
Treatment of cellulite

Part II. Advances and controversies

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Treatments for localized adiposities range from topical creams to liposuction. Most treatments lack a substantial proof of efficacy. The unpredictable treatment outcome can be related to the fact that cellulite adipose tissue is physiologically and biochemically different from subcutaneous tissue found elsewhere in the body. Part II of this two-part series on cellulite reviews the various treatment options that are currently available for human adipose tissue including, but not limited to, cellulite. It also focuses on newer techniques that can be potentially useful in the future for the treatment of cellulite. (J Am Acad Dermatol 2010;62:373-84.)

Learning objectives: After completing this learning activity, participants should be able to understand the wide range of treatments available for localized adiposities including, but not limited to, cellulite-prone areas, know the differences in their mechanisms of action and be able to make the most appropriate decision for patient care, and discuss and understand newer treatments for cellulite that are still being investigated along with the physiologic and biochemical basis for their mechanisms of action.

Key words: carboxy therapy; cryolipolysis; endermologie; laser lipolysis; liposuction; mesotherapy; subcision; ultrasonic fat destruction.

The best of the currently available treatments for cellulite have, at most, shown mild improvements in the appearance of cellulite, and most of these improvements are not maintained over time. Studies about cellulite treatments are often limited by small patient groups, the lack of control groups, inadequate blinding of investigators, and a failure to test for statistical significance. Therefore, the “success” of any treatment method for cellulite reduction should be regarded as speculation. Nonetheless, there are interesting treatments available for the reduction of cellulite and localized human adiposities that are commonly used by both

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Abbreviations used:

AR:	adrenoreceptor
BAT:	brown adipose tissue
BMI:	body mass index
c-AMP:	cyclic adenosine monophosphate
EMR:	electromagnetic radiation
FDA:	US Food and Drug Administration
LED:	light-emitting diode
MRI:	magnetic resonance imaging
Nd:YAG:	neodymium-doped yttrium aluminium garnet (laser)
PPAR:	peroxisome proliferator-activated receptors
RF:	radiofrequency
UCP-1:	uncoupling protein-1
WAT:	white adipose tissue

dermatologists and plastic surgeons (Table I). A brief overview of these currently available treatments and their proposed mechanisms of action are discussed herein. In addition, newer treatment options based on adipocyte physiology and biochemical behavior are also discussed as possible avenues for future research in cellulite therapy.

ATTENUATION OF AGGRAVATING FACTORS

Key points

- **Weight loss has a variable effect of cellulite severity depending upon the clinical grade, with grade IV cellulite being the most responsive**

- **Skin looseness or so-called skin compliance increases after weight loss, which can adversely affect the skin dimpling**

Weight loss

Cellulite occurs in lean women and obese women and men.¹ Weight gain, however, can accentuate the appearance of cellulite.

There have been reports of weight loss and its effects on cellulite. Smalls et al² revealed that weight loss can have variable effects on cellulite grade (Figs 1 and 2). It can improve or worsen the condition for some. Smalls et al² showed that on average, cellulite severity decreased following weight loss. This is especially true for affected individuals who have a higher body mass index (BMI) and a greater severity of cellulite grading. These individuals experienced improvement in cellulite severity with significant weight loss. They also found an increase in skin compliance (skin looseness) in all of their study participants. Increased skin compliance did not necessarily have an impact on subjects whose cellulite improved, but it adversely affected the individuals whose cellulite became worse with weight loss. It is not clear, however, if skin compliance plays a significant role in the etiology of cellulite. Their study also revealed that skin dimpling did not significantly improve with weight loss, with only a slight decrease in the depth of dimples. They attributed this finding to the fact that skin dimpling is caused by dermal collagenous septae that do not necessarily improve with weight loss.

Different regions of the body respond differently to weight loss (ie, abdominal vs. femoral). Mauriège et al³ revealed very interesting findings regarding adipose tissue; their research focused on the response to a low-calorie diet and the effects thereof on adrenoceptor (AR) sensitivity on adipocytes of the abdominal and femoral regions in both males and females. Their work showed that there is an overall significant reduction in fat cell weight in both sexes by 15% to 20% after an average 10-kg weight loss ($P < .1$ and $P < .05$). Basal lipolysis, maximal lipolytic response to isoproterenol (a β -AR agonist), and dobutamine and procaterol (which are β_1 - and

β_2 -AR agonists, respectively) as well as the maximum antilipolytic effects of epinephrine (an α_2 -AR agonist) were similar before and after weight loss. However, both β_1 - and β_2 -AR lipolytic sensitivities and overall β -AR density were increased in both genders after weight loss; this effect was more marked in the subcutaneous abdominal adipose tissue as compared to femoral adipose tissue ($P < .001$ to $.05$). α_2 -AR antilipolytic sensitivity was reduced in adipose cells from both regions in women, but only in abdominal adipose cells in men ($P < .05$), even though α_2 -AR density remained unchanged. In addition, femoral adipocytes are larger in women than in men. In their study, Mauriège et al³ found that this difference loses its significance after weight loss, because adipose cell size reduction was found to be the same order of magnitude in both genders.

