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ORIGINAL ARTICLE BODY CONTOURING

Cryolipolysis (CLL) for Reduction of Localized Subcutaneous Fat: Review of the Literature and an Evidence-Based Analysis

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Abstract

Introduction In recent years, cryolipolysis (CLL), a non-invasive approach based upon the inherent sensitivity of adipocytes to cold injury, has emerged. However, it is not clear whether available evidence to date about its efficacy justifies aggressive marketing and extensive widespread application by many practitioners without well-defined indications or objectives of treatment. The current review is intended to evaluate available evidence regarding CLL mechanisms of action and its efficacy not only in fat reducing but also in its ability to result in an aesthetically optimal outcome.

Materials and Methods A systematic search of PubMed and Scopus computerized medical bibliographic database was conducted with the search terms "cryolipolysis," "lipocryolysis," and "cool sculpting." Selection criteria included all matched reports with the search terms in their titles.

Results Thirty-two reports matched the inclusion criteria of this review. Five experimental studies were identified and included to further supplement the discussion.

Conclusion Most reports about CLL included in this review lacked rigorous scientific methodology in study design or in outcome measurement. Serious concerns about integrity of many of these reports, particularly with respect to validity of photographic outcome documentation in addition to objectivity, conflict of interest issues, and commercial bias, have been expressed. Further research should be encouraged to prove with methodological rigor positive effects of this treatment modality and to determine categories of patients in whom most favorable outcomes might be expected.

Level of Evidence III This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Cryolipolysis · Lipocryolysis · Non-invasive procedure · Body contouring

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Introduction

Body contouring and fat removal have become staples of the cosmetic market and are increasingly popular procedures with a worldwide rising demand [1, 2, 3, 4]. Conventional fat removal can be effectively achieved by liposuction; however, despite being generally safe, liposuction carries undoubtedly certain risks, costs, and downtime [5]. Given its invasive nature, interest in innovative noninvasive fat reduction modalities is growing [5] and research for the development of safe and effective techniques is ongoing [2, 6]. Various energy sources, such as laser, ultrasound, infrared light, and radiofrequency, have been suggested with reported variable efficacy [2, 4, 7]. In recent years, cryolipolysis (CLL), a noninvasive approach based upon the inherent sensitivity of

adipocytes to cold injury, has emerged. With controlled cooling, selective destruction of fat cells can be achieved without damaging surrounding tissues and without significant change in serum lipids levels or liver function tests [8, 9]. Anecdotally, the impression that cold exposure could damage subcutaneous fat tissue came from the observation of "popsicle panniculitis," a rare type of cold-induced fat necrosis in infant's cheek fat, and "equestrian panniculitis" another uncommon clinical entity [3, 7, 9]. US FDA clearance of the technology was obtained in 2010 and 2012 for fat reduction on the flank and abdomen. Recently, CLL is being applied in various parts of the body including upper and lower extremities, the buttocks, and submental area [3, 9].

In spite of being a new technology without a fully understood mechanism of action, promising results of CLL have been confirmed by experimental animal models and reported in numerous clinical studies [2, 8, 10]. Research on CLL has been growing and new evidence is emerging [11]. The latest systematic reviews show that reduction in the adipose layer may approach 30% per treated region [11, 12, 13, 14]. Currently, CLL is presented as the gold-standard noninvasive technique for subcutaneous fat reduction [4]. However, it is not clear whether available evidence to date about its efficacy justifies extensive widespread application by many practitioners without well-defined indications or objectives of treatment. The current review is intended to evaluate available evidence regarding CLL mechanisms of action and its efficacy not only in fat reducing but also in its ability to result in an aesthetically optimal outcome

Materials and Methods

To identify experimental and clinical studies or case reports assessing mechanism of action and outcomes of cryolipolysis, a systematic search of PubMed and Scopus computerized medical bibliographic database was conducted with the search terms "cryolipolysis," "lipocryolysis," and "cool sculpting." Selection criteria included all matched reports with the search terms in their titles.

Inclusion criteria for this review were reports with original data, randomized controlled trials, and prospective or retrospective cohort studies with outcome measures. Letters-to-the-editor and commentaries without abstracts were excluded same as reviews, case reports, and reports about management of CLL complications or about comparative studies of combination therapies where CLL was not the prime therapy investigated. Studies comparing different CLL applicators or systems were also excluded.

