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REVIEW

Noninvasive Body Sculpting Technologies with an Emphasis on High-Intensity Focused Ultrasound

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Abstract
Background Body-sculpting procedures are becoming increasingly popular in the United States. Although surgical lipoplasty remains the most common body sculpting procedure, a demand exists for noninvasive alternatives capable of reducing focal adiposity without the risks of adverse events (AEs) associated with invasive excisional body-sculpting procedures.
Methods This report describes the mechanism of action, efficacy, safety, and tolerability of cryolipolysis, radiofrequency ablation, low-level external laser therapy, injection lipolysis, low-intensity nonthermal ultrasound, and high-intensity focused ultrasound (HIFU), with an emphasis on thermal HIFU. The articles cited were identified via a PubMed search, with additional article citations identified by manual searching of the reference lists of articles identified through the literature search.
Results Each of the noninvasive treatments reviewed can be administered on an outpatient basis. These treatments generally have fewer complications than lipoplasty and require little or no anesthesia or analgesia. However, HIFU is the only treatment that can produce significant results in a single treatment, and only radiofrequency, low-level laser therapy, and cryolipolysis have been approved for use in the United States. Early clinical data on HIFU support its efficacy and safety for body sculpting. In contrast, radiofrequency, laser therapy, and injection lipolysis have been associated with significant AEs.
Conclusions The published literature suggests that noninvasive body-sculpting techniques such as radiofrequency ablation, cryolipolysis, external low-level lasers, laser ablation, nonthermal ultrasound, and HIFU may be appropriate options for nonobese patients requiring modest reduction of adipose tissue.

Keywords Adipose tissue · Body contouring · Body sculpting · High-intensity focused ultrasound · Noninvasive · Waist circumference

Body sculpting refers to the use of either surgical or noninvasive techniques to modify the appearance of the body. In general, four types of patients undergo body-sculpting procedures. Patients with focal adiposity may desire body sculpting for problem areas such as the abdomen, thighs, or hips. Patients with skin laxity of the face, neck, or arms may require treatments that tighten skin and deeper layers. Patients who have both focal adiposity and skin laxity require treatment that combines skin tightening with reduction in focal adiposity.

For patients requiring substantial fat reduction, surgical lipoplasty remains a popular method for body sculpting in the United States. However, the number of lipoplasty procedures performed annually has decreased dramatically as patients look for less invasive methods of body sculpting [1]. The total number of procedures performed declined to 198,000 in 2009 from 245,000 in 2008 (−19%) and from 350,000 in 2000 (−44%).

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Lipoplasty is associated with the highest potential for significant complications, morbidity, and mortality [2–5]. Mortality occurs for about 1 in 47,000 patients [2, 3] and is most often caused by embolism complications of anesthesia [5], necrotizing fasciitis, and hypovolemic shock [6]. Ultrasound-assisted [7] liposuction has reduced but not eliminated the risk of complications. Laser-assisted liposuction demonstrates only a minor incremental benefit over conventional lipoplasty and exposes the patient to the risk of burns and thermal injury to deeper tissue [8, 9].

Noninvasive alternatives to liposuction include cryolipolysis [10], radiofrequency ablation [10–12], laser therapies [10, 13, 14], injection lipolysis [10, 15], and low-intensity nonthermal (mechanical) focused ultrasound [16–18]. High-intensity focused ultrasound (HIFU) for the thermal ablation of adipose tissue [19, 20], a new therapeutic option being used in Europe and Canada, currently is under review by the United States Food and Drug Administration (FDA). Each of these technologies was developed to perform body sculpting for nonobese patients requiring reduction of focal adiposity, skin tightening, or both. Surgical liposuction remains the preferred treatment for patients in need of large-volume fat reduction or the treatment of multiple areas.

This report describes the mechanism of action, efficacy, safety, and tolerability of each noninvasive body-sculpting technology, with emphasis on reviewing the basic science and clinical utility of HIFU, which may be less familiar to practitioners, particularly in the United States.