The result of their work is interesting from the view-

point of cellulite management. Because we know that femoral adipose cells are predominantly α_2 -ARs, which are antilipolytic (as opposed to abdominal adipocytes, which are β -ARs with high lipolytic response to catecholamine stimulation), abdominal adipocytes are the main source of mobilizing energy sources during times of calorie deprivation. Of interest is the fact that the sensitivity of α_2 -ARs decreases during times of fasting. However, their number remains unchanged. Unless weight reduction is a continuous process, femoral adipocytes will regain their size and antilipolytic activity. Further studies need to be performed to investigate the effects of a low-calorie diet over a long period of time and what effect that diet will have on femoral adipocyte α_2 -AR density and sensitivity.

CAPSULE SUMMARY

- Treatment modalities for cellulite range from topical creams to invasive procedures, such as laser-assisted lipolysis and liposuction.
- There is no single treatment of cellulite that is completely effective.
- Given the complex and multifactorial etiology of cellulite, devices that combine radiofrequency, infrared lasers, and suction with massage have recently gained popularity.
- Future treatment options for cellulite depend upon our understanding of the molecular basis and hormonal influences of cellulite adipose tissue.

PHYSICAL, MECHANICAL, AND THERMAL METHODS

Endermologie

Key points

- **There is some evidence that thigh reduction can be achieved by Endermologie after repeated treatments over a period of time**
- **Thigh reduction seen after Endermologie treatments may be influenced by weight loss**

Table I. Various treatments of cellulite and their level of evidence as determined from various published studies

Cellulite treatment	References	Level of evidence*
Weight loss	Smalls et al ² and Mauriège et al ³	II-B and II-B, respectively
Endermologie	Collis et al ⁴ and Chang et al ⁵	II-A and II-B, respectively
Liposuction	Coleman et al ⁷	III
Subcision	Hexsel et al ⁹	IV
Mesotherapy	Hexsel et al ¹¹ and Rotunda et al ¹³	II-B and II-B, respectively
Topical phosphotidylcholine and LED	Sasaki et al ¹⁴	I-A
Radiofrequency devices	Sadick et al, ^{16,17} Goldman et al, ¹⁸ and Goldberg et al ²¹	II-B, II-A, and II-A, respectively
Ultrasound	Moreno-Moraga et al ²³	II-A
Laser-assisted lipolysis	Katz et al, ²⁶ Geronemus et al, ³⁰ and Prado et al ²⁸	IV, IV, and I-A, respectively
Topical herbs and retinol	Li-Balchin et al ³⁶ and Kligman et al ³⁸	II-A and II-A, respectively
Carboxy therapy	Brandi et al ^{40,41}	II-B
Cryolipolysis	Manstein et al ⁵²	IV

LED, Light-emitting diode.

*Level IA evidence includes evidence from metaanalysis of randomized controlled trials. Level IB evidence includes evidence from at least one randomized controlled trial. Level IIA evidence includes evidence from at least one controlled study without randomization. Level IIB evidence includes evidence from at least one other type of experimental study. Level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies Level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

The basis for various massage/suction techniques used for cellulite treatment rests on the premise that the condition is caused by impaired circulation. Endermologie ESI (LPG Systems, Valence, France) or skin kneading is a nonpharmacologic method that employs mechanical means to mobilize the subcutaneous fat in affected areas.⁴ Despite the high cost of Endermologie treatment, little evidence exists to support its efficacy. Proponents of this process claim that massage/suction improves the disorganization of subcutaneous tissue structures and improves lymphatic flow. The procedure is performed twice weekly, with each session lasting 10 to 45 minutes. A 12-week study by Collis et al⁴ compared healthy individuals with cellulite treated with Endermologie and/or aminophylline cream (a phosphodiesterase inhibitor) and found no statistical difference in thigh measurements between patients. Any subjective improvement noted by study participants was attributed secondary to weight loss and exercise rather than skin kneading. The results of this study were challenged by the fact that treatment duration was only 10 minutes and that improvement should have been analyzed by more objective criteria than subjective self-assessment alone. Chang et al⁵ showed promising results using Endermologie for the treatment of thigh circumference reduction. The study group exhibited a wide range of body types, initial weights, and final results. Out of 85 patients, 46

patients completed seven sessions of treatment and showed a mean index reduction in body circumference of 1.34 cm, while 39 patients who completed 14 sessions of treatments showed a mean index reduction in body circumference of 1.83 cm. A decrease in mean body circumference index was seen regardless of weight loss or gain in study participants. Even though evidence exists that Endermologie can reduce the thigh circumference in a dose- and time-dependent fashion, the long-term efficacy and longevity of these effects is still questionable. Randomized controlled trials need to be conducted with objective evaluation of response as opposed to subject's satisfaction, such as the use of noninvasive imaging techniques to monitor the response of massage/suction and the persistent changes that are claimed as proposed mechanisms of action over a period of time.