Results

Primary literature search revealed 173 publications with titles including one of the search terms; 42 letters-to-the-editor and short communications were excluded. All abstracts of identified reports were retrieved and screened for eligibility. Thirty-four reports matched the inclusion criteria of this review (Table1). Five experimental studies were identified and included in this review to further supplement the discussion (Table 2). One report in Spanish and another one in German, though matching the inclusion criteria as judged by their English abstracts, were excluded.

Discussion

Tissues can be irreversibly damaged by heat extraction and freeze/ thaw cycles as experienced with clinical cryosurgery [7]. There is evidence that adipose tissue is preferentially sensitive to cold injury, and studies suggest that temperatures as high as 1 **°C** can decrease adipocytes viability. With controlled cold application to the skin surface, selective damage to subcutaneous fat with preservation of dermis viability can be achieved [6, 7, 15, 16].

CLL safety and efficacy have been claimed in numerous clinical reports and case series studies; however, as evident from the current literature review, most suffer from serious methodological flaws, such as non-randomization with no comparator group. Moreover, most these reports fall short of setting clear treatment objectives besides reducing subcutaneous fat layer in the targeted areas and none considered the standard of care to which any new body sculpturing modality must be compared [17]. Many authors are also clinical advisors or sponsored by CLL equipment manufacturers [6, 7, 9, 18, 19, 20, 21, 22] a source of obvious conflict of interest and bias [11].

Little scientific evidence about efficacy of CLL has been published; important links of the mode of action and physiological changes that may lead to fat reduction are still not yet fully understood [18, 23]. Two main mechanisms have been proposed. Selective acute heat extraction induces panniculitis; inflammation results in adipocyte apoptosis, a decisive factor for fat layer reduction over a period of 4 to 6 weeks after treatment, or adipose tissue loss could be induced by thermogenic fat metabolism without cell disruption [8, 24].

Four experimental animal studies investigating the effect of CLL were identified by this literature search [6, 7, 16, 18]. A time line of histologic changes over 3 months after cold exposure in a pig animal model with different cooling devices has been described by Manstein et al. [7] documenting selective damage with subsequent

Table 1 Clinical studies. Level of evidence determined according to the American Society of Plastic Surgeons Levels of Evidence for Therapeutic Studies

