Lipodissolve for Subcutaneous Fat Reduction and Skin Retraction

According to the authors, Lipodissolve injections reduce the size of localized fat deposits and cause skin retraction in body regions containing small deposits of localized fat, cellulite, or postlipoplasty deformities. It will not replace traditional lipoplasty techniques, but is an excellent adjunct or alternative for those patients seeking minimally invasive treatment. Successful outcomes are highly dependent on the correct formula and injection technique, as well as proper patient selection. (*Aesthetic Surg J* 2005;25:530-543)

Lipodissolve is a combination of pharmaceutical agents in an injectable form administered using a technique developed in Austria in 2002 for the purpose of subcutaneous fat reduction (see History). According to recent journal articles[2-5] and various Internet sites,[6-9] Lipodissolve is considered a form of mesotherapy. However, the 348 worldwide physician practitioners of Lipodissolve do not consider this process to be mesotherapy.

Mesotherapy Versus Lipodissolve

Although the original purpose of mesotherapy was curing systemic disease, most mesotherapy practitioners today use various "cocktails" of pharmaceuticals for different indications, primarily skin and scalp rejuvenation. The American Society of Aesthetics and Mesotherapy (ASAM) recommends that injections be placed at the hypodermis level. The lack of formula standardization as well as concern regarding the possible interactions of injected drugs have generated much concern and criticism of mesotherapy techniques. Results are difficult to evaluate, and the effective ingredients are hard to isolate. Because mesotherapy is widely practiced by paramedical personnel without adequately documented pretreatment evaluation, treatment outcomes remain questionable.[10]

With Lipodissolve, both the injection formula and technique are standardized. In addition to using a standardized formula, a 100-mL limit, or 2500 mg of phosphatidylcholine (PPC), is observed per treatment session. All injections are placed into the superficial to mid layer of subcutaneous fat, never intradermally or intramuscularly. All practitioners from 28 countries are physicians. Fat reduction and smooth skin retraction are dual goals of treatment.

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Scientific Basis and Mechanism of Action of Injectable Fat-Reducing Formulas

Phosphatidylcholine is currently the main ingredient in most injectable fat reducing formulas.[11] When isolated, it is produced as a powder. When reconstituted, it is quite viscous and must be mixed with sodium deoxycholate to solubilize it enough to create an injectable form. Most formulas manufactured in the United States contain between 4.2% and 4.7% sodium deoxycholate. A small amount of benzyl alcohol is added as a preservative.[12,13]

Sodium deoxycholate is a bile salt that functions to make the PPC soluble in water; otherwise, the PPC would precipitate out of solution. Other pharmaceuticals, such as Fungizone (Bristol Myers Squibb, New York, NY) (injectable amphotericin B), are commonly combined with bile salts to enhance their solubility and make them compatible with intravenous delivery—the intended use of Lipostabil (Sanofi-Aventis, Bridgewater, NJ), the original PPC preparation.

Recent experimental studies using this PPC/deoxycholate formulation have demonstrated that deoxycholate causes significant cell lysis on cultured human keratinocytes, as well as in porcine fat in vitro. These lytic effects have been seen independent of PPC. Furthermore, necrosis of fat and muscle was histologically evident after tissue incubation with the PPC/deoxycholate formulation and with deoxycholate alone. These effects were comparable with positive controls using known laboratory detergents. It can be concluded that the detergent effects of the bile salt alone cause nonspecific cell lysis. Similar to injecting botulinum toxin, fillers, and sclerosing agents, correct placement of these substances is critical. Clinicians treat-

Table 1. ASAL Study criteria

1. Inform potential patients of the study protocol and obtain an informed consent.
2. Review with the patient the purpose of the study, the fact that these injections are not an FDA-approved use of the pharmaceutical formula, and that while short term risks are well known there may be long term sequelae that are not yet known.
3. Report clinical outcomes, side effects, and member study results to both Lipodissolve organizations.
4. Report physician member results annually at a worldwide conference in order to improve safety and efficacy in formula and technique.
5. Monitor and review safety and side effects, monthly, in all patients.
6. Members sign a confidentiality agreement that prevents them from sharing the formula and technique with other physicians or paramedical personnel who are untrained in Lipodissolve (to prevent self-taught practitioners from injecting themselves or others).

Table 2. Areas of treatment in the Lipodissolve study

Facial	Infraorbital fat pads, jowls, immediate submandibular jawline, chin, bulging reconstructive facial flaps, and submental fat deposits
Upper torso	Preaxillary fat pads, male gynecomastia, upper back rolls, axillary bra rolls, upper volar arms, overhanging skin and fat deposits at waistline, epigastrium, "six pack" area definition (in bodybuilders), male and female abdomen, male and female flanks, *buffalo hump* secondary to prednisone use
Lower torso	Medial buttock cellulite, lower lateral buttock, infragluteal *banana roll,* posterolateral thigh cellulite, outer thigh/saddlebags, inner thigh, anterior thigh, medial and suprapatellar knees, and upper calves

ing localized collections of fat should be particularly vigilant about injecting only into subcutaneous fat.