Liposuction

Key points

- **While liposuction can diminish fat deposits deep in the subcutaneous fat, its effect on the superficial components of fat as seen in cellulite is often disappointing**
- **Skin necrosis from devascularization after extensive undermining is one of the major limiting factors**

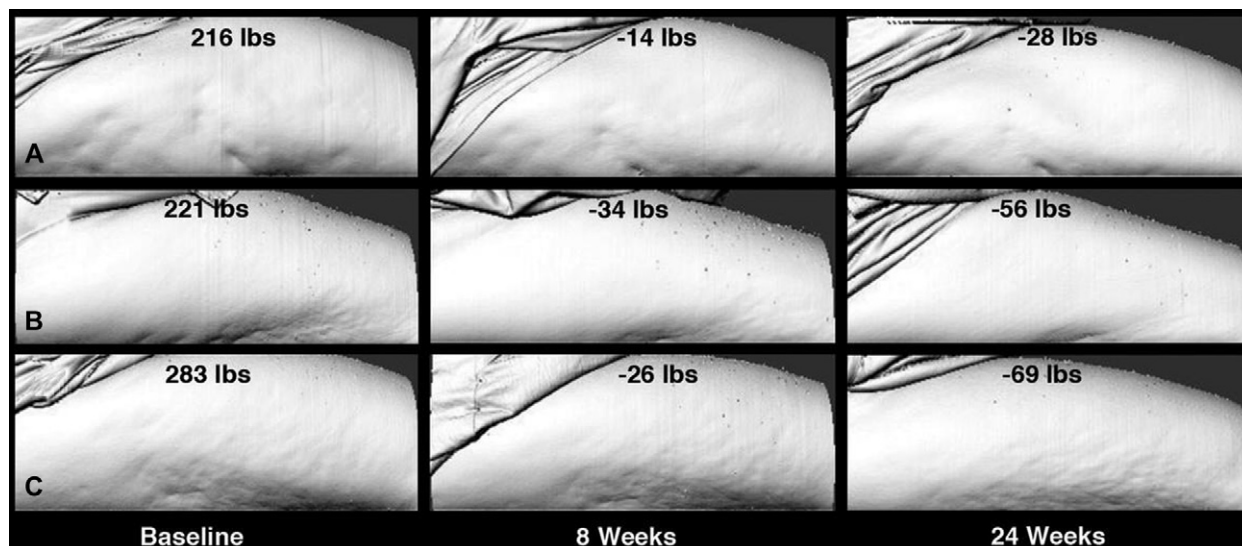


Fig 1. Three-dimensional laser scans from three patients. **A**, Patient 1 lost 28 pounds and experienced a decrease in cellulite severity by surface roughness analysis. **B**, Patient 2 lost 56 pounds and had a decrease in cellulite severity. **C**, Patient 3 lost 69 pounds and had a decrease in overall severity but retained the smaller scale roughness features. The variability in cellulite can be seen in this figure. (Reprinted with permission.²)

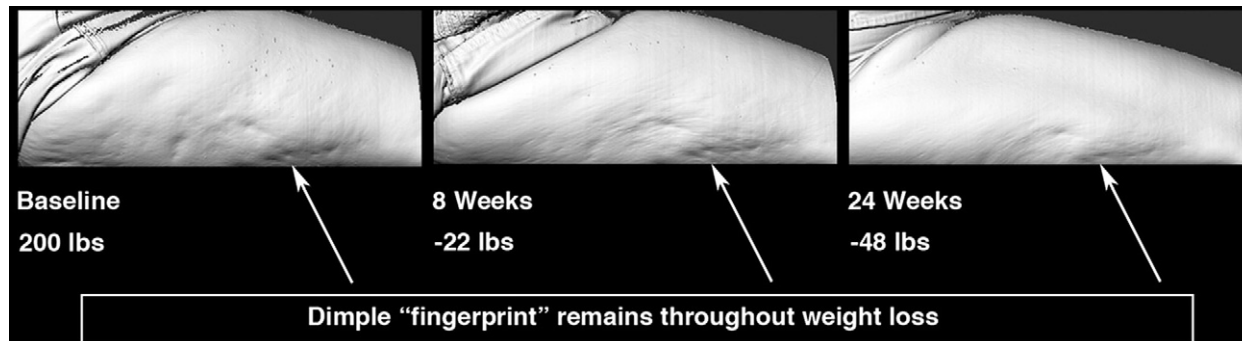


Fig 2. Cellulite dimple "fingerprint." The three-dimensional laser scans are shown in the figure for one subject who lost 48 pounds. Examination of the series of images indicates that the dimple or dimple pattern may be a permanent structure that does not change appreciably, even with considerable weight loss. (Reprinted with permission.²)

Although lipoplasty has been purported by some to be an excellent method to improve body contouring,⁶ others have reported increased skin dimpling after liposuction.⁷ Ultrasonic liposculpturing may be a superior, potentially safer, less destructive technique for cellulite reduction than traditional liposuction.⁸ Liposuction is still not a recommended treatment for cellulite. In part, that may be because cellulite adipose tissue is very close to the surface of skin, with only a thin layer of dermis overlying it.

Liposuction performed at a level so close to the surface of the skin can lead to more complications and a poor cosmetic outcome.

