

# Cryolipolysis for Reduction of Excess Adipose Tissue

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Controlled cold exposure has long been reported to be a cause of panniculitis in cases such as popsicle panniculitis. Cryolipolysis is a new technology that uses cold exposure, or energy extraction, to result in localized panniculitis and modulation of fat. Presently, the Zeltiq cryolipolysis device is FDA cleared for skin cooling, as well as various other indications, but not for lipolysis. There is, however, a pending premarket notification for noninvasive fat layer reduction. Initial animal and human studies have demonstrated significant reductions in the superficial fat layer thickness, ranging from 20% to 80%, following a single cryolipolysis treatment. The decrease in fat thickness occurs gradually over the first 3 months following treatment, and is most pronounced in patients with limited, discrete fat bulges. Erythema of the skin, bruising, and temporary numbness at the treatment site are commonly observed following treatment with the device, though these effects largely resolve in approximately 1 week. To date, there have been no reports of scarring, ulceration, or alterations in blood lipid or liver function profiles. Cryolipolysis is a new, noninvasive treatment option that may be of benefit in the treatment of excess adipose tissue.

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Fat treatment and removal is a worldwide, billion-dollar cosmetic industry, and liposuction remains the most common surgical cosmetic procedure performed in the United States.<sup>1</sup> Although liposuction is an effective therapeutic option for the removal of fat and can be safely performed on an outpatient basis, it remains an invasive procedure. In recent years, there has been a dramatic trend toward effective, noninvasive procedures. Unfortunately, current noninvasive fat treatments such as Endermologie (LPG Systems, Valence, France), radiofrequency treatment, and lasers have resulted in only modest clinical improvements in the appearance of fat and cellulite.<sup>2-8</sup> There is, therefore, a great demand and need for an effective, selective, and noninvasive treatment option for excess adipose tissue.

Cryolipolysis is based on clinical observations that cold exposure, under the proper circumstances, can result in localized panniculitis; this panniculitis ultimately results in the reduction and clearance of adipose tissue. Cold-induced panniculitis was initially described in infants, where it is frequently known as popsicle panniculitis.<sup>9,10</sup> However, it has also been observed in adult patients; for example, panniculitis occurring after horseback riding in cold environments is known as equestrian panniculitis.<sup>11</sup> Exogenous application of cold, particularly with aggressive cryosurgery, is known to cause epidermal damage as well as damage to the underlying adipose tissue.

Cryolipolysis attempts to use controlled fat cooling, also known as energy extraction, to cause localized panniculitis and fat reduction. By controlling and modulating the cold exposure, it could be possible to selectively damage the adipocytes, while avoiding damage to the overlying epidermis and dermis. This would result in an effective, localized, and noninvasive treatment for excess adipose tissue.

## Proposed Pathogenesis

The exact pathogenesis by which cold results in adipose tissue removal is unknown. Case reports of infants suffering from popsicle panniculitis and adults with equestrian panniculitis demonstrate that a perivascular inflammatory infil-

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trate consisting of histiocytes and lymphocytes develops approximately 24 hours after cold exposure. The inflammatory infiltrate results in a lobular panniculitis. The inflammatory cells cause a rupture of the adipocytes, aggregation of the lipids, and the formation of small cystic spaces. This panniculitis slowly resolves over the next several weeks, ultimately resulting in modulation of the fat without any persistent tissue damage or scarring.

