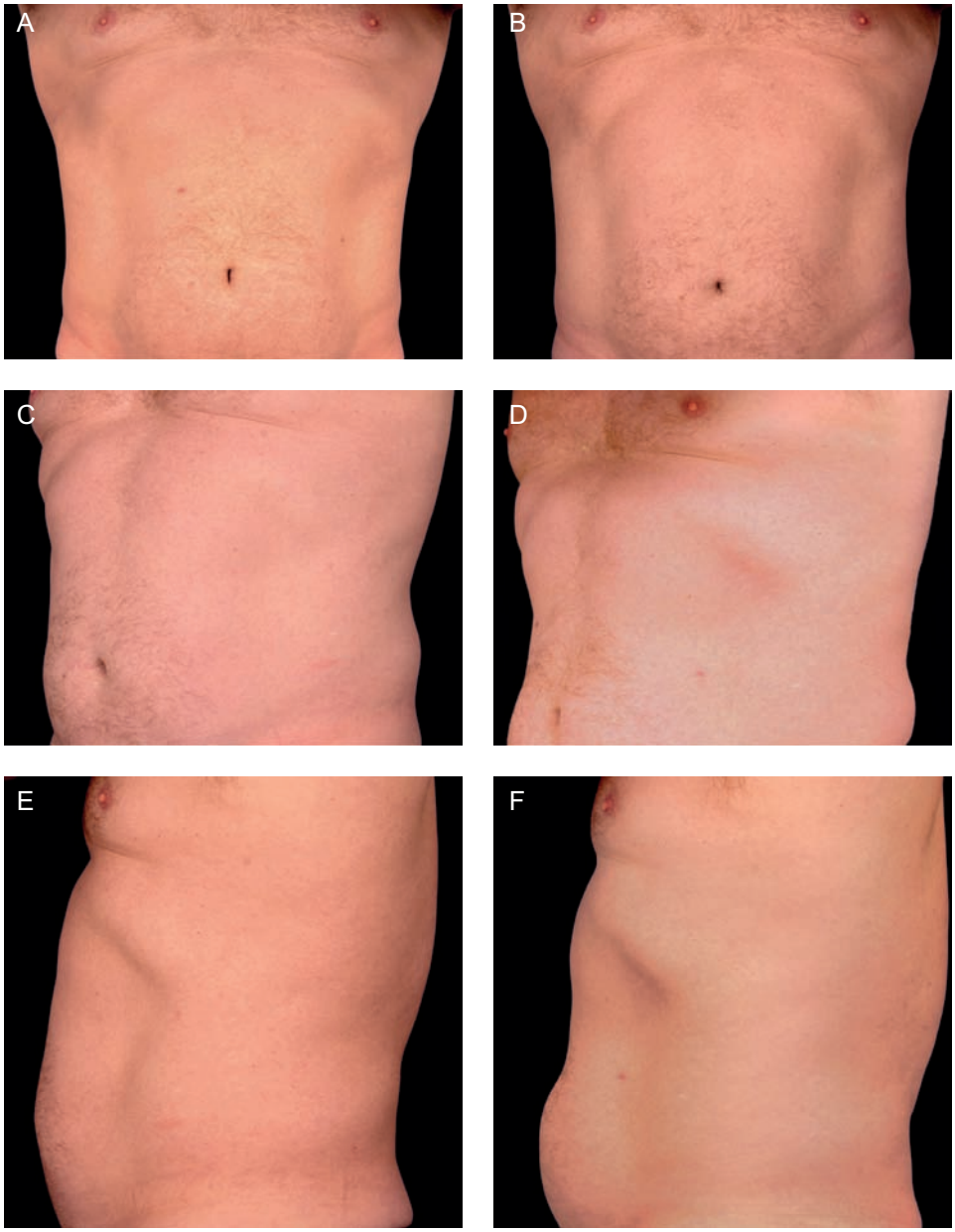

Figure 2. Case 2. (A, C, E, G, I) Baseline images of a 45-year-old male, pre-CS (weight, 155.23 lb). Note the presence of bilateral mild hypertrophy (anterior abdomen), as well as lateral flanks. (B, D, F, H, J) After 3 cycles of CS in the lower abdomen. Time point: month 16. Note a significant increase from baseline in volumization of the lower half of the anterior abdomen as well as the lateral flanks. Physical exam revealed significant hardness of tissue upon palpation (weight, 155.34 lb). CS, CoolSculpting.