Methods

A search of the PubMed MEDLINE database was performed to capture relevant articles published in the 5 years between 28 June 2005 and 28 June 2010. The following search terms were used, with asterisks indicating that all possible prefix or suffix combinations were searched: (noninvasive OR high intensity focused OR ultrasound OR ultrasonographic OR ultrasonography OR radiofrequency OR infrared OR laser OR Thermage OR cryolytic OR cryolysis OR cryotherap* OR cryolipolysis OR injection lipolysis OR injection lipolysis OR LipoSonix OR UltraShape OR Zeltiq OR ThermaCool OR VelaSmooth OR Accent XL OR Contour 1 OR Contour One OR Ulthera OR SmartLipo OR Regan OR SmoothShapes OR Titan OR Slimline OR Candela OR Cynosure OR Alma lasers OR Synergen) AND (aesthetic* OR esthetic* OR cosmesis OR cosmetic OR contour* OR ablation OR ablating OR ablates OR sculpt* OR laxity OR *lipolysis OR *lipolytic OR *liposuction OR lipoplasty OR reshape* OR reshaping OR smoothing OR abdominal fat OR subcutaneous fat OR waist circumference OR skin tightening OR cellulite OR striae) NOT (cancer* OR tumor OR tumour OR carcinoma OR sarcoma* OR metasta* OR radiologic* OR radiology OR diagnostic OR imaging OR spectroscop* OR spectromet* OR spectrograph* OR ophthalmology OR ophthalmologic OR cornea OR conjunctiva OR retina OR iridot OR iridoplas OR fundal OR eye OR vision OR acuity OR ocular OR lasik OR kerato OR microbe* OR microbial* OR bacteria* OR catheter OR percutan OR transluminal OR knee* OR shoulder* OR hand* OR joint* OR physical therap* OR arthriti* OR hair OR venous OR vein* OR vericos* OR sclerotherapy* OR resurfac* OR port wine OR psoria* OR acne OR face OR graft* OR tattoo* OR birthmark* OR dental OR dentist* OR implant* OR noise* OR speech OR music OR hearing OR prostate OR prostatic OR silicon* OR aneurysm* OR infant OR child OR children OR adolescent OR pediatric OR paediatric OR obstetric* OR *partum OR vagina OR uterus OR urethra* OR ureter* OR uterine OR utero OR pregnan* OR thyroid OR metabolic syndrome OR valve OR artery OR arteries OR arterial OR renal cyst OR lithotrip* OR lithias* OR cardiac OR psychiatr*).

Using this strategy, 1,183 references were identified, 118 of which were thought to be relevant and considered for inclusion in the manuscript. Additionally, abstracts presented at scientific congresses on HIFU were identified.

Results

Minimally Invasive Surgical Technologies

Tumescent liposuction, currently the standard of care for liposuction, is an invasive surgical procedure performed in an office setting or ambulatory surgical center by a surgeon or physician trained in liposuction [6, 21]. Tumescent liposuction involves the injection of a wetting solution containing dilute lidocaine and epinephrine into fatty tissue, which then is suctioned out through cannulas inserted through small incisions. The lidocaine allows for local anesthesia and generally eliminates the need for general anesthesia or sedation. Nonetheless, some lipoplasty procedures are performed with the patient under intravenous sedation or general anesthesia, depending on the patient's needs. Complications of tumescent liposuction include abnormal body contour, nerve damage, fibrosis, perforations, seroma, fat embolism, deep vein thrombosis, and pulmonary embolism [5, 22].

Laser-assisted lipoplasty requires fiberoptic delivery of laser energy to target tissues, followed by lipoplasty. Risks include effects of both laser energy and lipoplasty. Liposuction plus laser therapy has resulted in skin tightening by as much as 7.6% [8]. However, improvements in skin tightening using laser-assisted liposuction compared with liposuction alone appears to be only slight [23]. Moreover, skin temperatures have reached 42°C [8], and a report has documented deeper tissue temperatures as high as 55°C, which is hot enough to produce fat necrosis and inflammation from the bulk heating of tissue [24].

Thermal damage to skin is thought to occur at temperatures as low as 44°C, and skin blood flow ceases at 45°C [23, 25]. Therefore, clinicians should consider the potential for significant burns and deep tissue thermal injury with this treatment method, in addition to risks of surgical liposuction. It may be difficult to guard against thermal injury because thermal monitoring equipment that relies on surface temperature measurements cannot accurately measure deeper layer heat levels.

Noninvasive Technologies

Table 1 provides a summary of all the noninvasive techniques discussed in this review. The following sections consider noninvasive technologies in detail.

Cryolipolysis

Cryolipolysis is approved by Health Canada and the U.S. Food and Drug Administration (FDA) for the reduction of focal adiposity [26] and has received FDA approval for skin cooling or anesthetic use during dermatologic surgery. Cryolipolysis, also called “energy extraction,” is the controlled application of cold to subcutaneous tissue to reduce adipose tissue [10]. The procedure can be performed by any physician on an outpatient basis without anesthesia or analgesia [27].

When cryolipolysis is performed, suction is used to draw the target tissue into a cup-shaped applicator, in which contact is established between the treatment area and two opposing cooling panels [27, 28]. The rate of energy extraction is referred to as the cooling intensity factor (CIF), expressed in mW/cm^2 [27]. The treatment duration is 45–60 min per treatment site, with most patients receiving treatment at multiple sites [29].

The mechanism by which energy extraction kills fat cells is not clearly understood [27]. However, preclinical studies suggest that an inflammatory process culminating in necrotic cell death is initiated when fat cells are cooled to temperatures between −2 and 7°C. The preclinical data also suggest that cryolipolysis does not provoke this inflammatory response at the time of treatment [27]. Rather, the inflammatory response begins within 3 days after treatment and peaks within 14 days. From day 14 to day 30, macrophages and phagocytes engulf dead lipid cells. The inflammation declines, and the lipids are safely metabolized within 90 days [27, 30].