Subcision

Key points

- **Subcision can temporarily improve the skin dimpling seen in cellulite-prone areas**
- **The long-term efficacy of subcision remains controversial**

Subcision is an invasive method that is used to improve cellulite. It palliates skin dimpling by severing the septae that hold the fat lobules. After the injection of local anesthesia, a 16- or 18-gauge needle is inserted into the subcutaneous fat in a direction parallel to the epidermis and the septae are sheared. Hexsel and Mazucco⁹ investigated subcision as a treatment in 232 patients. Only 1% of the study subjects were dissatisfied with the results. However, no objective criteria were used to evaluate the study. It might seem reasonable that if the septae are responsible for the clinical appearance of cellulite, their sectioning should result in improvement in all affected individuals—but this is clearly not the result of invasive subcision. The pathophysiology of cellulite is likely more complex than just the orientation and configuration of the septae. As mentioned in part I of this article, Piérard et al¹⁰ showed that some of these septae in high grade cellulite are actually weak hypodermal stretch marks. In theory, sectioning of these fibrous strands might potentially destabilize the dermohypodermal junction, thereby facilitating the adipose tissue herniation.

Phosphotidylcholine and mesotherapy

Key points

- **Phosphotidylcholine induces lipolysis via the activation of cyclic-monophosphate and the activation of β -ARs**
- **Gluteofemoral adipocytes have a significantly lower number of β -ARs as compared to other localized adiposities**

Mesotherapy, a technique that uses the injection of various substances into the subcutaneous fat to dissolve the fat, is another highly popular treatment for cellulite.¹¹ However, few studies substantiate the benefit of this approach. The technique involves a series of injections delivered into the subcutis. The solutions have included compounds like methylxanthines, such as caffeine, aminophylline, and theophylline, etc, which cause lipolysis via phosphodiesterase inhibition and elevation of cyclic adenosine monophosphate (c-AMP) levels, as well as hormones, enzymes, herbal extracts, vitamins, and minerals. The one ingredient most consistently used is phosphotidylcholine (soybean lecithin extract), which is responsible for lipolysis via the activation of β -ARs. Rose et al¹² showed that a mixed septal and lobular panniculitis with abundant fat necrosis and serous lipoatrophy is seen after phosphotidylcholine injection. The lack of a precise treatment protocol, the unpredictable outcome, and the risk of localized adverse events—including edema, ecchymosis, tender subcutaneous

nodules, infection, urticarial reactions, and irregular skin contours—have discouraged many clinicians from attempting this technique.

Phosphotidylcholine injections alone have been used to treat localized fat accumulations in HIV lipodystrophy and lipomas.¹² Rotunda et al¹³ have identified sodium deoxycholate, a detergent that produces nonspecific destruction of cell membranes, as a major active ingredient in this therapy. Sasaki et al¹⁴ used topically applied phosphotidylcholine-based anticellulite gel with low intensity light treatment using a light-emitting diode (LED) array at wavelengths of red (660-nm) and near-infrared (950-nm) that is designed to counter the possible mechanisms that purportedly accentuate the presence of thigh cellulite. Subjects were randomly treated twice daily with active gel on one thigh and with placebo gel on the other. LED treatments were employed twice weekly for 15 minutes on both thighs, for a total of 24 treatments. Eight out of the nine subjects experienced significant improvement in the thighs treated with phosphotidylcholine-based anticellulite gel and LED treatments as evident by clinical examination, measurements, and ultrasound evaluations that showed a significant reduction in hypodermal thickness. These results also correlated with histologic significance. However, at the 18-month evaluation period, five of the improved thighs reverted back to their original cellulite grade, and three continued to maintain their improved status. The limitations of this study were the number of controls and the population size.

The results of this study are interesting from the standpoint that low-level light therapy alone failed to show improvement. But when combined with a topically applied fat dissolving gel, patients showed improvement in cellulite grade reduction. This raises questions regarding the mechanism of action of LED in the presence of “fat dissolving” gel; perhaps LED has a role in dermohypodermal remodeling after some “fat dissolution,” but not otherwise. Future studies are needed to verify these preliminary findings.

Bipolar and unipolar radiofrequency devices

Key points

- **Unipolar and bipolar radiofrequency devices are based on the principle of heat generation as a result of water and tissue interaction within adipocytes**
- **Small studies with the available systems have shown mixed results**

Recently, noninvasive devices employing radiofrequency (RF) technology have gained acceptance and supremacy in the treatment of cellulite. These

include the TriActive (Cynosure, Westford, MA) and VelaSmooth (Syneron Medical, Yokneam Illit, Israel). The purpose of integrating RF into cellulite treatment is to affect the connective tissue septae and fat, both of which contribute to cellulite. Of the available RF devices, only VelaSmooth has been approved by the US Food and Drug Administration (FDA) specifically for cellulite treatment. The TriActive laser combines a low-energy diode laser, contact cooling, suction, and massage. This system has been shown to reduce cellulite.¹⁵ The VelaSmooth combines infrared light (700-2000 nm), bipolar RF, and suction with mechanical massage. Like the VelaSmooth, the Alma Accent RF system (Alma, Buffalo Grove, IL) and ThermoCool (Thermage, Hayward, CA) use RF and maybe useful in the treatment of cellulite.¹⁶⁻¹⁸ Both the Accent and ThermoCool are approved by the FDA for the treatment of wrinkles and rhytides. The ThermoCool is a unipolar RF unit, while the Accent system is a combined unipolar and bipolar RF device. Of the two devices, only the Accent system has been evaluated for the treatment of cellulite.