A similar mechanism of action has been proposed for cryolipolysis. In animal models, cold exposure results in inflammation, damage to the fat cells, and ultimately phagocytosis of the adipocytes.<sup>12</sup> Immediately after the treatment, no fat damage is observed and the adipocytes are intact. Initial adipocyte damage is noted histologically at day 2, and increases throughout the next month. It is believed that adipocyte apoptosis stimulates the initial inflammatory infiltrate, though the exact mechanism is not fully characterized; pig adipocytes in culture undergo apoptosis and necrosis following exposure to cool temperatures.<sup>13</sup> At day 2 after treatment, pig biopsy samples demonstrate localized subcutaneous mixed inflammation, consisting of neutrophils and mononuclear cells, and the adipocytes remain unchanged. Over the next week, the infiltrate becomes denser and an intense lobular panniculitis develops. The inflammation appears to peak at approximately 14 days following treatment when the adipocytes are surrounded by histiocytes, neutrophils, lymphocytes, and other mononuclear cells. During 14-30 days, the inflammatory infiltrate becomes more monocytic, consistent with a phagocytic process. Macrophages begin to envelop and digest the apoptotic adipocytes, thereby facilitating their elimination from the body. As this process occurs, the average size of the adipocytes decrease, a wider range of adipocyte sizes are observed, and the fibrous septae of the fat layer become widened. The actual elimination of the adipocytes from the body occurs slowly over at least the next 90 days. The exact mechanism and pathway by which the phagocytosed adipocytes are eliminated from the body are not fully understood at present. Ultimately, the lobules of fat cells decrease in size, and the fibrous septae constitute a majority of the volume of the subcutaneous layer. Clinically, this corresponds to a decrease in the thickness of the subcutaneous fat layer.<sup>12,14</sup>

These initial animal studies have helped to shape the likely mechanism of cryolipolysis. However, it should be stressed that the exact mechanism has not been fully elucidated. It is unclear why adipocytes are more sensitive to cold temperature than other cell lines. It is also not fully established why adipocyte apoptosis occurs and how this leads to the observed inflammatory infiltrate. Finally, once the adipocytes are phagocytosed and mobilized, the full mechanism of elimination is not well characterized. The adipocytes are thought to be mobilized via the lymphatic system, but it remains to be determined how they are then eliminated or redistributed throughout the body in response to cryolipolysis. As the technology continues to be developed, future studies will need to further investigate these issues.

## Clinical Animal Studies

Manstein et al<sup>12</sup> performed the initial exploratory studies of cryolipolysis in Yucatan pigs. In their article, they described the results of 3 different studies: an initial exploratory study, a dosimetry study, and a study of treatment effect on serum lipid levels.

The initial exploratory study used a cold copper applicator, chilled by circulating antifreeze solution. The cooling device was maintained at a constant temperature of  $-7^{\circ}\text{C}$ , and was applied to the Yucatan pig for times ranging from 5 to 21 minutes. The highest degree of clinical effect was noted in a treatment area on the buttock; 3.5 months after the single treatment, 80% of the superficial fat layer was removed (40% of total fat layer).

Following the demonstration of efficacy with the copper applicator, a prototype clinical device (Zeltiq Aesthetics Inc., Pleasanton, CA) was developed, which contained a thermoelectric cooling element. This device allowed for the use of variable, present plate temperatures during treatments; the cold temperature was maintained at a constant level via temperature sensors imbedded within the treatment plates. Treatments were performed with this device in either a "flat configuration" with a flat panel cooling the skin or in a "folded configuration" in which the excess tissue was pinched between 2 cooling panels, allowing for cooling on both sides of the tissue. The tissue was exposed to cold ranging from  $20^{\circ}\text{C}$  to  $-7^{\circ}\text{C}$  for 10 minutes. All sites treated with cold exposure less than  $-1^{\circ}\text{C}$  developed perivascular inflammation, panniculitis, and ultimately fat layer reduction. Fat damage was significantly greater at lower temperatures, and increased over time.

In Manstein's lipid study, no significant changes in the lipid profiles of the animals were noted immediately or at any time point through 3 months post treatment. There was a temporary decrease in serum triglycerides immediately following the cold exposures, though this was attributed to fasting before and during general anesthesia.

A follow-up animal study was performed by Zelickson et al.<sup>14</sup> In this study, 4 pigs were treated with the cryolipolysis device. Three animals underwent a single cryolipolysis treatment, while the fourth pig underwent 7 treatments (90, 60, 30, 14, 7, and 3 days, as well as 30 min before euthanasia) with the cryolipolysis device. About 25%-30% of the total body surface of each animal was treated. Ultrasound assessments demonstrated a 33% reduction in the thickness of the superficial fat layer following cryolipolysis. Pathologic specimens revealed an approximate reduction of 50% in the thickness of the superficial fat layer. Erythema lasting approximately 30 minutes developed in treatment areas. The skin became cool, though not frozen, after treatment. There was no edema, bruising, purpura, or scarring observed in the trial. Lipid panels were performed for each animal at multiple time points; the baseline profile was after a 12 hour fast before treatment, with follow-up lipid profiles performed 1 day, 1 week, and 1, 2, and 3 months after treatment. There were no significant variations in the lipid profiles of the animals throughout the study.