References	Design, follow-up and CLL equipment	#	Anatom. location	Outcome	Level of evidence
Rodopoulou et al. [57]	Prospective, non-randomized; skinfold caliper measurements, pre- and post-treatment images assessed by a blinded panel, questionnaire; FU 12 wk (CLATUU Alpha, Classys Inc, Seoul, South Korea)	39	Neck	Significant fat layer reduction of neck of 35.3%, 82.05% of patients marked the results of fat reduction as exceptional; independent photographic review, the overall correct identification rate was 94.9%; bonus skin tightening effect noticed	IV
Abdel, et al. [43]	Prospective. Random 2 groups; 3 CLL with diet; second group diet only FU 3 m (ESM-8l00MO; EunSung global, Korea)	60	Abdomen	Significant improvements of waist-to-hip ratio, body mass index, total cholesterol, triglycerides, low- and high-density lipoprotein, and liver enzymes in favor of the study group	II
de Gusmão et al. [35]	Prospective. Single-arm, non-randomized 1 CLL; FU 3 m (CoolSculpting® system, Allergan)	36	Submental, arms, male breasts	Mean reduction of 19.1% BMI was the only variable with significant relationship with intervention results	IV
Pugliesse et al. [8]	Prospective. Non-randomized Study duration 60 d (Cryoliposculpt, Biotec s.r.l., Dueville [VI], Italy)	6	Abdomen	Patients underwent abdominoplasty after CLL. Histology: inflammatory response at the 15- and 45-day samples. Neocapillarization in the 45 and 60 day	IV
Jain et al. [24]	Retrospective cohort. Independent observer assessment of 2D photographs, 3D volumetric analysis, patient satisfaction FACE-Q. FU 12 wk (CoolSculpting System—Allergan USA Ltd, Dublin, Ireland)	35	Submental	Mean volume loss of about 20% FACE-Q score of 54.10	III
Oh et al. [3]	Retrospective record review evaluated 12 wk; clinical photographs, the pinch test, and US fat thickness (CoolSculpting; ZELTIQ Aesthetics, Inc., Pleasanton, CA, USA)	231	Different areas	Improvement pinch test 19.2%, US fat layer 22.8%. Upper arm differed significantly from abdomen and flank. No difference between sexes	III
Friedmann [44]	Prospective, single-center, open-label clinical trial. 1 CLL. Efficacy evaluated by blinded review of digital photographs. Subject satisfaction assessed at 10-week follow-up. 6 had second optional retreatment (CoolSculpting System, ZELTIQ Aesthetics, Pleasanton, CA)	20	Abdomen	77% correct identification of baseline photographs. 50% satisfaction, with 60% willing to recommend the procedure and 60% reporting visible fat reduction	IV
Falster et al. [11]	Randomized controlled comparative trial, concealed allocation and blinded assessor. 2 groups. Study group had single CLL; US evaluation, skinfold measurements, Abdominal circumference 30, 60 and 90 days (Crio Top Body Redux equipment—Advice, RO & SU IND E COM, LTDA, Brazil)	34	Abdomen	No significant differences at any evaluation time for US fat thickness 59% noticed no change only 18% and 23% reported slight and moderate change. None reported great improvement	I
Jones et al. [33]	Prospective, split-body, 2 CLL 6 weeks apart. US measured thickness of adipose tissue at 6 and 12 wk CLL equipment not specified	10	Male breast	7 completed study. Change in thickness 8.71 mm for the treated vs. 2.66 mm for the control breast at week 12. 57% were slightly satisfied with the treated breast, although satisfaction was higher in the treated breast, this did not reach significance Conclusion: effective in reducing the mean adipose tissue thickness	II
Suh [45]	Prospective, 1 CLL. Photograph, US, and fat thickness measured with a caliper at baseline and 8 wk (CoolMini applicator, ZELTIQ Aesthetics)	10	Submental	Reduction in thickness measured by caliper 4 mm (23.2%). By US 2.8 mm (35.2%). Patient self-evaluation: 4 marked improvement, 5 moderate improvement, 1 some improvement	IV

Table 1 continued

References	Design, follow-up and CLL equipment	#	Anatom. location	Outcome	Level of evidence
Savacini [46]	Prospective, assessment 30, 60, and 90 days after contrast CLL: measurements, questionnaire, photographs, blood studies (Polarys®—Ibramed, Indústria Brasileira de Equipamentos Médicos EIRELI)	21	Abdomen and Flanks	US fat layer reduction 21.6% in abdomen and 43.2% in flanks. No change in fasting glucose, liver-related tests, and serum lipids. Photographs show visibly reduced abdominal and flank areas	IV
Leal Silva et al. [22]	Prospective, single-center, non-randomized, and open label interventional cohort; 2 CLL with colder T and shorter time 10 weeks apart; assessment 12 wk; photographs, caliper, MRI, questionnaire (CoolSculpting System, ZELTIQ Aesthetics, Pleasanton, CA, USA)	15	Submental	Reduction skinfold caliper 33% (3.2 mm), MRI reduction 1.78 mm; photographs demonstrated positive response; questionnaire high satisfaction 80%. No significant change between first and second treatments	IV
Meyer et al. [47]	Prospective, experimental, without control group, with pre- and post-treatment evaluation by US and photograph. 2 m, 1 CLL (Cryolipolysis device, Galeno, South Korea)	15	Abdomen	Reduction in body circumference and fat layer thickness	IV
Klein et al. [48]	Same day simultaneous CLL. Blood tests at 1, 4, and 12 weeks (CoolSculpting System, ZELTIQ Aesthetics)	35	Abdomen and flanks	Procedures were well tolerated, it does not lead to changes in serum lipids or liver tests	
Bernstein et al. [49]	Prospective, CCL, second treatment delivered at 6 wk if needed; Caliper measurements, 2D and 3D imaging. FU 12 wk (CoolMini Applicator, CoolSculpting System; ZELTIQ Aesthetics)	17	Submental	Mean 2.3 kg weight loss during study period; submental fat thickness reduction 3.77 mm; volume reduction 4.82 cm^3, mean (SD) skin surface area reduction was 1.29 cm^2	IV
Carruthers et al. [50]	Prospective. 1 CLL; Photographic, measurements, and ultrasound documentation; blinded independent photograph review; FU 12 wk (CoolSculpting System; ZELTIQ Aesthetics, Pleasanton, CA)	30	Arms	85.2% correct identification by at 2/3 of reviewers, fat layer reduction 3.2 mm	II
Adjadi et al. [4]	Prospective. 1 CLL; visual analogue scale to assess tolerance, thigh circumference and US at 3 and 6 m (CryoSlim—BFP Electronique, Montrodat, France)	53	Saddlebags	5 lost to FU. Decrease in thigh circumference 2.81 cm and fat thickness 1.31 cm, 1 patient developed hyperpigmentation, 89.58% patient satisfaction	IV
Harrington et al. [9]	Prospective. 1 CLL; 3 independent photograph reviewers, written patient survey; 2 m CLL equipment not specified—first *author is a speaker for ZELTIQ Aesthetics (Pleasanton, CA), study funded by ZELTIQ*	31	Lat. chest wall post-mastectomy	Most patients felt cryolipolysis met their expectations, 84% baseline photographs were correctly identified	V
Kilmer et al. [19]	Prospective. 1 CLL, second optional 6 wk at investigator's discretion; US, independent photograph review from 3 blinded physicians (CoolSculpting, ZELTIQ)	60	Submental	91% correct identification of baseline clinical photographs; mean fat layer reduction of 2.0 mm; 83% subjects satisfied	II
Lee et al. [51]	Prospective. Comparative. Pilot single-side study. 1 CLL; FU 8 wk; digital photograph, US. Equalization treatments subsequently to opposite arm (CoolSculpting System; ZELTIQ Aesthetics, Pleasanton, CA)	7	Arms	Decrease fat layer 83.3%; mean reduction fat layer thickness 15.3% (2.03 mm)	II