In humans, cryolipolysis for isolated fat deposits in the flank or on the back has been associated with a reduction in fat content of approximately 20–26% at the treatment site 4–6 months after treatment [27, 31]. Although anesthesia is not used during treatment [27], treatment has been associated with pain, bruising, erythema, and numbness [28, 31]. Treatment also may cause mild to moderate short-term dysesthesia in peripheral nerves, but no long-term damage has been reported [29]. Additional studies in both animals and humans suggest that cryolipolysis has little or no effect on tissues adjacent to the treatment zone, including nerve bundles [30, 32]. The destruction of adipocytes does not significantly affect serum lipid levels or liver function tests [28].

Cryolipolysis does not use heat to achieve body-sculpting results. Therefore, it does not produce skin or deeper layer tightening. However, skin tightening after cryolipolysis may occur from the normal elastic recoil properties of skin tightening [33]. Consequently, a skin-tightening procedure may be required after cryolipolysis.

Radiofrequency

Radiofrequency is used for either facial skin tightening or circumference reduction and cellulite reduction (Table 1) [12]. No radiofrequency device has been approved for body sculpting in the United States or Canada [11].

Radiofrequency works primarily through skin tightening rather than destruction of adipose tissues, making it better suited for patients with cellulite than for reduction in waist circumference [34]. With monopolar radiofrequency devices, energy is passed from a single electrode into the skin and subcutaneous tissues and directed to a return pad in another area of the body, usually the back. With multipolar radiofrequency, two or more electrodes contained within the same handpiece are positioned at different points on the skin so that the waves pass between them to create heating [11, 12]. This latter method directs the trajectory of the current but not the depth. Skin and subcutaneous tissues are heated to the same extent [12]. Completion of a single treatment may require more than 1 h [34]. Radiofrequency-emitting devices generally use skin cooling to protect the epidermis from thermal damage.

In clinical trials, 6–10 radiofrequency treatments have produced 2- to 3.5-cm reductions in waist and thigh circumference [12, 34, 35]. However, it also has been proposed that reductions in circumference with radiofrequency therapy are temporary and secondary to skin tightening and that some apparent skin tightening is caused by transient postprocedure edema [10, 36]. It is therefore essential to distinguish between real improvements and transient effects when treatment response is evaluated.

Radiofrequency presents challenges in terms of managing pain during the procedure [37]. General anesthesia or intravenous sedation are not recommended [37]. Topical

Table 1 Summary of noninvasive body-sculpting treatments

Treatment	Brand Names[a]	MOA	Indications	Areas treated	Treatments needed	Common AEs	Time per treatment	Anesthesia and analgesia	Time to final result	Approval status
Radio-frequency	VelaSmooth Tri-Polar Thermage	Thermal destruction of adipocytes	Focal adiposity, skin tightening	Abdomen, thighs, buttocks, extremities, face	Multiple	Pain, scars, burning, fat atrophy	≤2 h	Oral analgesics	12 weeks	FDA Health Canada
Cryolipolysis	Zeltiq	Energy extraction (cooling)	Focal adiposity	Back, flank, abdomen	Multiple	Pain, loose skin, numbness, bruising, erythema	≤60 min	None	2 months	FDA Health Canada
Injection lipolysis	Lipostabil Flabjab Lipomelt Lipodissolve Fat-Away	Unknown	Focal adiposity, skin tightening	Abdomen, hips, face, thighs, flanks.	Multiple	Postprocedure pain, hematoma, allergic reaction, urticaria, necrosis, scarring, cutaneous granulomas, panniculitis, rapid release of lipids	Variable	Lidocaine	4–6 weeks	Unregulated
Laser ablation	Zerona	Nonthermal ablation of adipocytes	Focal adiposity, skin tightening	Abdomen, thighs, flanks, neck	Multiple	None	20–30 min	None	2–4 weeks	FDA Health Canada
Nonthermal ultrasound	UltraShape	Mechanical stress	Focal adiposity	Abdomen	Multiple	Mild pain, blisters	30–90 min	None	3–4 weeks	FDA-submitted Health Canada
HIFU	LipoSonix	Thermal destruction of adipocytes	Focal adiposity, skin tightening	Abdomen, flanks, buttocks	Single	Mild and transient pain, bruising, edema	90 min	Oral analgesics	90 d	FDA-submitted Health Canada

MOA mechanism of action, *AEs* adverse events, *FDA* U.S. Food and Drug Administration, *HIFU* high-intensity focused ultrasound

[a] Includes leading brand names at time of manuscript preparation. Other brand names may become available prior to publication

anesthetics that numb the epidermis also are not recommended because they actually may aggravate pain in the dermis [37], although topical anesthetic use has been reported for patients who had radiofrequency treatments for facial skin tightening [38]. Local anesthetic infiltration may interfere with delivery of radiofrequency waves [37]. Oral analgesics and short-acting anxiolytics are therefore the only recommended agents for pain management during radiofrequency [37].

In addition to pain, radiofrequency can cause scars, burns, and fat atrophy [22, 38]. Thus, a patient undergoing radiofrequency may require six or more sessions lasting up to 2 h that are associated with significant discomfort and questionable results.

External Laser Treatments

External low-level laser therapy is used as a noninvasive alternative to liposuction for adipose tissue reduction [13, 14]. Laser therapy is approved in the United States and Canada for adipose tissue reduction [39, 40].