In the above animal studies, the cryolipolysis treatments were well tolerated by the animals. Erythema of the treated areas was common. In the initial animal studies by Manstein et al,<sup>12</sup> whitening, hardening, and freezing of the skin was noted in 30% of the treated areas. Superficial epidermal necrosis was observed in some of the frozen areas, with resulting transient hypopigmentation following re-epithelialization. However, no scarring or ulceration was noted in any of the animal studies.

## Human Clinical Studies

Following the promising animal studies, the Zeltiq System (Zeltiq Aesthetics Inc, Pleasanton, CA) was developed. This device consists of a control console, with a treatment applicator attached by a cable. A thermal coupling gel is placed on the area to be treated, and the applicator is then applied. Tissue is drawn into the cup-shaped applicator with a moderate vacuum to optimally positioning the tissue between 2 cooling panels; this allows for more efficient cooling of the tissue. A cooling intensity factor (CIF) is then selected by the treating clinician. The CIF is an index value representing the rate of heat flux into or out of tissue opposite the cooling device. Treatment with the cold exposure for up to 60 minutes then begins. The energy extraction rate, or cooling, is controlled by sensors that monitor the heat flux out of the treated areas and is modulated by thermoelectric cooling cells. Following completion of the treatment, the system automatically stops the cold exposure and the clinician releases the vacuum. Depending on the surface area to be treated, multiple applications may be necessary to effectively expose the entire area to cryolipolysis. It is important to note that the Zeltiq device is presently FDA cleared for skin cooling and

other various indications. However, the Zeltiq device is not currently FDA cleared for lipolysis, although there is a pending premarket notification for noninvasive fat layer reduction.

A multicenter, prospective, nonrandomized clinical study evaluating the use of cryolipolysis for fat layer reduction of the flanks (ie, love handles) and back (ie, back fat pads) was conducted at 12 sites.<sup>15</sup> Patients underwent cryolipolysis treatment to 1 area, while a symmetric, contralateral area was left untreated to serve as a control for observing clinical efficacy. An interim subgroup analysis of all patients in the “love handle” group, 32 patients, was performed. Clinical efficacy was determined at 4 months post-treatment using visual assessment with digital photography, physician assessment, and subject satisfaction. Most patients had a clinical improvement with a visible contour change, as assessed by physician observation and digital photography (Fig. 1). A subset of 10 patients underwent pre- and post-treatment ultrasound imaging. Of these 10 patients, all had a decrease in the thickness of their fat layer, with an average reduction in thickness of 22.4%. Importantly, regardless of the assessment protocol, the best cosmetic results were achieved in those patients with a modest, discrete fat bulge. The treatment was well tolerated by patients with no adverse events related to the device or treatment.

Kaminer et al,<sup>16</sup> demonstrated that cryolipolysis results in a visible cosmetic improvement in the flank/love handle region. A blinded comparison of preprocedure and 6 month postprocedure photographs was performed on 50 subjects. Three physicians specializing in dermatology, cosmetic surgery, or plastic surgery performed the photographic review. The physicians were able to accurately differentiate between the pre- and post-photographs in 89% of the cases. When the



**Figure 1** A representative example of clinical improvement following 1 treatment with cryolipolysis for fat layer reduction of the flanks (ie, love handles). The patient's left side was treated, while the right side served as an untreated control. The top pictures show the baseline, while the bottom pictures demonstrate the clinical improvement 4 months after treatment. The patient's weight on the baseline and 4 month follow-up day remained unchanged. This figure is obtained and used with permission of Flor Mayoral, MD.<sup>15</sup>

evaluation was limited to those subjects who maintained their original weight,  $\pm 5$  lb after the procedure, the physicians were able to accurately differentiate 92% of the cases. This study demonstrates that the improvement following cryolipolysis treatment is clinically apparent on visual inspection, further documenting the usefulness of this technology.