Table 1 continued

References	Design, follow-up and CLL equipment	#	Anatom. location	Outcome	Level of evidence
Wanitphakdeedecha et al. [56]	Prospective. CLL to 10 arms and 30 inner thighs, FU 6 m. photographs, body weight and circumference of arms and inner thighs (CoolSculpting system; ZELTIQ Aesthetics, Pleasanton, CA)	20	Arms, Inner thighs	17 completed the FU. circumference of treated areas reduced at 3 and 6 m by 0.41 and 0.72 cm, respectively. More subjects graded worst or no improvement at 6 months when comparing to 3 months (35.3 vs. 23.5%)	IV
Zelickson et al. [27]	Prospective. FU 16 wk; Circumference, US, photographs by 3 blinded reviewers (CoolFit applicator, CoolSculpting System, ZELTIQ Aesthetics, Pleasanton, CA)	45	Inner thigh	Visible reduction of inner thigh contour, reviewers correctly identified the baseline images 91%, mean circumference reduction 0.9 cm, US mean fat layer reduction 2.8 mm	II
Stevens et al. [52]	Prospective, non-randomized, interventional cohort, multicenter study, contralateral thigh as control. FU 4 m. US, photographs 3 blinded independent reviewers (CoolSmooth Applicator, CoolSculpting System, ZELTIQ Aesthetics, Pleasanton, CA)	40	Lateral thigh	37 subjects completed the study. 87% correct identification of baseline images; mean fat layer reduction 2.6 mm	IV
Munavalli et al. [21]	Prospective. 2 CLL at 60 d interval; 11 randomized to bilateral treatment and 10 randomized to unilateral treatment; FU 120 d; after equalization treatments, subjects returned 180 and 240 d from baseline; photographs, US, Subject survey (CoolSmooth Applicator, CoolSculpting System, ZELTIQ Aesthetics, Pleasanton, CA)	21	Male breasts	Improved visual appearance and 89% reported reduced embarrassment; mean fat layer reduction of 1.6 mm; blinded reviewers correctly identified 82% of baseline photographs; modest fat layer reduction produced a significant improvement in quality of life	II
Garybian et al. [13]	Prospective. 1 CLL to 1 flank, the second acted as control, randomized side of treatment. 2D Photograph and caliper measurements. FU 2 m. Evaluation by blinded dermatologists (CoolSculpting, ZELTIQ, Pleasanton, CA)	11	Flank	Mean amount of volume loss in the treated flank at 2 months post-treatment was 56.2 Mean volume loss 39.5 cc; Caliper fat thickness reduction 14.9%; 79% correct identification of baseline images	II
Kim et al. [53]	Prospective, Split body trial. FU 3 m. Improvement was assessed with clinical photography two independent dermatologists (Micool–Hironic Co., Seongnam, Korea)	15	Multiple areas	Males with flanks CLL had excellent improvement and expressed significant satisfaction. The most dissatisfactory area was the bra line followed by the inner thigh. Conclusion: CLL appears to be a safe and effective treatment	II
Sasaki et al. [29]	Prospective. 6 patients in pilot study group with subdermal T recording and 112 in clinical treatment group without T recording. Photographs, caliper measurement, US. 2 independent evaluators evaluated photographs FU 6 m (ZELTIQ Aesthetics, Pleasanton, California)	6 + 112	Multiple sites	Gradual temperature decline to lowest level at 45 to 60 min and then gradual elevation to baseline levels at 60 min. From clinical group 85 completed study; abdomens, brassiere rolls, lumbar rolls, hip rolls, inner thighs, and medial knees average fat reduction 21.5%, highest for abdomen, hip, and brassiere rolls	IV
Carruthers et al. [32]	Prospective. Non-comparative study in 2 centers. FU 16 wk. Written survey; use scale to grade skin improvement by patient and investigator CLL equipment not specified	25	Multiple sites	Observed consistent improvement in skin texture and laxity; subjects were more positive than the investigator; no correlation found between patient age and improvement	IV
Boey et al. [25]	Prospective. 10 patients 1 CLL to ½ abdomen with massage, the opposite side without. Photographs and US; FU 4 m; 7 patients in safety group to assess side effects; histological analysis at 0, 3, 8, 14, 30, 60, and 120 d (CoolSculpting, ZELTIQ Aesthetics, Pleasanton, CA)	17	Abdomen	Mean fat layer reduction 12.6% with (2.6 mm) for the non-massaged side and 14.9% (2.7 mm) for massaged side. histological timeline inflammatory response peak at 30 d	IV

