

Body Contouring: The Skinny on Noninvasive Fat Removal

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Historically, the approach to body contouring has largely involved invasive procedures, such as liposuction. Recently, several new devices for noninvasive fat removal have received clearance by the Food and Drug Administration for the treatment of focal adiposity. Modalities are aimed primarily at targeting the physical properties of fat that differentiate it from the overlying epidermis and dermis, thus selectively resulting in removal. This review will focus on 3 novel approaches to noninvasive selective destruction of fat. *Semin Cutan Med Surg* 31:121-125 © 2012 Published by Elsevier Inc.

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Popular culture is consumed by fat reduction and weight loss. On a daily basis, the average American is inundated through various media outlets with “too good to be true” weight loss supplements, exercise regimens, and images of the idealized prototypical body. In addition to societal pressures, as our knowledge of the detrimental effects of obesity grows, there is further motivation for weight loss and fat reduction.

Body contouring refers to the optimization of the definition, smoothness, and shape of the human physique. Historically, the approach to body contouring has largely involved invasive procedures, such as liposuction. Liposuction is among the top 5 cosmetic surgical procedures performed in the United States.¹ A recent study found that upward of 33% of women and 15% of men, across all age-groups, are interested in liposuction.² Despite its popularity, there remain rare but significant risks regarding liposuction, including complications from anesthesia, infections, and even death. Along with safety concerns, several other factors have influenced the development of noninvasive nonsurgical approaches to body contouring. These factors include both an

increased patient and physician interest and the relative expense of surgical procedures.

Although less-invasive surgical techniques, including tumescent liposuction and laser-assisted lipoplasty, have advanced the efficacy and safety of traditional surgical approaches, only recently has noninvasive fat reduction become available. Modalities primarily target the physical properties of fat that differentiate it from the overlying epidermis and dermis, thus selectively resulting in removal. Novel approaches involve heating, cooling, and selective targeting of adipocyte ultrastructural components. This review will focus on 3 novel approaches to noninvasive selective destruction of fat. Devices using cryolipolysis, lipid selective wavelengths of laser light, and high frequency-focused ultrasound will be discussed. Emphasis will be placed on preclinical and clinical studies, efficacy, and safety of the devices. It should be noted that this article will not review devices aimed at the treatment of cellulite, which should be thought of as a distinct topic from noninvasive fat removal.

Cryolipolysis

The concept of cryolipolysis, a novel approach to noninvasive fat removal with freezing, was introduced in 2007 and was cleared in 2010 by the US Food and Drug Administration (FDA). The development behind selective cold injury stems from the clinical observation of “popsicle panniculitis” in which a transient indurated nodule was observed in infants at the site of prolonged contact with a popsicle. Histologically, a panniculitis was observed.³ Subsequently, a temporary and focal lipomatrophy was noted in these infants. These observa-

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tions, along with other reports of cold-induced fat injury,⁴ suggest that fat cells are more susceptible to cold at certain temperatures than surrounding tissue. This finding was exploited in the development of cryolipolysis for the noninvasive removal of fat and body sculpting.

Manstein et al.⁵ performed the initial preclinical studies aimed at determining the feasibility of selective destruction of fat with controlled cooling. An initial pilot exploratory study used a -7°C copper plate cooled with antifreeze solution applied under firm pressure to a single Yucatan pig. The animal was followed for 3.5 months to evaluate for localized fat loss and then euthanized for histologic analysis. In all 10 sites tested, there was visible indentation noted, with a maximal relative loss of the superficial fat layer of nearly 80%. Effects on the epidermis were limited to transient hyperpigmentation 1 week after application of the cold plate. There was no hypopigmentation, textural changes, or scarring noted at any of the test sites. Subsequent dosimetry studies revealed that fat damage was significantly greater at lower temperature and increased gradually over 28 days after exposure. Cholesterol and triglyceride levels post-treatment were monitored and were found not to be significantly elevated at various time points up to 3 months after treatment. Zelickson et al.⁶ performed a follow-up animal study in 3 Yucatan pigs that underwent a single cryolipolysis treatment. Ultrasound assessments demonstrated a 33% reduction in the thickness of the superficial fat layer in the treatment area following cryolipolysis. On examination of gross tissue, a reduction of approximately 50% thickness was noted in the superficial fat layer.