A feasibility study of using cryolipolysis to reduce abdominal fat is currently ongoing.<sup>17</sup> A total of 42 subjects were enrolled in this study. Symmetric abdominal fat bulges, typically to the left and right of the umbilicus, were treated with cryolipolysis. An interim analysis of the subjects' self-assessments indicated that 79% (31 of 39) subjects reported clinical improvement within the first 2-4 months after the procedure (Fig. 2). Further clinical end points, including blinded physician assessments and ultrasound measurements of fat layer thickness, have not been reported as of yet. The interim analysis appears to support that cryolipolysis may be effective for noninvasive contouring of abdominal fat and body sculpting.

Cryolipolysis seems to be an effective treatment option for the reduction of excess adipose tissue, as shown in these clinical studies. It is important to note that the clinical improvements were most pronounced in patients with localized, discrete fat bulges. The technology does not appear to be as effective in patients with significant skin laxity or who are obese. Thus, cryolipolysis is an effective treatment option for the reduction of fat, particularly when the proper patients are selected for treatment.

## Safety Profile

As with any new technology, it is important to establish whether the device results in any significant adverse events. In the previous clinical studies, the device has been well tolerated by the subjects. Patients typically develop erythema of the treatment area, lasting up to a few hours following cryolipolysis. As the device uses a vacuum to increase clinical efficacy, patients may also develop bruising of the treatment area, which may last approximately 1 week. The treated skin also becomes cold and firm following cryolipolysis. In all clinical studies to date, no ulceration or scarring has been reported.

Cryolipolysis has been reported by human subjects to result in a temporary dulling of sensation and numbness in treated areas. To better characterize this phenomenon, Coleman et al<sup>18</sup> performed cryolipolysis on 10 subjects with flank fat bulges. Following cryolipolysis, a 20.4% reduction in the thickness of the fat layer was observed, as assessed by ultrasound. Thus, the patients had achieved an effective cryolipolysis treatment. These subjects underwent neurologic assessment by a board-certified neurologist during the study, including light touch evaluated with a soft tissue, two-point discrimination, temperature sensitivity (cold temperature sense), and pain sensitivity (assessed with a pinprick). Neurologic assessments were performed at baseline and weekly following treatment. One subject underwent skin biopsy for histologic analysis of nerve-fibers. Patients reported numbness in 24 of the 25 treated sites (96% of treated sites), though by 1 week following treatment the numbness had



**Figure 2** A representative example of clinical improvement following 1 treatment with cryolipolysis for fat layer reduction of the abdomen. The patient underwent a single treatment with cryolipolysis, though 2 applications (1 application to the right and 1 application to the left side) were required to treat the entire abdomen due to the larger surface area. The top pictures show the baseline, while the bottom pictures demonstrate the clinical improvement 4 months after treatment. The patient's weight at the 4 month follow-up day had increased by 3.5 lb from the baseline day. This figure is obtained and used with permission of Ivan Rosales-Berber, MD.

largely resolved. Transient reductions in sensation were reported in 6 of 9 patients (67%), most commonly manifested as reductions in pain sensitivity. However, reductions in light touch, 2 point discrimination, and temperature sensitivity were also reported by a minority of patients. These reductions in neurologic sensation lasted between 1 and 6 weeks, with a mean duration of 3.6 weeks. All reductions in neurologic sensation had resolved by 2 months after the cryolipolysis treatment. No changes were noted in the nerve biopsy 3 months after the cryolipolysis compared with the baseline biopsy. These results indicate that cryolipolysis results in a decrease in sensation of treated areas, but this altered sensation is transient and appears to resolve without any further intervention.

As previously discussed, the exact mechanism of cryolipolysis is not well understood. It is possible that as the fat is destroyed and phagocytosed, the fat could be released into the blood. Many of the clinical studies have therefore analyzed the patient's lipid profiles and liver function tests following cryolipolysis. In the animal studies by Manstein and Zelickson, no significant changes in the lipid profiles following cryolipolysis were observed. In all human studies to date, no clinically significant alterations in lipid profiles or liver function tests have been observed. Klein et al,<sup>19</sup> reported on 40 patients with bilateral fat bulges on their flanks (ie, love handles) treated with cryolipolysis. The patients were treated on 1 or 2 sites on each flank, depending on the size of the fat bulge, to a maximum of 4 treatment applications. Patients were treated at a CIF of 42 for 30 minutes. Lipid values were obtained, including triglycerides; total cholesterol; and very-low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein (HDL) cholesterol. Additionally, liver-related blood tests, including: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and albumin were obtained before treatment. Follow-up values were determined 1, 4, 8, and 12 weeks after treatment. Triglyceride values were noted to increase slightly in the 12 weeks following cryolipolysis, from a mean of 82.1 to a mean of 93.2; this increase was not statistically significant ( $P = 0.22$ ) and the mean value remained well below the upper limit of the reference range. There was, however, a statistically significant decrease in HDL cholesterol in the first few weeks following cryolipolysis ( $P = 0.0296$ ), though the HDL values did return to baseline by 12 weeks. No statistically significant changes from baseline for any of the liver function tests were observed following cryolipolysis.

