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Review article

Review of high-intensity focused ultrasound for lipolysis: clinical and preclinical studies

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High-intensity focused ultrasound (HIFU) is an increasingly popular treatment modality that is used for non-invasive body contouring. Several clinical studies have reported a significant reduction in subcutaneous adipose tissue after HIFU treatment, along with the histologic degradation of adipocytes and fat membranes. Similarly, preclinical studies have confirmed the safety and efficacy of HIFU and identified two mechanisms, namely heat-induced apoptosis and acoustic cavitation. Although the lipolytic effects of HIFU are well documented, insufficient research has been done on the metabolic changes caused by HIFU lipolysis yet. A recent meta-analysis of the outcome of non-invasive fat removal suggests that HIFU may positively lead to weight loss and wasit circumference reduction in the serum lipid profiles, potentially expanding its use from aesthetic to metabolic treatments. In conclusion, HIFU is emerging as an effective and safe tool for fat reduction via heat-induced apoptosis and acoustic cavitation and its use is expected to increase in body contouring. As more data emerges on its metabolic effects, HIFU may also find a place as adjunctive therapy for metabolic disorders.

Key words: Body contouring; High-intensity focused ultrasound; Lipolysis

INTRODUCTION

The removal of unwanted fat for body contouring has a long history. In 1921, the French surgeon Charles Dujarier performed a lipectomy using a uterine curette to remove fat from both the knees and calves of a ballerina but damaged the femoral artery and had to amputate a leg. Since then, new liposuction techniques have been developed and refined; however, these techniques are still invasive and have been reported to have some side effects such as hematoma, seroma, and scarring [1,2].

Several non-invasive body sculpting techniques have been used to address existing issues, such as radiofrequency, cryolipolysis, laser, and high-intensity focused ultrasound (HIFU) [3].

Ultrasound devices have been proposed for lipolysis; however, the clinical efficacy of external devices has not been confirmed. In 2005, a non-thermal-based device, the Contour I device (UltraShape Ltd.), received CE mark approval, which showed significant improvements in circumference and skin fat thickness for 12 weeks after a single treatment on the abdomen and thighs in 2007. This was achieved by delivering acoustic energy to disrupt fat tissue without causing an increase in temperature [4,5].

HIFU can increase the temperature of a selected, isolated tissue volume to at least 55°C and maintain this temperature for at least 1 second, which is known to lead to coagulative necrosis and immediate cell death. HIFU

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Table 1. Characteristics of HIFU lipolysis clinical studies

Reference	Equipment	Sample size, n (mean age, yr)	Treatment area	Protocol and parameters	Clinical outcomes	Adverse events
Fatemi, 2009 [7]	LipoSonix	282 (41.3)	Anterior abdomen and flanks	Mean energy dose 137 J/cm^2 divided in 2 passes, 2 different focal depths	CBWC decreased by an average of 4.7 cm after 1 treatment after 3 months	Temporary adverse events reported in 38 (13.5%) patients: pain during treatment, prolonged tenderness, edema, hard lumps, ecchymosis
Gadsden et al., 2011 [8]	Investigational HIFU Device	152 (36)	Study 1: abdomen (scheduled to be removed by abdominoplasty) Study 2 and 3: anterior abdomen	166-210 J/cm^2 (single pass), 59-74 J/cm^2 (two passes), or 47 J/cm^2 (three passes), total HIFU energy doses of 47-331 J/cm^2, 2 MHz frequency, focal depth of 1.1-1.8 cm	Well-demarcated disruption of adipocytes within the targeted SAT in histopathology Phagocytosis occurred after 14-28 days and healing process was 95% complete after eight to 14 weeks	Total 703 adverse events reported: temporary treatment discomfort, edema, erythema, dysesthesia, and ecchymosis Greater incidence in higher energy levels No changes in clinical laboratory parameters
Robinson et al., 2014 [9]	Liposonix (Model 2)	118 (45.2)	Abdomen, or abdomen and flanks	1: 30 J/cm^2, GR, 5 passes 2: 30 J/cm^2, GR, 6 passes 3: 30 J/cm^2, SR, 5 passes 4: 60 J/cm^2, GR, 3 passes 5: 60 J/cm^2, SR, 3 passes (total fluence 150-180 J/cm^2)	Primary endpoint: 2.3 ± 2.9 cm ($p < 0.0001$) reduction of CBWC at 12 weeks, significant differences between treatment groups Secondary endpoint: significant CBWC reduction starting as early as 4 weeks in all groups (−1.1 ± 1.9 cm, $p < 0.0001$)	Pain scores were significantly higher with the 60 J/cm^2 groups vs. the 30 J/cm^2 treatment groups ($p < 0.01$)
Lee et al., 2016 [10]	LIPOcel	3 (33)	Abdomen and flanks	2 stacking passes of 95-130 J/cm^2	1.5-5.0 cm reduction in CBWC, and postoperative fat reduction (87.89-140.99 cm^3) measured by computed tomography after 4 weeks	Not mentioned
Fonseca et al., 2018 [11]	Sonofocus	Total 31, G1: 7 (41) G2: 23 (34)	Abdomen	G1: 6 sessions, 3 passes, once a week G2: 10 sessions, 2 passes, twice a week	Improvement in body contouring and reduction of the thickness of the fat layer observed by sonography in both groups in 15 days after the final treatment: G1 ($p < 0.001$), G2 ($p < 0.0001$)	Only mild discomfort in treatment area
Hong et al., 2020 [12]	SCIZER	20 (35.80)	Abdomen	150 J/cm^2 divided to 3 passes, 2 MHz, focal depth 13 mm, treatment was repeated at week 4 with 135 J/cm^2	Reduction of 3.43 cm in mean CBWC at week 8	No notable clinical and laboratory findings
Kwon et al., 2021 [13]	Shurink/ Ultraformer	40 (40.5)	Submental area	80 lines of 6.0 mm probe at an energy setting of 0.8-1.0 J, 60 lines of 4.5 mm probe at 0.5-0.7 J, and 3.0 mm probe at 0.3-0.5 J	Treatment responders ≥ 1-point improvement in CR-SMFRS: 62.5%, satisfied patients (score ≥ 4 on the SSRS): 67.5% at post-treatment week 8	Only mild and transient side effects were observed