Cryolipolysis is thought to induce apoptosis of fat cells.⁷ Other mechanisms include possible cold-induced reperfusion injury of temperature-sensitive adipocytes, resulting in free radical damage, oxidative stress, and subsequent cell death. Histologic analysis from animal studies indicates that the reduction in fat is coincident with a predominantly inflammatory lobular panniculitis. Immediately after treatment, there is no damage observed to the adipocytes. In the porcine model, a mixed inflammatory infiltrate is seen at approximately 2 days following treatment. At 1 week post-exposure, the infiltrate evolves into a lobular panniculitis. The peak inflammatory response is at 2 to 4 weeks after treatment, although residual inflammation can be seen up to 3 months after treatment. During this time, the inflammatory infiltrate is predominately composed of macrophages that are hypothesized to ingest and clear the apoptotic fat cells. As this process occurs, there are variably sized adipocytes and subsequent widening of the fibrous fat septae. This process occurs slowly over 90 days post-treatment, concurrent with the gradual reduction of fat that is observed clinically.^{5,6}

Human clinical studies were conducted using a cup-shaped treatment applicator with 2 cooling panels. Moderate vacuum suction is used to draw tissue into the applicator and optimize position and contact between the cooling plates. It also causes vasoconstriction, which allows for more rapid cooling of the skin. The clinician then selects a cooling intensity favor, a value representing the rate of heat flux in or out of the tissue. After 60 minutes, the treatment is complete, and



Figure 1 Post-treatment erythema of the abdomen immediately after cryolipolysis treatment. Erythema is confined to the treatment area and is visible immediately after removal of the device applicator.

the device is removed. Multiple clinical studies have demonstrated the efficacy of cryolipolysis for fat layer reduction in humans. In 1 study, 32 treated patients with localized fat accumulation of the flanks (“love handles”) demonstrated clinical improvement, as measured by digital photography, physician assessment, and subject satisfaction. Of these, 10 patients underwent ultrasonography of their treatment area, with an average reduction of fat layer thickness of 22.4%.⁸ In a subsequent study, 50 patients underwent treatment of 1 flank and photography of the treated and untreated sides. Three blinded physicians were able photographically to differentiate between pre- and post-treatment sites in 82% of patients.⁹ Based on these data, the device has gained FDA clearance for the treatment of localized fat of the flanks. Further studies investigating the efficacy of cryolipolysis to other treatment sites, including fat layer reduction of the abdomen, are ongoing.

Since FDA approval in 2010, more than 200,000 treatments were completed. Composite data from 2 multicenter clinical trials indicate that the safety profile of the device seems favorable. Common and immediate adverse effects include localized erythema that can last for several hours after treatment (Fig. 1). Because the device uses a vacuum suction applicator, localized ecchymosis can also be observed, especially in patients using aspirin or anticoagulants. In the initial clinical studies, decreased cutaneous sensation was reported in the treatment subjects. Coleman et al.¹⁰ reported a case series in which 98% of patients experienced numbness of the treatment sites. This numbness was largely improved by 1 week post-treatment. A minority of patients also reported reduction in pain sensitivity, light touch, 2-point discrimination, and temperature sensitivity. A nerve biopsy taken from 1 patient 3 months after the procedure revealed no pathologic changes when compared with baseline biopsy specimens. In all cases, the neurologic side effects were reliably reversible, and all had resolved by 2 months post-treatment. No statistically significant changes in triglyceride levels or

liver function tests—including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and albumin—have been reported in human studies.¹¹