For body sculpting, it is postulated that low-level laser therapy creates pores in adipose cell membranes through which lipids are released [13, 41]. Treatment may involve six to eight sessions lasting approximately 20–30 min [13, 14]. Modest reductions in waist circumference have been reported [13, 14].

In a randomized, placebo-controlled trial of 67 patients [14], six laser treatments over a period of 2 weeks were associated with a mean reduction of 2.6 cm in waist circumference versus baseline value. In a second randomized [13], placebo-controlled trial of 40 healthy men and women, laser therapy administered twice weekly for 4 weeks resulted in a 0.87-cm reduction in waist circumference after eight treatments compared with an increase of 0.47 cm in the placebo group, but this difference was not statistically significant. The fat released from treated adipocytes appears to be released into the blood stream and therefore has the potential to affect the lipid profile adversely, but this has not been investigated.

Injection Lipolysis

Injection lipolysis is a term applied to various unregulated therapies that involve chemicals injected into the mesoderm (subcutaneous tissues) supposedly to promote adipose tissue reduction (Table 1) [10]. Injection lipolysis can involve 3–15 treatment sessions consisting of 8–300 injections [42] with a 4- to 6-mm needle [43]. Treatment is performed on an outpatient basis using a topical or injected anesthetic such as lidocaine [44].

Typically, injection lipolysis consists of phosphatidylcholine combined with the detergent solvent, deoxycholic acid [10]. Phosphatidylcholine is a naturally occurring glycerophospholipid involved in the metabolism of fat and the maintenance of cell wall integrity [42]. The mechanism of action of phosphatidylcholine and deoxycholate has not been identified conclusively, but it has been suggested that both agents may destroy the adipocyte cell membrane, with phosphatidylcholine facilitating the metabolism of the lipids released from the disrupted cells [45].

The efficacy of injection lipolysis for body sculpting has not been demonstrated, and clinical studies published to date are typically of poor quality [15, 46]. Moreover, no standardized methods exist for injection lipolysis, leaving clinicians to experiment with their own preferred combinations of chemicals [15, 46]. Treatment has been associated with hematoma, allergic reactions, urticaria, necrosis, scarring, cutaneous granulomas, folliculitis, infection, ulcerations, and panniculitis [10, 15, 47]. Published data demonstrate that injection lipolysis is associated with long-term inflammation in deeper tissue layers [44].

Given the risks of adverse events (AEs) with injection lipolysis and the lack of clinical standards, the FDA has issued a warning letter about the use of phosphatidylcholine injections. In addition, the American Society for Aesthetic Plastic Surgery has released a statement suggesting that efficacy has not been established and that the treatment may in fact be dangerous [46].

Ultrasound for Noninvasive Body Sculpting

General Principles Ultrasound can lyse adipocytes through mechanical and thermal mechanisms. A review of ultrasound technology will facilitate an understanding of these two mechanisms of action for body sculpting.

Ultrasound is a mechanical compression wave with a frequency above the range of human hearing (>20 kHz) [48]. Ultrasonic waves are characterized by intensity, expressed in W/cm^2, and frequency, expressed as kilohertz (kHz) or megahertz (MHz) in medical applications [49]. When ultrasonic waves penetrate and travel through tissue, they lose energy as they are reflected, scattered, or absorbed by the tissues they encounter [48].

Together, these mechanisms account for the observed attenuation of the forward-propagating ultrasonic wave. With increasing frequency, ultrasonic waves become increasingly attenuated, resulting in less depth of penetration. For example, ultrasound transmitted with a frequency of 2 MHz will lose 50% of its power by the time it travels 3 cm through human tissue, whereas ultrasound transmitted at 200 kHz will lose 50% of its power only after traveling 30 cm [48].

Sufficient quantities of absorbed energy create molecular vibrations in body tissues, generating heat [49]. At lower frequencies, ultrasound can easily cause cavitation, creating holes (cavities) when the ultrasound wave has sufficient negative pressure to overcome the adhesion of the medium molecules to each other [50]. This phenomenon (bubble creation) can be easily observed in water behind a boat's rotating propeller blades. In stable cavitation, existing bubbles grow in the presence of ultrasonic waves and eventually collapse or break up. In inertial cavitation, if the intensity of the ultrasound is high enough, large bubbles are created quickly, and these bubbles then rupture violently. The mechanical effects of both types of cavitation can create lesions that are irregular, unpredictable, and perhaps harmful.

Diagnostic Versus Therapeutic Ultrasound Diagnostic ultrasound typically generates waves of low intensity (range 0.1–20 W/cm^2) [48] and high frequency (range 1–20 MHz) [51]. Diagnostic ultrasound systems capture backscattered (reflected) energy from tissue interfaces to create an image of internal structures. The ultrasonic energy generally is focused to both transmit and receive to increase the resolution of the image. The very low intensities used in diagnostic ultrasound have no effect on tissues, generating virtually no heat or cavitation.