HIFU, high-intensity focused ultrasound; CBWC, change from baseline in waist circumference; SAT, subcutaneous adipose tissue; GR, grid repeat; SR, site repeat; CR-SMFRS, 5-point Clinician-Reported Submental Fat Rating Scale; SSRS, Subject Self-Rating Scale.

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can destroy adipose tissue through thermal stimulation as well as acoustic energy; however, due to technical problems, there have been concerns about side effects such as tissue necrosis in unwanted areas [6]. Nevertheless, HIFU lipolysis has been reported to be effective and safe for body contouring and is currently one of the most widely used techniques.

For lipolysis with HIFU, clinical studies were mainly conducted before theoretical studies. Therefore, this article will review the relevant clinical and preclinical studies accordingly.

CLINICAL STUDIES

In 2009, 282 patients underwent anterior abdominal and flank HIFU treatment with LipoSonix (Medicis Technologies Corporation) and showed a mean waist circumference reduction of 4.7 cm and the histologically confirmed collapse of adipocytes and membranes at 3 months [7].

In a 2011 study involving 152 patients treated with an investigational HIFU device, phagocytosis of fat and cell debris occurred after approximately 2 to 4 weeks, with 95% recovery within 14 weeks. The incidence of adverse events was generally higher at higher energy levels; nevertheless, sufficient improvement was observed at relatively low energy levels [8].

Robinson et al. [9] also reported no significant difference in effectiveness between low and high fluences when the total fluence was set at 150 to 180 J/cm^2 and the treatment passes were divided into 3 to 6 passes per group; however, pain was greater at high fluences. There was no difference in efficacy between the grid repeat (treating each site sequentially once and repeating multiple times) and site repeat (treating all passes at one site and then treating another site) methods; thus, it seems there may be no significant difference when performing multiple passes. Lee et al. [10] showed that combining HIFU with a cooling system could reduce side effects while using a high fluence setting.

In addition, studies have consistently reported that various HIFU devices are effective for subcutaneous fat reduction in various areas, including the submental area [11-13]. The above studies are summarised in Table 1.

PRECLINICAL STUDIES

In a study using a porcine model conducted by Jewell et al. [14], 166 to 372 J/cm^2 HIFU treatment of the abdomen resulted in a transient temperature increase of up to 70°C in the focal zone after 1-2 seconds, and only a non-lethal increase was observed in the surrounding zone. In addition, gross and histopathologic examination showed that the arterioles, nerves, etc. in the treatment zone were intact. Disrupted adipocytes including lipids and cell debris were removed by macrophages, and the treated lesions healed normally. In another study with a porcine model, Lee et al. [10] observed a significant reduction in ecchymosis with simultaneous contact cooling, with lipolysis also occurring in the adipose tissue.

In HIFU, acoustic beam patterns measured with the Acoustic Intensity Measurement System (AIMS III; Onda) showed similar round to oval thermal injury zones (TIZs) formed in the elliptical zone and cadaveric skin. TIZs became larger with repeated sessions, and larger columnar TIZs were observed to form under saline infusion conditions that mimicked tumescent infiltration conditions. This may be of interest if greater effects are desired in the treatment of humans [15].