Recently, rare reports of severe pain have emerged after treatment with cryolipolysis. This pain is characterized as a severe “shooting” and “jabbing” pain onset within 1 week of treatment. Although the mechanism of action remains unclear, the incidence is approximately 0.05% and most commonly follows cryolipolysis treatment of a large surface area with the larger applicator. This may in fact represent a more robust panniculitis or nerve inflammation that may result in allodynia and hyperneuralgia. In the 23 reports, pain was adequately controlled with topical and oral analgesics and resolved spontaneously within 1 to 4 weeks.¹² It is important to note that caution should be exercised in treating patients with cold-induced dermatologic syndromes, including cryoglobulinemia, cold-induced urticaria, Raynaud syndrome, or paroxysmal cold-induced hemoglobinuria, until further studies have been conducted.¹³

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) has been used for nearly half a century for the noninvasive treatment of tumors of various organs but has only recently been evaluated as a method for the selective destruction of adipose tissue. High-energy ultrasonic waves are focused into the subcutaneous tissue, quickly raising the temperature above 56°C, resulting in coagulative necrosis of the adipocytes and a subsequent reduction of the fat layer. The prototype first-generation device uses a proprietary programmable pattern generator that moves the ultrasound wave to consecutive focal points within the treatment area, resulting in a homogenous matrix of lesions. A high degree of focusing allows individual lower-energy ultrasound beams to travel through the epidermis and dermis without causing undue heating. When focused in the appropriate plane, it results in rapid heating and ablation of subcutaneous fat.

Preclinical animal studies performed in a porcine model evaluated the use of HIFU in the treatment of abdominal adipose tissue. In this study, the application of high-energy levels generated focal temperature elevation within the adipose tissue. Histology revealed localized damage within the fat with intact vasculature and nerve fibers within the treatment area. Gross examination of tissue from various organs showed no evidence of fat accumulation or emboli.¹⁴

Initial evidence for efficacy and safety in humans was based on 2 case series. Fatemi et al.¹⁵ reported a retrospective case series of 282 patients who underwent a single HIFU treatment of their anterior abdomen and flanks. Primary outcome measures included waist circumference measured before and 12 weeks after a single treatment. An additional 85 men and women treated with HIFU to the abdomen and flank in a single session were also later reported.¹⁶ In both case series, subjects noted an average waist circumference decrease of 4.4 and 4.7 cm, respectively. Subject satisfaction

was greater than 70% of subjects in both series 3 months after treatment. It is important to note that in both case series, the range of waist circumference change was variable and varied from a loss of 9 cm to an increase of 4 cm. Furthermore, it is unclear that diet was controlled in these case series.

Jewell et al.¹⁷ published a randomized controlled trial of 180 patients who were randomized 1:1:1 to 1 of 2 treatment groups or a sham-treatment control group. Subjects with subcutaneous abdominal fat of 2.5 cm or greater were enrolled in the study and randomized to 2 treatment groups with variable energy levels or a sham-treated control group. Primary outcome measures included waist circumference measured at the iliac crest. There was a statistically significant decrease in waist circumference in both treatment groups when compared with the sham-treated control group at 12 weeks following a single treatment. It is important to note that there was no significant change in body mass in either of the treatment or control groups, and patients were instructed to continue their routine diet and exercise regimen in all treatment groups at the onset of the study. In addition to the statistically significant difference in waist circumference between the treatment and control groups, there was also a 1.2-cm decrease in waist circumference of the sham-treated control group at the 12-week follow-up.

Historically, HIFU has been used safely in medical applications that often require higher energy than used for body contouring. These include treatment of kidney stones, epicardial tissue ablation for arrhythmias, and destruction of uterine fibroids.¹⁸⁻²⁰ With the limited clinical reports available thus far, the device appears to have a favorable safety profile in regards to body contouring. Adverse events were limited to less than 12% of patients and included prolonged tenderness, edema, ecchymosis, and hard lumps. All adverse events resolved within 1-3 months after treatment. Some treatments were terminated because of excessive pain during the procedure, but the pain resolved after termination of treatment.^{15,16} Moreover, there were no increases in laboratory values of serum lipids or liver function tests in the multiple clinical studies conducted thus far. In 2011, the first- and second-generation HIFU devices received FDA clearance.