Ultrasound used for physical therapy generates high-frequency (1–3 MHz), low-intensity (0.5–3 W/cm^2) ultrasonic waves [52]. Within this frequency range, therapeutic ultrasound can be delivered into shallow or deep tissues, depending on the frequency selected. Only mild warming is generated given the low intensity of the beam. Therapeutic ultrasound for the treatment of musculoskeletal and other injuries has shown modest benefits in clinical practice [52], although clinical trial data are inconclusive [53].

Low-Intensity/Low-Frequency Nonthermal Ultrasound for Body Sculpting

Ultrasound used for body sculpting can be divided into two broad categories: relatively low-intensity/low-frequency nonthermal ultrasound and HIFU. With nonthermal ultrasound, a low frequency is chosen to increase the likelihood of cavitation while generating little heat through absorption mechanisms. The ultrasound can be highly focused to confine the cavitation effects to the focal zone of the ultrasonic beam.

Low-intensity nonthermal (mechanical) ultrasound is approved by Health Canada and is under FDA review for circumference reduction of the waist, hips, and thighs [54] (Table 1). Because this technology does not work primarily through heating, it may not be advantageous for patients in need of skin tightening. Nonthermal ultrasound may be appropriate for nonobese patients (body mass index $\leq$ 30) with focal adiposity [16].

Nonthermal focused ultrasound applied for body sculpting uses mechanical stress generated from inertial cavitation to disrupt adipose tissue. The focal volume of this nonthermal ultrasound device instrument is claimed to be 0.625 cm^3 so that 1,000 spaced pulses treat 625 cm^3.

Nonthermal ultrasound devices include a transducer and an external guidance system to direct a focused beam of ultrasound energy [17]. The ultrasound energy is delivered in pulse waves at a low frequency (200 kHz) and a low intensity (17.5 W/cm^2), creating repeated compressions and rarefactions in target tissues [16–18, 55, 56]. Rarefactions in the target tissue generate cavitation events, causing cell death due to mechanical cell disruption.

Although nonthermal ultrasound is designed to disrupt tissue in only a narrowly defined target zone, cavitation generally is less predictable and harder to control than the thermal effects of ultrasound delivered at higher frequency and energy levels [56]. In clinical trials, a single treatment reduced mean waist circumference by 1.3–2.5 cm [16–18]. Three treatments reduced waist circumference by 2.3–3.5 cm [16, 17].

HIFU

Used for body sculpting, HIFU delivers focused, high-intensity ultrasonic energy to deep subcutaneous tissue, producing heat capable of ablating adipose tissue and thermally modifying collagen [33] (Table 1). It seems intuitive that the rate of heating should be proportional to the intensity and frequency of the ultrasound, with higher frequency and intensity resulting in more rapid heating in the focal zone. In reality, high intensities in the HIFU focal zone result in nonlinear effects in the ultrasonic beam that multiply the already high heating rate several-fold. This results in much shorter treatment times than those calculated using linear intensity levels. Exposure of adipocytes to a temperature of 56°C or higher for 1 s is adequate to cause rapid cell death by coagulative necrosis [50, 56].

For body sculpting, thermal HIFU focuses energy adequate for ablation of targeted adipose tissue using ultrasonic waves at a frequency of 2 MHz and an intensity exceeding 1,000 W/cm^2. Findings have identified 2 MHz as the optimal HIFU frequency, which is capable of disrupting adipocytes and contracting collagen fibers to tighten skin [57].

Benefits of Focusing A high degree of focusing allows ultrasonic energy to pass through the skin and intervening tissue layers above the focal zone at an intensity low enough not to cause undue heating in them. The high intensity in the focal zone, enhanced by nonlinear effects, results in a high heating rate and coagulative necrosis if treatment parameters are chosen properly. High intensity in the focal zone also causes nonlinear effects in the ultrasonic beam that enhances the already high heating rate, resulting in much faster treatment times.

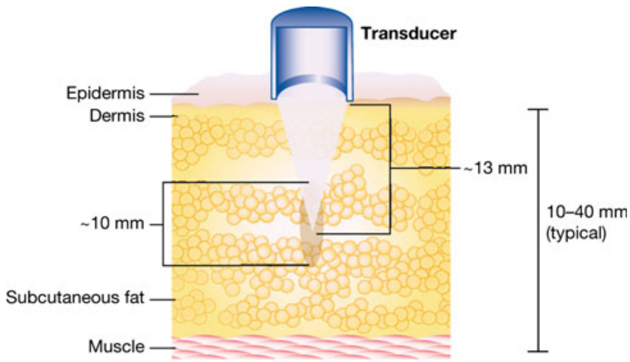

Fig. 1 High-intensity focused ultrasound (HIFU) beam passing through the skin and superficial tissues without causing injury. The temperature at the focal point causes rapid cell death, but tissues immediately above and below the focal point are unharmed

High-frequency waves with approximately 1-mm wavelengths make it easy to focus the ultrasonic beam, with a small transducer focused either internally or with a separate lens [49]. At 2 MHz, a tightly focused HIFU beam creates a lesion in adipose tissue about 1 mm in diameter and 10 mm in length [48]. High frequency also maximizes absorption while minimizing tissue penetration [49].