Tan et al. [16] suggested a combination therapy for the rapid removal of subcutaneous fat based on different mechanisms, which can accelerate the metabolism of HIFU-destroyed fat by supplying energy to muscles via electrical stimulation. The acoustic cavitation effect of HIFU treatment was confirmed using ex vivo porcine tissue in another study [17]. In mouse pre-adipocytes, HIFU led to the increased expression of nuclear and mitochondrial p53, apoptotic signals (BAX/BAK), and autophagy (ATG5, BECN1, and LC3II/LC3I) and the decreased expression of antiapoptotic signals (BCL2/BCL-xL) [18]. The above studies are summarised in Table 2.

DISCUSSION

HIFU disrupts subcutaneous adipose tissue noninvasively via heat-induced tissue necrosis and physical acoustic cavitation [17,18]. It has been reported that non-thermal focused ultrasound can also effectively remove subcutaneous fat. Although no direct comparison of the efficacy between HIFU and non-thermal focused ultrasound has been reported, future studies would likely focus on HIFU as more HIFU devices are introduced, and studies would be conducted based on the dual mechanism of HIFU.

Although the lipolytic effects of HIFU have been well reported, there is a lack of research on overall metabolic changes [19]. A meta-analysis of metabolic changes with non-surgical fat removal including HIFU conducted by Badran et al. [20] found that 2 units of body mass index, 1 kg of body weight, 5 cm of waist circumference, and 1.5

cm of abdominal fat thickness were maintained up to 60 days after treatment. Transient increases in total cholesterol, low-density lipoprotein, and triglycerides were observed after 2 weeks of treatment; however, significant differences were no longer observed thereafter. If HIFU alone can positively affect weight loss without significant changes in serum lipid profiles, it may be used as an adjunct to metabolic treatments rather than only aesthetic treatments in the future.

CONCLUSION

HIFU may be effective and safe for fat reduction through heat-induced apoptosis and acoustic cavitation. With further research on the metabolic system, it may be used not only for body contouring but also as an adjunctive treatment for metabolic disorder.

Table 2. Characteristics of HIFU lipolysis preclinical studies

Reference	Model	Equipment	Site	Main outcomes
Jewell et al., 2011 [14]	Porcine (Yorkshire breed)	Several different prototype devices	Ventral area	HIFU (166-372 J/cm^2) raised tissue temperature 70°C restricted to the focal area Application of 68 and 86 J/cm^2 did not produce clinically-significant changes in plasma lipids and liver function test Gross examination of tissue from various organs showed no evidence of fat emboli or accumulation and histology showed well-preserved vasculature and intact nerve fibers within the HIFU treatment area Treatment with 85.3-270 J/cm^2, normal healing response included the migration of macrophages into the damaged tissue and removal of disrupted cellular debris and lipids
Lee et al., 2016 [10]	Porcine	LIPOcel	Dorsal area	Left side was treated with contact cooling, and right side was treated without the cooling system (60-300 J/cm^2) Ecchymosis was observed on the non-cooled area immediately after HIFU treatment, but not on the cooled area Histologically the cooled and non-cooled areas were identical, with liphophagic histiocytes observed at week 4 and lipodystrophy with resolution of inflammation at week 12
Lee et al., 2017 [15]	Cadaver	LIPOcel	Abdomen and thigh	HIFU acoustic beam pattern formed an ellipsoid zone at the depth of 38 mm (2 mm × 19 mm, measured by AIMS III) HIFU treatment at a penetration depth of 13 mm generates round to oval ablative TIZs in the subcutaneous fat layer of abdomen and thigh skin Repetitive HIFU pulses created larger and more remarkable ablative zones Saline infusion facilitated the creation of larger oval or columnar HIFU-induced TIZs
Tan et al., 2020 [16]	Porcine	Self-developed HIFU applicator	Abdomen	4 Groups: sham, HIFU only, HIFU plus electrical stimulation I, and HIFU plus electrical stimulation II Waist circumferences decreased in HIFU plus electrical stimulation I and II groups, whereas they increased for the sham and HIFU-only groups
Filippou and Damianou, 2022 [17]	Porcine	HIFU with custom-made concave transducer	Ex vivo porcine adipose tissue	Formation of cavitation in porcine tissue
Byun et al., 2023 [18]	Rat (Sprague-Dawley)	LinearZ	Dorsal area, mouse pre-adipocyte	The dorsal subcutaneous adipose tissue thickness in the HFD/HIFU group at was significantly lower than that of the HFD only group Apoptotic signal and autophagy increased and anti-apoptotic signal decreased by p53 activation in mouse pre-adipocyte

HIFU, high-intensity focused ultrasound; AIMS, Acoustic Intensity Measurement System; TIZs, thermal injury zones, HFD, high fat diet.

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AUTHOR CONTRIBUTIONS

Conceptualization: KHY. Data curation: YGK. Investigation: KRK. Methodology: YHL. Project administration: HSH. Writing–original draft: YGK. Writing–review & editing: all authors.

CONFLICT OF INTEREST

Kwang Ho Yoo is the Editor-in-Chief, Hye Sung Han is an editorial board member of the journal, but they were not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

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