Histologic evaluation of tissue treated with HIFU was obtained from patients who underwent treatment and subsequent abdominoplasty.¹⁵ Abdominoplasty specimens revealed well-demarcated zones of damage that were clearly visible on gross inspection. These zones were limited to the treatment area and did not appear to spread to surrounding tissue or the overlying dermis or epidermis. Microscopically, adipocyte necrosis is evident as demonstrated by disruption of cell membranes immediately after treatment. Two weeks after treatment, a localized inflammatory infiltrate consisting primarily of scavenger macrophages is observed within the treatment area. The scant macrophage migration results in phagocytosis of cellular debris and extracellular lipids. This can be visualized by the presence of lipid-laden macrophages present within the treatment zone. Resorption of lipid and healing is complete at approximately 14 weeks after a single

treatment corresponding to the observed clinical decrease at that time point.^{15,21}

There are other ultrasound technologies designed to target fat noninvasively, but currently do not have FDA clearance.

Low-Level Laser Therapy

Low-level laser therapy (LLLT) was FDA cleared in 2010 for fat reduction. Initial enthusiasm regarding LLLT for the treatment of fat stemmed from the *in vivo* observation that a 635-nm laser caused a transitory pore within the adipocyte, resulting in release of lipids into the interstitial space, and subsequent deflation of the adipocyte. The pore itself does not damage the cell, but allows for the efflux of lipid contents from the cell into the interstitial space, which is then theorized to pass through the body.²² The mechanism of action is hypothesized to result from photoexcitation of cytochrome-*c* oxidase, a terminal enzyme of the respiratory chain within the mitochondria.²³ Numerous reports highlight the role of laser-induced adipocyte modification as an adjunct to liposuction; however, data regarding the use of LLLT alone for fat reduction are more limited.

The commercially available device contains multiple low-power laser diode modules operating at a wavelength of 635 nm, suspended from 4 adjustable arms. Treatment typically involves 6 to 8 sessions, with each session lasting up to 30 minutes. In addition, the device manufacturer recommends concurrent use of a nutritional supplement containing niacin, *Ginkgo biloba*, green tea extract, and L-carnitine. The manufacturer hypothesizes this supplemental diet enhances the lymphatic and circulatory systems.

Clinical studies exploring the use of LLLT alone for non-invasive fat reduction are mixed. An initial, double-blind, placebo-controlled trial demonstrated an overall combined reduction of 3.51 inches by adding the results of 3 combined treatment sites (waist, hip, and thighs) in the treatment group compared with 0.6 inches in the control group.²⁴

However, unlike the other aforementioned FDA-cleared devices, there was no histology performed. A subsequent investigator-initiated trial using the same device with fewer subjects failed to reveal statistically significant efficacy. Primary end points included waist circumference and ultrasound measurements of fat layer thickness. Blinded investigator evaluation and low patient satisfaction concurred with the negligible clinical efficacy.²³

Infrared Lasers

Selective photothermolysis involves the selection of a wavelength of light and pulse duration that sufficiently heats a specific target without damage to the surrounding tissue. This confinement of heat allows for the targeting of individual chromophores without disruption of bystander tissue. Recently, infrared vibrational bands have been found to be useful for the selective targeting of lipid-rich tissues, such as fat. Anderson et al.²⁵ measured the absorption spectrum of fat, identifying peaks at 1210 and 1720 nm, where the absorption coefficient of lipid is greater than that of water

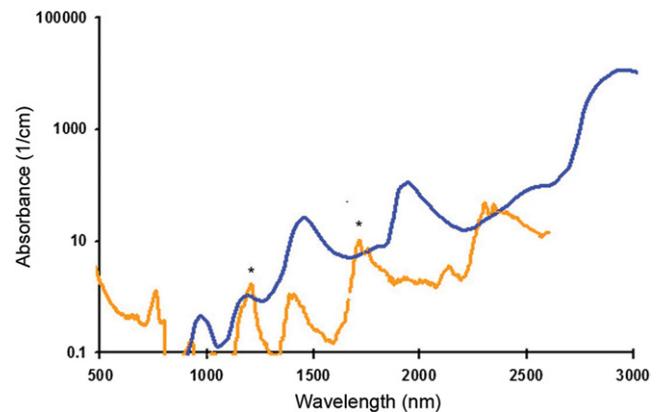


Figure 2 Absorption spectrum of lipid as compared with water. Asterisks represent peaks at 1210 and 1720 nm where the absorption coefficient of lipid is greater than water. Figure courtesy of Fernanda Sakamoto, MD, PhD.