The precise mechanism by which these combination platforms work is yet to be elucidated. Bipolar RF devices are based on the principle of heat generation as a result of poor electrical conductance, according to Ohm's law:

$$H = J^2\rho, \text{ or heat generation is directly correlated with tissue resistance}$$

The heat that is generated is strong enough to cause thermal damage to the surrounding adipose tissue and connective tissue septae. Bipolar RF devices have a penetration depth of >3 mm and allow for better control and localized adipose tissue alteration.

Unipolar devices use high frequency electromagnetic radiation (EMR). High frequency EMR induces high frequency rotational oscillations in water molecules which in turn produces heat (ie, the greater the presence of water, the greater the tissue heat generation). The depth and breadth of thermal damage is greater and in a diffuse pattern, with less control than that provided by bipolar RF devices. In addition, low-energy lasers have wound healing properties, affecting endothelial cells, erythrocytes, and collagen,¹⁹ which potentially aids in the healing of localized chronic inflammation, which is still believed to be one of the factors in the etiology of cellulite. A combination of RF and laser light may eventuate in enhanced localized fat metabolism, similar to what is seen in mesotherapy.

In the largest study of VelaSmooth to date, Sadick and Mulholland¹⁶ evaluated 35 patients who

completed either eight or 16 treatments with VelaSmooth. A dermatologist blinded to the study group evaluated the photographs and found 40% improvement on average.

A more recent study of VelaSmooth found a statistically significant decrease in thigh circumference at 4 weeks, but no immediate change or a persistent decrease at 8 weeks postprocedure.¹⁷ Visual improvement of <50% was noted in the majority of subjects. Thirty-one percent of the subjects experienced bruising.

Goldman et al¹⁸ compared the efficacy of treatment of cellulite using two novel modalities: TriActive and VelaSmooth. Patients were treated twice weekly for 6 weeks with either VelaSmooth or TriActive. They calculated a 28% versus a 30% improvement rate, respectively, in the upper thigh circumference measurements, while a 56% versus a 37% improvement rate was observed, respectively, in lower thigh circumference measurements. The results were statistically significant ($P > .05$). Incidence and extent of bruising was higher for VelaSmooth than in TriActive system, which maybe attributed to mechanical manipulation.

Alvarez et al²⁰ used animal models to reveal interesting results regarding the effects of RF treatment on dermal cellularity and collagen formation. They employed six sessions of RF treatment on the backs of guinea pigs (1 session/week) and took biopsy specimens both after each session and 2 months after the last treatment. They found relevant changes in the papillary dermis that underwent an expansion related to edema and vascular congestion. These changes were followed by an increase in cellularity and an accumulation of intercellular substances. Subsequently, an increase in collagen, elastic fibers, and mucopolysaccharides was observed. These changes led to increased dermal thickness and collagen content.

Goldberg et al²¹ used an Accent unipolar RF device for cellulite treatment. Their study included subjects with higher grade cellulite on the upper thighs. They were treated every other week for a total of six treatments. Results obtained 6 months after the last treatment showed an average 2.45-cm reduction in thigh circumference with minimal side effects. No changes in posttreatment magnetic resonance imaging scans were observed, and no lipid abnormalities were seen. They attribute their longer-lasting effects to the formation of dermal fibrosis with subclinical scarring in the papillary and reticular dermis and increased contraction between the dermis and Camper fascia, which has been previously reported in ultrasound imaging studies.²² The presence of thickened dermal

fibrous bands might temporarily improve the appearance of cellulite. However, the long-term efficacy of this treatment modality still needs to be investigated.

Ultrasound

Key points

- **Ultrasound waves can induce adipocyte destruction by various mechanisms such as cavitation and thermal damage**
- **Although ultrasound can be a useful adjunct to other treatments used for cellulite, its efficacy as the sole treatment lacks substantial evidence**

It is too early to determine whether noninvasive ultrasound may have a cellulite application. The UltraShape (UltraShape, San Ramon, CA) is a non-FDA approved device that has been recently shown to decrease subcutaneous adipose tissue thickness. In a conducive setting, ultrasonic energy affects tissue destruction through three mechanisms: cavitation, micromechanical disruption, and thermal damage. Noninvasive ultrasound works either by thermal or micromechanical effects on the tissue at a certain depth. In a study conducted by Moreno-Moraga et al²³ of 30 subjects (who maintained constant weight during the study period), the researchers found a mean decrease of 2.3 cm in local fat deposits after three treatments.²⁴ Although this finding is statistically significant, it is not known whether ultrasound treatment is effective in changing the architectural component of cellulite to cause lasting effects. Further studies of this device are needed.