Based on these methods of calculation, the manufacturer has previously suggested the incidence rate of PAH to be 1 in 4000 cycles (0.025%). Before the current review, the largest study to investigate the incidence of PAH consisted of 398 French patients treated with cryolipolysis.[11] Our findings contribute to and extend this data by evaluating PAH in a multicenter design study based on a larger (ie, 2114 patients; 8658 cycles) Canadian sample.

Although we report higher incidence rates than are currently reported by the manufacturer, it is important to note the trend that rates of PAH have displayed since this condition was originally reported. The first paper to describe PAH following cryolipolysis estimated an incidence rate of 0.0051%, or approximately 1 in 20,000 patients.[5] This calculation was based on the 33 confirmed cases reported to the device manufacturer at the time, as part of postmarketing surveillance data. Since that preliminary report, others have reported higher rates, up to 1%.[9,17-19] The increase in reported rates is possibly due to the growing popularity of the CS treatment, which

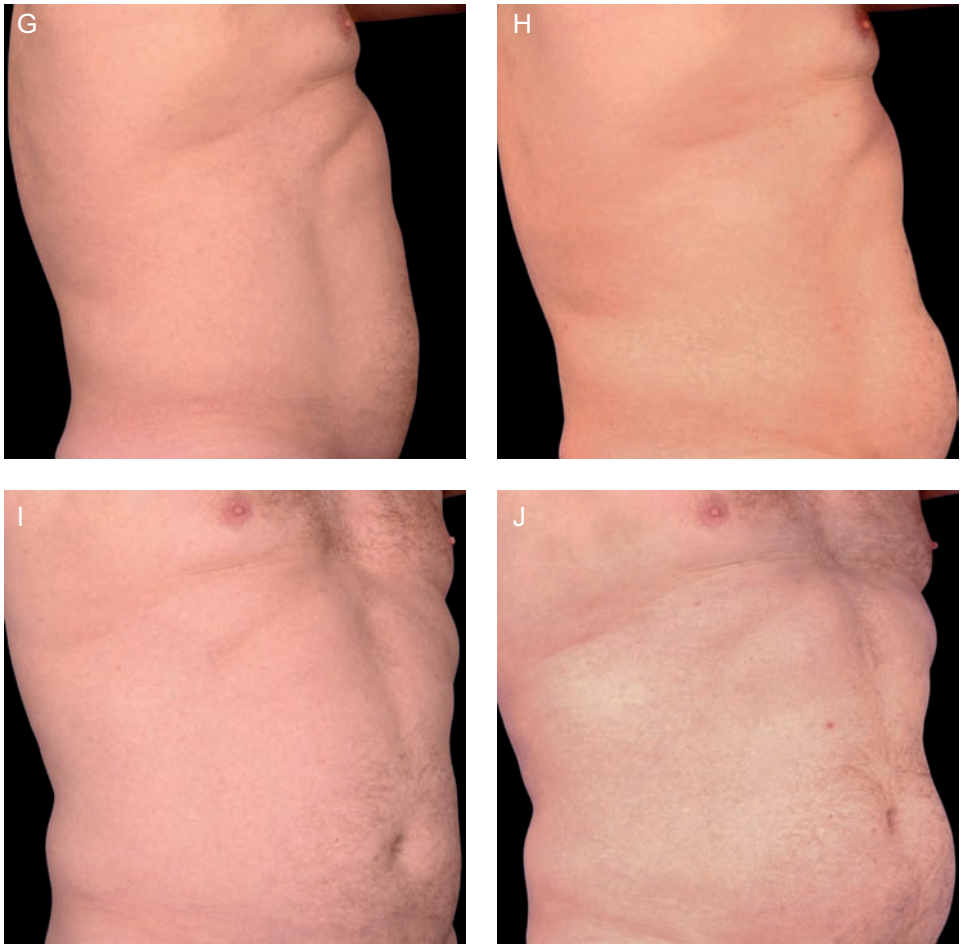

Figure 2. Continued.