(Fig. 2). *In vitro* exposure of fresh, intact, full-thickness porcine tissue samples at wavelengths near 1210 nm reproducibly caused thermal damage of subcutaneous fat with little or no injury to the overlying skin.

A subsequent pilot human study used a continuous wave 1210-nm diode laser with variable fluences, a 10-mm spot size, and a 3-second exposure time. In all, 24 adult subjects were exposed with adequate precooling to variable fluences noninvasively on the abdomen. Six-millimeter punch biopsies were taken either at 1 to 3 days or 4 to 6 weeks after laser exposure. Staining with nitroblue tetrazolium chloride, a viability stain, revealed selective dose-dependent damage to the subcutaneous fat and dermis. Lipomembranous changes of the fat were seen in biopsy specimens obtained 4 to 6 weeks after exposure.²⁶ This pilot study offers preliminary evidence for the noninvasive destruction of fat with a 1210-nm device. The observation that reticular dermis can be targeted as well may indicate a possible future role of this device in the treatment of cellulite. However, although microscopic samples revealed damage to the adipocytes, to date, there has been no evidence presented to support its clinical efficacy over larger treatment areas. Nevertheless, with optimization, a 1210-nm wavelength laser may become a useful tool for the noninvasive selective destruction of fat and other lipid-rich tissue. Further study and optimization of treatment parameters, including pulse duration, are needed.

Discussion

For years, what has remained an elusive goal has finally become a reality: noninvasive fat removal. Through various targeting strategies, adipose tissue can be effectively destroyed in both animal models and human subjects. The observed destruction of adipocytes translates to a modest, albeit real, improvement in fat reduction. Strategic applications of these technologies can result in improvement of localized collections of fat, offering options for slenderizing and contouring. Although far from being optimized, many of these first-generation devices have proven efficacy with a

favorable safety profile. However, there are several caveats to these new technologies of which clinicians should be aware. First, none of the modalities currently available are an alternative to a healthy diet and lifestyle. They do not serve as a significant method for weight loss, and as such, realistic expectations should be set with patients. These devices do not target visceral fat, which is implicated in cardiovascular disease; therefore, health benefits are largely cosmetic. Second, these treatments do not approach the efficacy of liposuction, particularly with a single treatment session. Benefits are modest, and consumers should be made aware that multiple treatments are necessary to achieve the desired end point. The future optimization may result in more efficient removal of large volumes of fat. Patients should also be made aware that results are often delayed and may take up to 3 months to note an appreciable improvement.

Although many of the clinical devices reviewed here have shown mild-to-moderate efficacy in preliminary clinical trials, physicians and consumers should have a healthy amount of skepticism when interpreting these studies. In many of these trials, study end points were objective measures that are inherently error prone, such as waist circumference. Few studies utilized ultrasonography as an objective measure of thickness, but no study of any of the reviewed devices has shown efficacy through volumetric analysis of 3D images or magnetic resonance imaging. Many of the preliminary reports also are not controlled for weight changes, lifestyle modifications, or other subject interventions that may have an effect on the study outcome. Although the limited data points to efficacy, one must keep these caveats in mind when counseling patients regarding clinical outcome as well as when evaluating future devices.

All initial reports of these devices point to the fact that they are relatively safe, well tolerated, and with foreseeable, and transient, post-treatment effects. Multiple studies evaluating lipid levels and liver function after treatment have shown no significant clinical increase in circulating lipids or evidence of compromised hepatic function. Nonetheless, these devices have only been available for limited periods, thus a long-term safety profile is yet to be determined.

As with any new technology, the medical community should approach future devices with appropriate scrutiny. Fat removal has a tarnished history and a poor track record. Review of data should include objective measures to show reliable and reproducible efficacy and safety. With this in mind, physicians can protect their patients' health and welfare, while lending credibility to scientifically proven efficacious devices.

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