In contrast, radiofrequency and microwave radiation capable of penetrating deeply into tissue cannot be easily focused because of the resultant long wavelengths and very large radiating antennas required. External lasers can be focused easily, but absorption of light energy severely limits the depth of penetration. Ultrasound is unique in that the penetration depth can be freely selected with the choice of frequency, and precise focusing can be easily achieved with a small handheld transducer. The ability of HIFU to be focused in tissues near the skin surface with minimal penetration contributes to its safety [49, 58].

The ultrasonic energy used by the LipoSonix system (Medicis Technologies Corporation, Scottsdale, AZ, USA) is generated by an internally focused transducer, which focuses the ultrasonic waves so they converge at a specified depth and location [49] (Fig. 1). The system includes a pattern generator to ensure that the HIFU waves are directed evenly and at a predetermined depth within the treatment area [20].

Because the waves are diffuse as they leave the transducer, they do not generate sufficient fluence to damage skin, nerves, blood vessels, or organs encountered before or beyond the focal point. High-intensity focused ultrasound energy can easily reach intensities greater than 1,000 W/cm^2 at the focal point while remaining at only 1–3 W/cm^2 at the skin surface. Thus, heat sufficient for ablation of adipose tissue is generated only at the point where the focused beams converge, combining their energy [49]. This ensures that tissue lysis will be confined to the treatment zone [58, 59].

Tissue Effects of Thermal HIFU With surgical lipoplasty, excess adipose tissue is physically removed from the body. Preclinical and pilot clinical studies of a HIFU system have characterized the effects of treatment on fat and surrounding tissues [60–64]. It is evident from these studies that the lipids contained in adipocytes ablated by HIFU and residual cellular debris are safely ingested by tissue macrophages in a mild local inflammatory response, do not become liberated systemically, do not raise serum lipid levels or alter the lipid profile, and do not provoke prolonged or diffuse inflammation.

Pilot studies have involved the use of HIFU to ablate abdominal adipose tissue in human subjects before they undergo elective abdominoplasty [60–62, 64]. The volume of treated adipose tissue has ranged from 25 to 225 ml. Tissues excised during abdominoplasty have been studied for histologic changes in adipose tissue. After treatment, diagnostic ultrasound have shown discrete and well-defined treatment zones, with changes restricted to the target layer of adipose tissue and no injury to tissue above or below the treatment area [60–62, 64]. Gross pathology (Fig. 2), computed tomography, and magnetic resonance imaging have confirmed discrete areas of coagulative necrosis of the adipose tissue at the focal point and no damage to skin, surrounding tissues (rectus muscle, dermis, fascia), or organs [60–62, 64].

Histologic examination has shown well-demarcated adipocyte disruption [60–62, 64]. Adipocytes have exhibited pyknotic nuclei and loss of architecture. The presence of vacuoles in extracellular material has been observed. At the site of the HIFU-induced lesion, histology has shown minimal inflammatory response with recruitment of scavenger macrophages and little expression of neutrophils, plasma cells, or lymphocytes [60, 62]. Phagocytosis of extracellular released lipids has been observed 14–28 days after treatment.

Histology at 7 days has shown a minimal inflammatory response consisting of macrophages (Fig. 3). Week 4 histology has shown scavenger macrophages with abundant foamy cytoplasm in the treatment zone (Fig. 4). Week 8 histology has shown 75% reabsorption of extracellular lipids within the tissue of the treated zones and collapse of surrounding fibrovascular stoma [60, 62]. Typically, the majority of the treatment zone has been reabsorbed within 8–12 weeks (Fig. 5), and 95% resolution of the treatment site has been observed by 18 weeks [60, 62].

In addition to local adipocyte necrosis, evidence of collagen remodeling from the thermal effects of HIFU has been observed [19]. Depending on the frequency, the application of heat using HIFU causes collagen fibers to denature, thicken, and shorten in the subcutaneous fat layer [57]. Application of HIFU at a frequency of 1 MHz to adipose tissue leaves collagen fibers intact, but at a

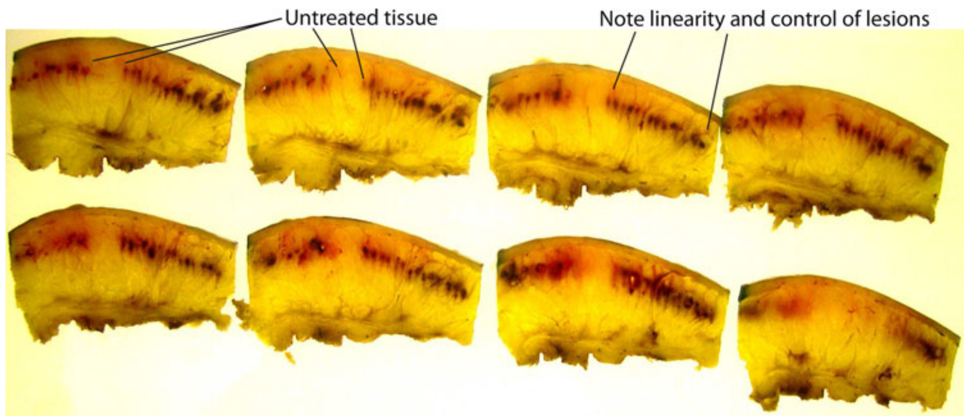

Fig. 2 Gross examination showing the clear demarcation of treated versus untreated tissue