Table 1 continued

References	Design, follow-up and CLL equipment	#	Anatom. location	Outcome	Level of evidence
Dierickx et al. [30]	Retrospective chart review of 891 CLL treatment sites on 518 patients; endpoints assessment of safety and tolerance (CoolSculpting, ZELTIQ Aesthetics, Pleasanton, CA)	518	Multiple sites	Erythema reported in 100% of cases; rare vasovagal reaction (2.1%); 96% of patients reported minimal to tolerable pain; little or no treatment benefit for the thighs, buttocks, and knees	III
Shek et al. [54]	Prospective. 1 CCL to 21 patients and 2 CLL to 12 patients 3 m apart. FU 2 m after treatment. Photographs, questionnaire (ZELTIQ Breeze System®)	33	Multiple sites	First group reported significant improvement. Second treatment was not as dramatic as the first treatment	IV
Klein et al. [55]	Prospective. 1 CLL. Serum lipid levels and liver tests measured prior to treatment, and at 1 day and 1, 4, 8, and 12 wk post-treatment. FU 12 wk (ZELTIQ Aesthetics, Pleasanton, CA)	40	Flanks	No meaningful changes in mean values	IV

loss of subcutaneous fat confined to the superficial fat–dermis interface without epidermis, dermis nor underlying muscle tissue injury. Despite some variation in serum lipid levels over time following CLL, Kwon et al. [6] noted that their levels remained within the bounds of normal. They suggested as well that cooling devices could affect lipid catabolism and activate endogenous lipid metabolites through the peroxisome proliferator-activated receptors (PPAR) pathway.

For their part Pinto et al. [18] demonstrated that when exposed to cold, lipids inside adipocytes undergo physical crystallization, a necessary step for unleashing apoptotic stimulus; however, they could not provide correlation between crystallization that may be permanent and lipid-to-gel transition overlapping nor could they determine whether injury to adipose tissue could be the result of apoptotic pathways activation or actual cellular damage and necrosis nor whether this effect is immediate or delayed. The authors noted, rightly so, that variations in lipid composition and ratio of mono- and poly-unsaturated and saturated fatty acids that have different lipid-to-gel transition and crystallization temperatures, may have profound clinical implications regarding effectiveness of various CLL protocols. Outcome may also be affected by crystal size that differs with cooling temperatures and duration of exposure [18].