Lasers for fat removal: Possible role in the treatment of cellulite

Key points

- **Laser-assisted liposuction has become very popular among surgeons and dermatologists as a preferred treatment for localized adiposities**
- **Laser-assisted lipoplasty might be a better option for small surface areas**
- **Its efficacy and superiority over traditional large-volume liposuction is questionable and requires further blinded controlled studies**

The advantages of laser-assisted lipid destruction over the traditional tumescent liposuction have made headlines since the approval of the neodymium-doped yttrium aluminium garnet (Nd:YAG) laser for fat removal.

The Nd:YAG (1064-nm) laser (Smartlipo; Cynosure, Westford, MA) targets selected areas of fat for destruction in addition to simultaneously

tightening the skin.^{25,26} This technology is less invasive compared to conventional liposuction. It employs a 300- μ m fiber in a 1-mm diameter cannula that is threaded under the skin, in comparison to the 3- to 5-mm cannulae used in traditional liposuction.

The ultrashort, high-peak power of the laser pulses generates a photoacoustic effect that selectively disintegrates adipocyte membranes, resulting in discharge of the cellular contents with minimal risk of tissue charring. The laser also coagulates tissue to promote collagen tightening and hemostasis.²⁷ The thermolysis of the laser will ablate fat tissue, which can then be aspirated by either syringe suction or peristaltic pump. Although laser-assisted liposuction has gained a tremendous amount of interest among surgeons and dermatologists, its efficacy and superiority over traditional liposuction has been questioned. Prado et al²⁸ found no major clinical differences for suction-assisted lipoplasty versus laser-assisted lipoplasty. They also found increased levels of free fatty acids in the blood after laser lipoplasty. However, Goldman et al²⁹ and Kim and Geronemus³⁰ did not show any significant changes in serum lipid profile.

Laser-assisted lipoplasty may be best suited for smaller surface areas. Of concern is the fact that thermal energy, when used for therapeutic purposes, always has the potential for and risk of scarring. Lasers delivered via cannulas can also cause “end hits” of burns. The results are promising, but additional work needs to be performed.

Based on the theory of selective photothermolysis,³¹ laser light in the range of far infrared can be used to selectively target fat. Fat can be selectively coagulated or destroyed using lasers in the far infrared spectrum. Anderson et al³² reported that the 1210-nm and 1720-nm laser wavelengths were able to selectively heat adipose tissue; however, no devices associated with these wavelengths are commercially available. In addition, at the time that this article was written, no studies of these devices in the treatment of cellulite have been published. Selective laser irradiation of fat at these wavelengths may be an important breakthrough in the treatment of “cellulite.”

O'Dey et al³³ showed fatty tissue ablation using a high-powered diode laser ($\lambda = 940$ nm) using fat cells harvested from the anteromedial thigh in vitro. Their study showed that $\lambda = 940$ nm achieves an increased absorption of both fatty tissue and water while maintaining a penetration depth of several millimeters. Water in the connective tissue septae might be responsible for some of the side effects, such as carbonization and enhanced collateral damage leading to the vaporization of fat cells. These results are preliminary, yet encouraging.

Pharmacologic agents

Key points

- **Several pharmacologic agents available for the treatment of cellulite lack scientific evidence of long-term efficacy**
- **It is unlikely that topically applied pharmacologic agents can alter the fundamental architectural alterations that exist in cellulite-prone areas**
- **Topically applied retinoic acid for 6 months can enhance dermal collagen production and improve the strength of the hypodermal septae**
- **Carboxy therapy can induce lipolysis because of its positive effect of physiologic oxidative lipolytic process**
- **Peroxisome proliferator-activated receptors are a recently discovered family of nuclear transcription factors that are shown to enhance skin tightening and induce the uncoupling protein-1 on adipocytes**

Catecholamines

Numerous pharmacologic agents are used to treat cellulite. These include methylxanthines, retinoids, lactic acid, and herbal agents.³⁴ Despite the plethora of topical treatments available at the dermatology office, pharmacies, spas and boutiques, and over the Internet, there are no large scale studies showing the effectiveness of any of these therapies. Only two agents—aminophylline and retinoids—have been critically evaluated. Aminophylline stimulates β_2 -AR activity and causes a localized lipolytic effect. Collis et al⁴ evaluated the effectiveness of topical aminophylline gel in combination with 10% glycolic acid and concluded that this therapy fails to improve cellulite. Even though it has been hypothesized that topically applied aminophylline can penetrate through the dermis to cause significant lipolysis, this has not been scientifically proven. As stated previously, the majority of ARs in the femoral area are α -ARs rather than β_2 -ARs, which upon stimulation with nonselective catecholamine will have an antilipolytic effect. Nonetheless, these treatments are still used, and patients have reported subjective improvement.