has been performed over 7 million times worldwide (Zeltiq Aesthetics Inc, personal communication, January 3, 2019) and an improvement in the detection of PAH with increased education. In support of this, following the original report describing PAH, the manufacturer of CS created an outreach program aimed at educating users about this AE, which led to increased awareness and reporting. Accordingly, with greater education and reporting, incidence rates increased from approximately 1 in 20,000 patients (0.005%) to 1 in 10,000 treatment cycles (0.01%), to the manufacturer's latest data indicating 1 in 4000 cycles (0.025%).[11] The device manufacturer now reports that incidence rates of PAH are remaining relatively stable, fluctuating between 0.021% and 0.026%. Prior to the addition of our cases, their most recent data included 473 cases of PAH in 291 patients.[19]

Presently, our review has revealed 13 PAH cases in 9 patients, from a population of 2114 patients treated with 8658 CS cycles. The most interesting finding of this review is that the newer unit and applicator models have demonstrated a dramatic decrease of over 75% in the occurrence of PAH. This decrease becomes even more significant when considering that participating clinics have increased their use of CS by over 133%. This strongly suggests that mechanical issues present in older models may have contributed to the high rates of PAH. However, the reason why the first-generation probes seem to produce a higher incidence of PAH remains unknown. Based on our most recent data (obtained with the newer models), we estimate the incidence of PAH to be approximately 1 in 2000 cycles.

For the treatment of PAH, some authors have described an aggravation of PAH symptoms with additional sessions of cryolipolysis,[12] so although we observed a slight improvement in the appearance of PAH in 1 patient who underwent corrective CS, we would not recommend this strategy. To date, it is unknown whether other noninvasive treatments that locally affect subcutaneous fat can treat PAH, or if injections of deoxycholic acid would possibly offer a useful solution. Surgical options (ie, liposuction, abdominoplasty) are essential in improving PAH and remain the authors' primary method of treatment. However, future studies are needed to better elucidate the pathophysiology

Table 1. Number of CS Cycles Performed Within 8 Canadian Medical Clinics Between January 2015 and December 2019

Year	Number of cycles	Number of patients	Mean number of cycles per patient	Mean number of visits per patient
2015	1174	140	8.39	2.80
2016	1423	210	6.78	2.71
2017	1402	199	7.05	2.82
2018	1769	346	5.11	2.22
2019	2890	1219	2.37	1.31
Total	8658	2114	4.10	2.37

CS, CoolSculpting; PAH, paradoxical adipose hyperplasia.

Table 2. Incidence of PAH Following CS Within 8 Canadian Medical Clinics Between January 2015 and December 2019

	Years 2015-2016 (old units)	Years 2017-2019 (new units)	Total
Incidence of PAH by patients, *n* (%)	7/350 (2.0%)	2/1764 (0.11%)	9/2114 (0.43%)
Incidence of PAH by cycles, *n* (%)	10/2597 (0.39%)	3/6061 (0.05%)	13/8658 (0.15%)

CS, CoolSculpting; PAH, paradoxical adipose hyperplasia.

Table 3. Anatomic Areas Treated With CS Within 8 Canadian Medical Clinics Between January 2015 and December 2019

Area	Percent of total treatments
Lower abdomen	31.82
Upper abdomen	13.83
Flank	13.58
Inner thigh	10.15
Submental	9.55
Outer thigh	9.45
Back/bra fat	4.45
Upper back arms	3.42
Knee	3.2
Gluteal	0.55

"Bra fat" refers to the adipose tissue anterior to the axilla and superior to the tail end of the breast tissue, which exceeds the bra strap on the lateral chest wall. The terminology "bra fat" implies that the adipose tissue accumulates once the bra strap compresses the skin of that region.

of PAH and its causative mechanisms, as these may help guide instructional procedures in preventing PAH, or suggest methods for its treatment.