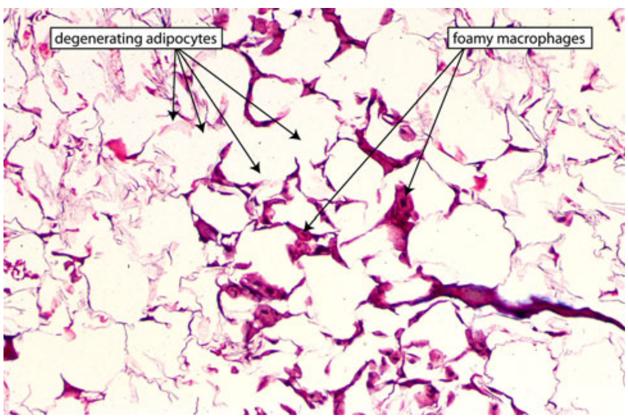

Fig. 3 Histology at 1 week (magnification ×100) showing adipocyte disruption with an influx of macrophages

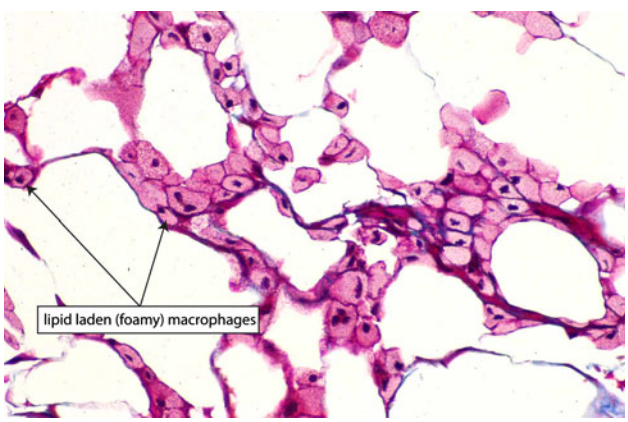

Fig. 4 Histology at 1 month (magnification ×200) showing influx of lipid laden (foamy) macrophages that have engulfed the degenerated adipocytes

frequency of 2–3 MHz, diffuse contraction of collagen fibers has been observed. Histology performed after the procedure has confirmed that HIFU disrupts or denatures collagen fibers, resulting in new collagen formation accompanied by a general tightening of the septal fibers and skin [19]. The dual tissue response represents an

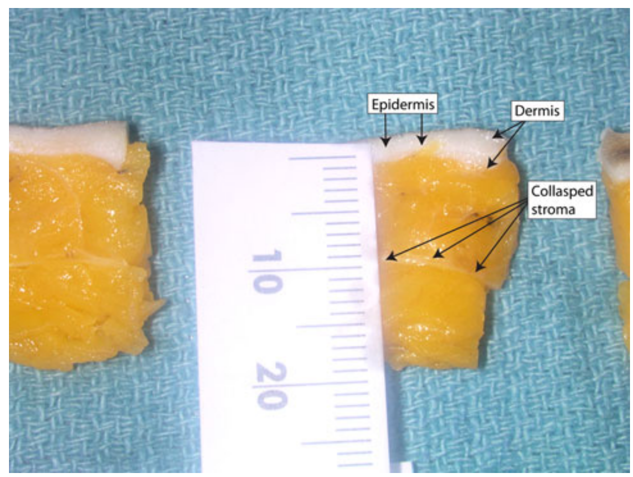

Fig. 5 Gross examination at 4 months showing uneventful healing with minimal fibrosis in the treatment zone and no damage to surrounding tissues

important difference in mechanism of action between HIFU and nonthermal mechanical ultrasound.

Evidence of HIFU Safety High-intensity focused ultrasound has demonstrated safety in several medical indications, including those requiring much higher HIFU energy levels than required for body sculpting. Currently, HIFU is used safely in several noncancer medical applications, including the dissolution of kidney stones [65, 66] and the ablation of epicardial tissue to correct arrhythmias [67, 68]. In addition, HIFU has been used safely for the destruction of benign uterine fibroid tumors at energy levels up to tenfold greater than those used for body sculpting [69–71]. In 12 patients, HIFU at 3,200–6,400 W/cm^2 ablated uterine fibroids with no adverse effects on surrounding tissues [70]. The only AE was limited to mild (first-degree) burns at the application site in a single patient.

In the treatment of malignant tumors, HIFU administered at even higher energy levels (5,000–20,000 W/cm^2) than those used for uterine fibroids has shown a good safety profile, as seen in studies of HIFU for cancer [72–74]. As with body sculpting, treatment effects have been limited to the target zone, with no damage to adjacent organs. In 1,038 patients with solid tumors, HIFU induced a necrotic lesion at the treatment site without damaging surrounding tissues. No thermal lesions in intervening areas were observed.