Herbal products

The herbal product Cellasene (Medestea Internazionale, Torino, Italy) contains ginkgo biloba, sweet clover, seaweed, grape seed oil, lecithins, and evening primrose oil has been marketed internationally as a “miracle cure” for cellulite.³⁵ A parallel, placebo controlled clinical study comparing the effects of Cellasene with those of a control cream

on the appearance of cellulite in 24 women between 25 and 45 years of age failed to reveal significant changes after a 2-month course.³⁶ Of note, seven of the 11 women using the study cream gained weight. It is important to note that many of the ingredients in purported topical treatments for cellulite are not known, and therefore the risk for adverse effects may be increased. In one study, there were 232 ingredients in the 32 different cellulite creams examined—these ingredients were predominantly botanicals, emollients, and caffeine.³⁷ One-fourth of these materials were noted to cause allergic reactions.

Retinoic acid and its effect on cellulite adipose tissue

Topically applied retinol 0.3% over a period of 6 months or more has been shown to improve cellulite.^{38,39} These effects may be related to the known effects of retinoids (increasing dermal collagen thickness and improving the contour of elastic fibers). Studies have also shown an increase in factor XIIIa—positive dendrocytes. Retinol itself can act as an antiadipogenic agent by inhibiting the differentiation of human adipocyte precursor cells.

Carboxy therapy

Carboxy therapy is a treatment in which carbon dioxide is injected into the subcutaneous tissue. This treatment purports to affect fat cells and circulation.⁴⁰ Brandi et al⁴¹ showed increased skin elasticity up to 55.5% when combined with liposuction for the treatment of cellulite on lateral thighs. A proposed mechanism may be related to a hypercapnia-induced rise in capillary blood flow, a drop in cutaneous oxygen consumption, or a right shift of the oxygen-dissociation curve (Bohr effect). This effect might account for the positive affect on the physiologic oxidative lipolytic process.⁴¹

Peroxisome proliferator-activated receptor agonists and their effect on cellulite

Peroxisome proliferator-activated receptors (PPARs) are a recently discovered family of nuclear transcription factors,^{42,43} and three PPAR receptor types (PPAR- α , PPAR- β , and PPAR- γ) have been characterized. PPARs bind to the peroxisome proliferator response element within the promoter region of the DNA in the target gene in the form of heterodimers with the retinoid X receptor (RXR). All PPARs are found in adipocytes. Petroselinic acid and conjugated linoleic acid have been reported as potent PPAR- α activators, improving epidermal differentiation, reducing inflammation, increasing extracellular matrix components, and eliciting skin

tightening. They are also known to induce uncoupling protein-1 (UCP-1) levels. Like retinoids, they also deliver pleotropic benefits. In vitro studies have shown that conjugated linoleic acid can prevent lipid accumulation in adipocytes.

ADVANCES AND NEWER APPROACHES IN THE TREATMENT OF CELLULITE

Key points

- **Perilipin A protein, located on adipocytes, controls adipogenesis and adipolysis—effects that are mediated via estrogen-receptor related receptor- α and PPAR- α , respectively**
- **Characterization of cellulite adipose tissue (white vs brown) is essential in order to better understand the cellulite physiology and to explore newer treatment options**
- **Selective cryolysis is a new technique that might have potential for cellulite treatment**

Perilipin A, estrogen-related receptor- α , and PPAR- γ in adipocyte regulation

Perilipin A is one of the most abundant proteins of adipocytes; it regulates adipogenesis and adipolysis. The process is regulated through phosphorylation by the catecholamine c-AMP/protein kinase A cascade.⁴⁴ Expression of perilipin-A is markedly elevated during adipocyte differentiation. It has been proven that PPAR- γ is responsible for this regulation.⁴⁵ PPAR- γ is the master regulator of adipogenesis, but the orchestrated actions of many other transcriptional factors are also important for the full development and maintenance of adipocytes. Estrogen-related receptor- α (ERR- α) is likely to be one of such transcriptional factors, based on its elevated expression during adipogenesis and the lean phenotype of ERR- α null mice.⁴⁶ Perilipin A is located on the lipid droplet surfaces in adipocytes and steroidogenic cells. It plays a major role in both the accumulation and mobilization of lipids in adipocytes. At a basal rate, this protein protects the stored triglyceride core in the lipid droplet from the attack of lipases. Once phosphorylated by protein kinase A upon stimulation by catecholamines, perilipin allows or even recruits lipases to access lipid droplets, resulting in active lipolysis. Perilipin gene is a target of ERR- α , which under basal conditions promotes adipogenesis. In addition, ERR- α is present in white adipose tissue, a major lipid storage depot of the human body. This might explain the high affinity of gluteal and femoral receptors to circulating estrogen and high rate of adipogenesis and considerably lower rates of adipolysis under normal conditions. The perilipin gene is also a target for PPAR- γ ; the stimulation of which

leads to inhibitory effects on adipogenesis and promoting lipolysis.⁴⁷ Therefore, the control of adipocyte differentiation varies greatly among different body sites, and a complex network of transcriptional factors controls energy metabolism. Other newly discovered hormones, such as grehlin and PYY-36, might have a role in controlling hunger at the level of satiety center in the hypothalamus and central obesity. However, their role in the pathophysiology of cellulite still remains to be shown.