Interestingly, the patients in our sample who developed PAH developed the condition in all areas treated, suggesting that individual characteristics may predispose some patients. Moreover, as a patient's risk of developing PAH did not increase with additional cycles, this too suggests an individual predisposition. As other researchers have suggested,[10] one such predisposition may be male sex, or more specifically, increased levels of the male sex hormone, testosterone. This is supported by the finding that our sample consisted of an overrepresentation of males (5/9 patients, 55%). Additionally, 1 patient who developed PAH was taking a medication indicated for male pattern baldness, which increases testosterone levels and could have posed as a risk factor.[10] Furthermore, as areas that developed PAH were those most frequently treated with CS (eg, upper and lower abdomen, flanks),[19] it does not appear that anatomic sites differ in their relative risk.

To further improve AE reporting, more patient-centered education is needed, as in our sample 7 out of 9 (78%) of cases were identified during a follow-up visit. The majority of patients presenting with PAH were unaware they had the condition, and instead simply thought that fat had returned to the area. These findings reflect the importance of appropriate follow-up, for at least 1 year following treatment. This leads to a limitation of the present study; given that some examiners may have mistaken PAH for "poor outcomes," it remains possible that the rates indicated herein remain underreported. Likewise, whereas this study did not evaluate subject satisfaction, a review of this parameter may

Table 4. Patient Demographics, Treatment Characteristics, and Outcomes

Case number	Patient sex, age (years), delta weight (lb)	Treatment area	Unit serial number	Applicator used	Total number of cycles per area (per visit)	Number of treatment visits	Treatment for PAH	Outcome
1	Male, 54, –1.70	Abdomen	XXXXX15001	CoolCore	4	1	Liposuction	Resolved
		Flanks	XXXXX18001	CoolMax	3	1		
2	Male, 68, –0.45	Lower abdomen	XXXXX15001	CoolCore	2	1	Liposuction	Resolved
		Flanks	XXXXX18001	CoolCurve	2	1		
3	Female, 53, –0.13	Upper abdomen	XXXXX86004	CoolMax	2	1	Liposuction	Resolved
			XXXXX15001					
			XXXXX18001					
4	Male, 58, –2.12	Upper abdomen	XXXXX15001	CoolCore	4 (2 + 2)	2	Additional CS cycles	Unresolved
		Lower abdomen	XXXXX18001	CoolCore	6 (2 + 2 + 2)	3		
5	Female, 50, –1.37	Lower abdomen	XXXXX86004	CoolCore	2	1	Unknown	Unknown
		Bra fat	XXXXX15001	CoolCore	2	1		
6	Male, 47, –1.22	Lower abdomen	XXXXX86004	CoreAdvantage	4 (2 + 2)	2	Liposuction	Resolved
			XXXXX15001					
7	Male, 45, +0.11	Abdomen	XXXXX15001	CoolCore	6 (2 + 2 + 2)	3	Liposuction	Resolved
8	Female, 55, +0.77	Bra fat	XXXXX18001	CoolAdvantageCore	2	1	TBC	TBC
9	Female, 48, –1.40	Inner thighs	XXXXX18001	CoolAdvantageFit	4	2	Liposuction	Resolved

CS, CoolSculpting; PAH, paradoxical adipose hypertrophy; TBC, to be confirmed. Displayed age was at time of first treatment. Delta weight represents the change from starting weight to weight at PAH diagnosis.

reveal additional cases of PAH. Other contributing factors that may have led to the underreporting of PAH include patients being lost to follow-up and the duration of onset of PAH symptoms.

CONCLUSIONS

Our findings provide evidence that the development of PAH may be related to a combination of factors, including older models of the CS unit and applicators, as well as individual characteristics that predispose certain patients. Clinical sites experiencing exceptionally high incidence rates should consider replacing older CS models and advise patients, especially males, of the risk of developing PAH post-CS. Until more predictive factors are identified, all patients consulted for CS should be made aware that the risk of PAH is less than 1 in 2000.

Disclosures

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