Histologic examination showed coagulative necrosis at the tumor site, with no damage to surrounding tissues. Blood vessels supplying tumors were destroyed but not surrounding blood vessels. Adverse events were reported in 5–10% of patients, mostly due to the patients' malignancies. Tumor bleeding and large blood vessel rupture did not occur. Four patients with bone cancer had nerve fiber damage, which resolved completely in two patients and partially in two patients. It is important to remember that HIFU does not produce ionizing radiation.

At the lower energy levels used for body sculpting, AEs associated with thermal HIFU generally have been mild and self-limiting. In two retrospective chart reviews of 387 patients, less than 15% of the patients in each series reported one or more AEs, which included significant pain during the procedure, prolonged tenderness, ecchymosis, lumps, and edema [19, 20]. None of these events were serious, and procedural pain resolved immediately at completion of treatment. Tenderness, lumps, and ecchymosis all resolved within 4–12 weeks.

In pilot studies, release of fat from adipocytes has not been accompanied by changes in lipid profile, including free fatty acids, total cholesterol, low-density lipoprotein, very-low-density lipoprotein, high-density lipoprotein, and triglycerides [60, 61, 63]. Similarly, no changes in a comprehensive metabolic panel, amylase, lipase, or blood count have occurred [60] and no evidence of dystrophic calcification, inflammatory fat necrosis, abscess, or fistulas [60, 61, 64]. As in the case series, AEs have included mild and transient occurrences of ecchymosis, discomfort during and after the procedure, edema, dysesthesias, and erythema.

The pivotal U.S. trial of HIFU submitted to the FDA for review is awaiting publication [75]. The trial randomized 180 patients to receive a single treatment with HIFU administered in three passes at either of two energy levels or as sham treatment. The primary outcome measure was a change from baseline waist circumference at 12 weeks. Secondary end points included two subjective measures: a patient satisfaction survey and a physician-rated global aesthetic improvement scale. Patient discomfort during and after the treatment and AEs throughout the 12-week study period were monitored.

Clinical Considerations With HIFU The LipoSonix system has been approved for use in Canada, has the Conformité Européene mark within the European Union, and currently is under FDA review [76]. The system has been used for ablation of adipose tissue in the abdomen, waist, hips, outer and inner thighs, and buttocks, and in male breast hypertrophy [19, 20]. Patients receiving HIFU should have a body mass index less than 30 kg/m^2 and an adipose tissue depth at least 1 cm beyond the focal point at the intended treatment site [20]. The procedure typically involves two or three passes over the treatment area, with each pass taking 15 to 20 min, for a total treatment time of 45 min to 1 h [20, 48].

The clinical response typically is evident within 2 weeks and complete within 3 months [19, 20]. In two published retrospective chart reviews, 367 patients who received a single HIFU treatment to the abdomen and flanks had mean reductions in waist circumference ranging from of 4.2 to 4.7 cm 12 weeks after the procedure [19, 20]. Typical postprocedure effects included mild to moderate discomfort, ecchymosis, and edema [19, 20]. These effects generally were mild and transient.

Summary

Patients wishing to reduce abdominal adipose tissue desire noninvasive alternatives to liposuction, which is a minimally invasive surgical option compared with excisional body sculpting but nonetheless carries its own risks of AEs. Tumescent liposuction is emerging as the standard-of-care liposuction technique because of less blood loss and pain compared with dry liposuction. Nonetheless, tumescent liposuction, although generally considered safe, has been associated with significant complications, including death. Laser-assisted liposuction may slightly enhance tightening of skin overlying areas from which fat is removed but may cause skin burns, thermal damage to deeper tissue, and prolonged inflammation in treated tissues.

Noninvasive techniques such as radiofrequency ablation, cryolipolysis, injection lipolysis, external low-level lasers, injection lipolysis, laser ablation, nonthermal ultrasound, and HIFU may be particularly appropriate options for nonobese patients requiring modest to moderate body sculpting. Each of these treatments can be administered in an outpatient setting with little or no need for anesthesia or analgesia and typically result in fewer complications than liposuction. However, with the exception of HIFU, these procedures require multiple treatments to achieve meaningful results. Radiofrequency and laser therapy have significant potential for AEs, as does injection lipolysis, which is largely unregulated and may cause significant pain, hematoma, allergic reactions, necrosis, scarring, panniculitis, and rapid release of lipids into the bloodstream.

The safety of HIFU at much higher energy levels than those used for body sculpting has been demonstrated in patients treated for benign uterine fibroid tumors and solid malignancies. Early clinical trials of thermal HIFU for body sculpting support its use in aesthetic medicine. The unique physics of thermal HIFU permit effective ablation of adipocytes and a thermal effect on collagen contained within the tissue matrix. The HIFU procedure does not rely on bulk heating of tissue to produce its effect on adipose tissue reduction and tightening. No serious AEs or alterations in lipid profiles or other laboratory parameters have been reported. Trials evaluating HIFU administered at different energy levels to multiple layers of adipose tissue are currently underway.

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