Conversion of white adipose tissue to brown adipose tissue and vice versa

Because of the antilipogenic properties of retinoic acid agonists and PPAR receptor agonists, along with their unique ability to induce UCP-1, they have become targets in the search for the cure of cellulite.

Although evidence to support their use both in humans and in vivo is still lacking, there have been interesting reports of the use of these agonists to convert white adipose tissue (WAT) to brown adipose tissue (BAT) in vitro mainly via the induction of UCP-1. An in vitro study by Alvarez et al⁴⁸ investigated the effects of various retinoic acid receptors (RARs) on the induction and expression of UCP-1. UCP-1 is exclusively found in BAT. Their work concluded that cotransfection of murine expression vectors for the different RAR and RXR subtypes indicates that RAR- α and RAR- β , as well as RXR- α , are the major retinoid receptor subtypes that are capable of mediating the responsiveness of UCP-1 to retinoids. The effects of retinoids on UCP-1 transcription involve both RAR- and RXR-dependent signaling pathways. The responsiveness of BAT to retinoids in vivo relies on a complex combination of the capacity of RAR and RXR subtypes to mediate UCP-1 induction and their distinct expression in the differentiated brown adipocytes.

Other interesting studies by Tiraby et al^{49,50} have identified a PPAR- γ coactivator 1 α (PGC-1 α), which is expressed in higher levels in BAT than in WAT. Its expression is increased in response to cold and β -AR stimulation, leading to higher levels of UCP-1 in conjunction with RXR- α and an increase in mitochondriogenesis. These changes ultimately promote the conversion of WAT to BAT. This might be a new paradigm for further research into the treatment of cellulite.

Selective cryolysis

Cryolysis is an interesting concept that might have future applications in the reduction of cellulite and localized adiposities. There is evidence that adipose

tissue is selectively sensitive to cold injury, such as “popsicle panniculitis.”⁵¹ The most likely mechanism hypothesized when popsicle panniculitis was first described is that crystallization of cytoplasmic lipids in adipocytes occurs at temperatures well above the freezing point of tissue water. The potential for tissue-specific cold injury was first investigated and recently reported by Anderson et al⁵² in an animal model. Black Yucatan pigs were exposed to temperatures of 20, -1, -3, -5, and -7 °C for 10 minutes using the Zeltiq prototype device (Zeltiq Aesthetics, Pleasanton, CA). At 3.5 months of follow-up, some treated areas showed grossly obvious loss of several millimeters of subcutaneous fat. The investigators did not find any significant change in serum lipid values. In this study, inflammation and adipose tissue loss were well correlated. Both proceeded for many weeks after a single, local exposure to cold, reaching an apparent maximum at 4 weeks after and resolving about 3 months after cold exposure. In its early inflammatory phase, panniculitis may further damage adipocytes. In its later phase, however, phagocytosis appears to account for removal of adipocytes and loss of fat tissue.

Many important details about selective cryolysis remain to be studied. Most importantly, there is not enough information available in the published literature regarding the mechanisms of adipocyte injury in adult humans when subzero temperatures are applied to the surface of skin. In addition, selective cryolysis might be challenged by the fact that human fat is rich in unsaturated fatty acids with a much lower freezing point as opposed to pig fat, which is rich in saturated fatty acids with a rather higher melting point.

The precise nature of the fatty acids and other lipids of cellulite fat have yet to be defined. Selective cryolysis is a newer, noninvasive treatment option for localized adiposities. Its role in the treatment of cellulite is still under investigation.

Excessive localized adipose tissue is one of the main etiologies of cellulite. In addition, the depth, breadth, and extent of cellulite vary from one part of the body to another in a rather unpredictable manner. Skin surface cooling with either a flat or a suction device might offer some advantage for liposculpting similar to other noninvasive treatment modalities, such as ultrasound and radiofrequency devices. Well controlled comparison trials are needed to better define the superiority of one treatment over another.

CONCLUSION

Cellulite is an architectural disorder caused by multifactorial etiologies. Despite a large number of

treatments available—all of which claim to work somehow—few actually do work, and many work with unpredictable results.²⁴ Limited therapeutic options are available that can alter the genetic factors responsible for dermohypodermal heteromorphism among both affected and unaffected individuals. The connective tissue septae that traverse and subdivide the hypodermis serve as suspenders that hold the adipose tissue. Theoretically, if the volume of herniated adipose tissue in the hypodermis can be reduced in a selective, predictable, controlled, and safe manner, it might clinically improve cellulite. In addition, increasing the dermal thickness can also potentially strengthen the dermohypodermal junction, thereby reducing adipose tissue herniation. The configuration of fat found in the cellulite (WAT vs BAT) by receptor analysis of the adipocytes in the gluteofemoral area needs to be better identified using techniques such as polymerase chain reaction. Understanding the mechanisms governing the acquisition and persistence of white and brown adipocytes can have novel implications in terms of the pathophysiology and therapeutic strategies used in the future for the management of cellulite.

Recently introduced noninvasive cryolysis might have promising results in the reduction of subcutaneous fat, at least temporarily. Its role in the treatment of cellulite adipose tissue as a noninvasive modality remains to be explored.

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