These initial safety reports support that the Zeltiq cryolipolysis device results in a significant reduction in fat layer thickness with no significant adverse events. During the informed consent process before cryolipolysis treatment, it is important to emphasize known risks including erythema, bruising, and temporary altered sensation. To date, there does not appear to be significant risk of altered lipid profiles or liver function tests associated with cryolipolysis treatment. It remains to be determined whether patients with rare, cold-induced dermatologic conditions, such as cryoglobulinemia, cold urticaria, or paroxysmal cold hemoglobinuria, can be safely treated with cryolipolysis. Patients with a known his-

tory of cold-induced disease should probably not be treated with the cryolipolysis device until further data are available.

## Discussion

Cryolipolysis is a novel procedure, which uses controlled cold exposure, known as energy extraction, to produce non-invasive, effective, and selective damage to adipocytes. In animal and human clinical studies, cryolipolysis has been shown to result in significant improvement in the clinical appearance of fat. Additionally, reductions in the thickness of the subcutaneous fat layer of up to 50% can occur following a single cryolipolysis treatment. Clinical studies have shown potential efficacy in the treatment of excess back fat, flank fat, and abdominal fat; the potential efficacy of cryolipolysis in other treatment areas and for the treatment of cellulite remains to be determined. In these initial studies, cryolipolysis treatments have been well tolerated by patients with transient, mild adverse events such as erythema and bruising occurring in treated patients. No cases of ulceration, scarring, or significant changes in lipid profiles and liver function tests have been reported following cryolipolysis. Cryolipolysis therefore appears to be a safe and effective treatment option for reduction of excess adipose tissue.

The exact mechanism of cryolipolysis remains to be fully elucidated. It has been shown that cold exposure results in apoptosis of the adipocytes, followed by an inflammatory infiltrate. Ultimately, the inflammatory infiltrate results in phagocytosis and mobilization of the treated adipocytes. The exact mechanism and pathway for this fat elimination are unclear. No significant alterations in blood lipid profiles, other than transient decreases in HDL values, or liver function tests have been observed following cryolipolysis. Further studies to determine the exact mechanism of action for cryolipolysis remains an active area of research.

Although cryolipolysis is a promising new technology, it is important to bear in mind a few potential limitations. In the human clinical studies, results were most visible in patients with discrete, localized fat bulges. Cryolipolysis does not appear to be as effective in obese patients or patients with excess skin laxity. It is unclear whether the device itself is less effective in these patients, or whether the potential improvement associated with cryolipolysis treatment is harder to observe in these patients. Additionally, the improvement following cryolipolysis is not immediate, but rather occurs slowly over the course of 2-3 months. Finally, the currently available data seem to support that cryolipolysis is most effective for localized, discrete fat bulges. Thus, patients seeking large scale fat removal, which can be achieved with liposuction, may not achieve their desired outcomes with cryolipolysis. It is therefore important for physicians to carefully select potential cryolipolysis treatment patients, as well as educate them regarding their expected outcomes and potential limitations.

Cryolipolysis is a new, selective, effective, and noninvasive treatment option for excess adipose tissue. While the device is currently FDA cleared only for skin cooling, a premarket notification application for lipolysis is pending. The device is

particularly appealing given that it is noninvasive, requires not much or no downtime for patients following treatment, and does not require local or regional anesthesia. Ongoing clinical studies will help to determine the full potential and efficacy of this device. Cryolipolysis appears to be a promising new technology for safe, effective, and noninvasive treatment of fat.

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