Fat cooling takes time. More than 3 min are needed for the superficial fat to reach 10 °C at the dermis–fat interface [7]. An interesting software simulation recently described provided qualitative understanding of how temperature varies within tissues. It demonstrated that temperature drop in deeper subcutaneous layers is not very consistent and reduction in thickness of these layers is not to be expected [1].

In vivo adipocyte histologic changes in human subjects have been investigated only in few clinical studies. CLL to the lower abdomen in a patient candidate to have an abdominoplasty was reported by Meyer et al. [2]. A blinded pathologist observed fibrosis, adipocytes lysis and areas with localized infiltrates and macrophages suggesting an inflammatory state. Reduction in the fat layer thickness was also observed by both histology and US evaluations. The study of Boey et al. [25] demonstrated increasing inflammatory response in similar abdominoplasty specimens excised at various intervals following CLL, peaking at 30 days with dense inflammatory infiltrate and reduction of adipocyte size. Subsequently, inflammation decreased at 60 and 120 days with further reduced adipocyte size. Pugliese et al. [8] have moved with this study methodology a step further. They evaluated the effects of a single standard application of CLL in 6 patients. A blinded pathologist performed histological examination of tissue biopsies. Described histopathology was somewhat comparable to what has been demonstrated by other investigators. However, this study indicated that the gradual process of apoptosis lasts longer than the peak described earlier. It was still observed 60 days after CLL treatment and probably would exceed this period. Moreover, some differences in capillary vasculature were evident at the advanced stages of the observation period indicative of a reparative process with reticular architectural changes in areas of apoptosis with widespread involvement of the stromal scaffolding of the subcutaneous tissues.

Among the plethora of repots about favorable clinical results, a recent randomized controlled trial with a blinded assessor and well-controlled methodology of CLL application and outcome measurement, evaluating the effects of one single session of CLL on the subcutaneous adipose layer thickness of the lower abdomen [11] stands alone against the current trend and is the first reliable study to report an unfavorable outcome. Adipose layer thickness evaluation of the study and control groups was performed

Table 2 Experimental studies

References	Design, Follow up & CLL equipment	#	Anatom. location	Outcome	Level of evidence
Majdabadi et al. [1]	Software simulation of CLL temperature–time variations within a sample fat of the human body	N/A	N/A	T variation in deeper layers of tissue is not very considerable. Drop in T is limited to superficial dermis subcutaneous fat layer	II
Kwon et al. [6]	Experimental animal study. 1 CLL, second optional 6 wk at investigator's discretion; FU 12 wk; US, independent photograph review from 3 blinded physicians (CRYOLIPO II—Classys Inc.)	2 pigs	Abdomen	Reduced abdominal fat Gross and microscopic histology confirms selective subcutaneous fat destruction	IV
Pinto et al. [18]	Experimental animal study. White adipose tissue was extracted from each animal; isolated adipocyte suspension was placed in slides and exposed to 8 °C for 0, 10 or 25 min	4 rats	N/A	Changes inside unaltered-resembling-adipocytes were seen; fat crystallization was observed. Lipid crystals present different levels of structural complexity	IV
Zelickson et al. [16]	Experimental animal study. 3 pigs CLL at 22 sites. Photography, US, Histology. Lipids were at various times points. One additional pig underwent CLL at various days (Prototype ZELTIQ cooling control device—ZELTIQ, Pleasanton, CA)	3 pigs	N/A	CLL can selectively damage subcutaneous fat without damage to overlying skin or rise in lipid levels	IV
Manstein et al. [7]	Experimental animal studies performed at different time points with distinct emphasis (ZELTIQ prototype device—ZELTIQ, Pleasanton, CA)	11 pigs	N/A	Prolonged, controlled local skin cooling induces selective damage fat, without damaging the overlying skin or rise in lipid levels	IV

15 days prior to CLL application and then 30, 60, and 90 days thereafter. Investigators could not demonstrate any significant difference between the 2 groups. The high level of evidence of this well-conducted study should seriously question current practices.

Reporting of CLL clinical outcomes has focused mainly on degree of fat reduction and has been primarily assessed by means of circumference measurements, caliper measurements, ultrasound, patient satisfaction questionnaires, and observer impressions that are all subject to bias. Currently, there are no objective, noninvasive, quantitative, reliable, and practical techniques to measure changes in the subcutaneous fat layer [26]. Caliper measurements are unlikely to be sufficiently precise for reliable comparisons, and ultrasound imaging is affected by pressure on the transducer [17, 24]; both are operator dependent. More reliable techniques such as high-resolution ultrasound and MRI are cumbersome in the outpatient setting and are associated with high costs [26]. Interpretation of pre- and post-treatment photographic documentation is highly subjective and cannot be a reliable tool for comparison particularly when changes are in the order of few millimeters. Moreover, monitoring treatment response over time over a period not less than few months during which weight gain or loss may have happened is also not very accurate. Several investigators have reported results relying on correct identification of baseline clinical photographs by independent reviewers as a proof of efficacy [19, 27] as if a change from pre-treatment state indicates a good outcome. Three-dimensional (3D) imaging to analyze volume reduction independently of observer impression and patient satisfaction scores is a newly introduced assessment tool that could bring some objectivity to outcome measurement even though it does not totally eliminate operator error [24]. Its utilization, however, is still very limited.

Best optimistic reports about CLL do not claim more than 21% favorable results following 1 CLL application to the abdomen and fat layer reduction of 17.4% to 20.4% after 2 months and 21.5% to 25.5% after 6 months of treatment to other areas [11, 28]. Some, however, have reported less than 5% improvement 6 weeks post-treatment judged by independent evaluators [29], while others did not find any benefit with CLL treatment of the thighs buttocks and knees but claim 23% fat reduction following abdomen, back, and flank treatment [30]. Regardless of the significance and validity of reporting results as % improvement, when examining actual reduction in thickness, cost-to-benefit value of a method that actually reduces fat thickness by 2.5 mm in 16 weeks should raise serious questions [31]. Carruthers et al. [32] reported 3.2-mm fat layer reduction on the upper arms, and Zelickson et al. [16] reported 2.8 mm reduction on the inner thigh. Submental fat layer reduction of 2.0 mm is also reported [10]. In some reports, conclusions are not even supported by presented data.

While reporting in a split-body study that 57% of male patients treated by CLL for gynecomastia were slightly satisfied with the treated breast, and although overall satisfaction was not significance, Jones et al. [33] concluded that CLL is effective in reducing the mean adipose tissue thickness in male breasts. It is difficult to imagine how clinically significant three-dimensional body sculpturing that requires fat removal from deep and superficial layers and from confluent areas, could be achieved with such minimal changes in the superficial subcutaneous fat layer that would only become evident 3 months after treatment. Despite somewhat obvious fat reduction, demonstrated CLL treatment aesthetic results in publications are mostly suboptimal and in some patients are frankly objectionable [19, 24, 29]. Better results could have been achieved almost immediately with liposuction and with reasonable downtime. Definitely, as conceded by Sasaki et al. [29], CLL does not match liposuction that remains the gold standard for body sculpturing to which other modalities should be compared.

There is no need to argue whether CLL induces adipocyte apoptosis and cellular death or not and how much fat tissue layer can be reduced; in the final analysis, the main concern should be how effective this treatment modality is in meeting patients' expectations and in producing a harmonious aesthetically pleasing outcome. No clear answer to this crucial question was provided by any of the investigators reviewed. Munavalli et al. [21], while admitting to the modest improvement that could be achieved with CLL treatment of male gynecomastia, stated that patients reported significant improvement in quality of life with less embarrassment. Obviously, cognitive dissonance makes it difficult for patients to admit to themselves that they have spent money on an ineffective treatment as rightly said by Swanson [17]. Instead of attracting patients with the noninvasive nature of the modality and its hypothetical expected % reduction in circumference or in fat layer thickness that may be irrelevant if not misleading, patients should be allowed to decide and be able to make an informed consent based on solid evidence provided by controlled blinded clinical studies about body sculpturing outcome with CLL compared to that of liposuction, the gold standard for body contouring.

It should be mentioned that numerous CLL equipment are available from different manufacturers with various applicators and application protocols. Till today, there is no consensus in the literature regarding the most appropriate equipment and the ideal CLL treatment protocol regarding parameters of the device, periodicity, and number of sessions required per body region [11, 12, 14]. Moreover, it is still not clear what is the patients' BMI range for which a reasonably favorable outcome may be expected [5, 11, 25, 34, 35].

The good safety profile is one of the advantages of noninvasive CLL [10]; it is not, however, painless or entirely without risk. Besides disappointing, asymmetrical or unfavorable results, serious skin necrosis, though rare, has been reported. Redness, bruising, discomfort, and temporary numbness are common; nodules can also occur [17, 31, 36, 37]. Paradoxical adipose hyperplasia is another complication most commonly reported in men [38].

Skin tightening is another factor to be considered besides fat layer reducing when evaluating outcome of any body contouring procedure. Though CLL has not been recognized as a skin-tightening procedure, skin adherence to new body contour and firmness has been observed in patients with previous flaccidity. It occurs in a verifiable way according to some authors in 25% of cases [2, 8, 39]. It is believed that cryolipolysis delivers a cold-based thermal insult to the skin, which similar to insult caused by heat-based therapy, chemical peels, microneedling, or filler injections, results in fibrosis and skin tightening [32]. Vacuum applicators used for delivery of most CLL treatments pull a tissue bulge into the treatment cup; this results in mild stretching and could be a contributing factor as well to neocollagenesis [32]. It is still not known however how predictable is skin-tightening. It is not known also how it may be affected by patient's age, skin condition, and BMI [39]. Claim of skin tightening based on very few patients without objective and valid outcome assessment cannot hold up to scientific scrutiny [17].

Conclusion

Since beauty is mostly subjective, assessing aesthetic surgery novel procedures and outcomes is difficult; the notion of success largely depends on ill defined subjective rather than objective measurements [24]. It is true that plastic surgeons need to listen to their "inner Michelangelo" [40] and "be innovators, pioneers, creators, visionaries, and communicators, not only scientists" [41], unfortunately, in vaunting the merits of noninvasive alternatives to liposuction, commercial acceptance has largely outpaced scientific scrutiny [17, 42]. Excluding few experimental and clinical experiences, most reports about CLL included in this review lacked rigorous scientific methodology in study design or in outcome measurement. Serious concerns about integrity of many of these reports, particularly with respect to validity of photographic outcome documentation in addition to objectivity, conflict of interest issues, and commercial bias, have been expressed [31]. In some of these reports, it is difficult to appreciate the change due to CLL nor to distinguish the before and after images. In other reports, the after images do not demonstrate pleasant optimal and aesthetic outcomes despite some evident fat

reduction. An unhappy disillusioned patient is not a source of professional satisfaction and certainly will not help to gain attention and build a practice; with it comes physician demoralization, which may be a cause of physician burnout as warned by Swanson [40].

Despite lack of solid evidence, new methods even with questionable scientific foundation deserve our close attention. Claimed potential benefit of CLL should not be dismissed lightly. At the same time, it is unethical to use an innovative procedure as powerful selling point to patients without valid scientific proof. Innovation and creativity are celebrated in our specialty; however, we need to be cautious and question without hesitation claims of some investigators who may have an evident conflict of interest. Moreover, before considering any new treatment modality or novel device, principles of evidence-based medicine should not be overshadowed by tempting financial benefits. Rethinking these principles is not an option. Sound scientific basis and solid evidence of clinical efficacy empower us as service providers and are not incompatible with a thriving practice in a highly competitive surgical and medical cosmetic domain [40].

To claim that CLL is a noninvasive technique that could be a good alternative to liposuction in patients with moderate excess fat as claimed by some [4] is not justified. Certainly further research should be encouraged to prove with methodological rigor positive effects of this treatment modality and to determine categories of patients in whom most favorable outcomes might be expected. It must be kept in mind, however, that mere fat layer reduction is not and should not be the main goal of any body contouring modality; it is rather achieving 3D harmonious body shape to our satisfaction as well as to that of patients.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest to disclose.

Human and Animal Rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study, informed consent is not required.For this type of study informed consent is not required.

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