Injections of deoxycholate alone into lipomas (AM Rotunda, written communication, June 2005) resulted in a significant reduction in lipoma size after 1 to 3 injections of varied concentrations. These effects were confirmed by ultrasound. It was observed that increasing concentration of deoxycholate did not cause any additional benefit, but rather only contributed to adverse effects such as prolonged burning and tenderness. Based on data from all current studies, both PPC and deoxycholate appear to be active ingredients and contribute to the location-specific adipocyte cell membrane damage and subsequent apoptosis when a critical concentration of formula is reached. Additional Institutional Review Board (IRB)–approved studies using deoxycholate alone in human subjects are pending.

Author's Current Study of Lipodissolve Efficacy and Safety

More than 18,000 injections of Lipodissolve have been performed by the 429 physician members of the European Network Lipodissolve (ENL) and the American Society for Aesthetic Lipodissolve (ASAL). Based on the treatment protocol of these 2 organizations, the author performed a clinical study between October 2004 and May 2005 in which 43 patients were injected in a total of 117 injection sites. The study follows the criteria of the ENL and the ASAL (Table 1).

The primary goal was to determine the efficacy and safety of the Lipodissolve formula and technique in achieving both fat reduction and smooth skin retraction in areas of localized fat deposition. Three skin conditions were addressed: cellulite, rippling, and *divots* (skin contour irregularities following lipoplasty). Several patients with localized excess skin were also treated as an alternative to surgical resection.

Adults from 19 to 73 years of age in good general health were included. In these patients, 1 or 2 localized areas of fat deposition and/or skin laxity were treated that had proven resistant to diet and exercise. All but one of these study subjects was within 15% of ideal body weight; none was obese. Each patient had 1 or more treatments in 1 or 2 areas up to 150 cm. Patients were excluded from the study for the following reasons: pregnancy or breastfeeding; recent aspirin, ibuprofen, or anticoagulant use; acute or severe chronic illnesses; obesity; unrealistic expectations; or unwillingness or inability to follow the treatment protocol. Table 2 indicates the anatomic areas that were treated. The areas that were not treated include female breasts, any area previously treated for cancer, the neck, the upper and mid facial regions, and the anterior torso or axilla in breast cancer patients.

History

The traditional French method of mesotherapy was originally practiced as microinjections of pharmaceuticals delivered intradermally, using a technique known as *nappage*. Until recently, the primary focus of mesotherapy was the treatment of more than 200 diseases, as well as skin and scalp rejuvenation. In 1959, phosphatidylcholine (PPC) was isolated and used intravenously in Odessa, Russia, for the treatment of fat embolism. In 1988, Sergio Maggiore reported use of PPC injections for cosmetic purposes. Maggiore's use of this substance for treating xanthelasmas was soon expanded in Europe and then in South America.

In 1989, Bobkova et al[1] published a treatise on the metabolic effect of Lipostabil Forte (Aventis, Bridgewater, NJ) on serum lipid concentrations. His study demonstrated a significant decrease in serum triglyceride levels, reversal of insulin resistance, and an improvement of thyroid function. Many others have substantiated these findings, including a decrease in LDL and VLDL, an increase in HDL, as well as improvement in liver fibrosis in patients with cirrhosis and hepatitis. Aventis markets Lipostabil in Europe primarily for the treatment of coronary atherosclerosis. PPC is also used as a surfactant in treating neonates with immature lungs.

In 1995, Rittes reported success in using PPC injections to reduce lower lid fat pad prominence. In 2001, she suggested that in some patients this procedure could replace surgical lower lid blepharoplasty. By 2003, widespread reports of Lipostabil use by lay individuals, combined with a lack of clinical or safety studies, prompted ANVISA, to recommend banning the use of Lipostabil in Brazil as a fat reducing injection. At this time Rittes had reported using Lipostabil for body contouring in 50 patients. In 2003, Hasengschwandtner performed a larger study of 187 patients in Austria, using a modified formula. His current series of more than 3500 patients shows both safety and efficacy in treatment. In 2004, Ablon and Rotunda confirmed the beneficial effects of the infraorbital PPC formulation injection introduced by Rittes with a similarly designed but smaller open-label study on 10 patients. They demonstrated clinical benefit in 7 of 10 patients and reported localized swelling and erythema as the most common adverse effects.

In late 2003, a UCLA study was presented at the American Society for Dermatologic Surgery meeting describing the "detergent" effect of sodium deoxycholate on fat dissolution in a porcine in vitro study. This widely quoted treatise describes the nonspecific effect of deoxycholate on both adipose and muscle cells.

Study protocol

Participants received a thorough review of participation requirements and signed an agreement to follow the study protocol. Pretreatment photographs were taken, and participants signed a written informed consent. Where appropriate, the author took skin fold and/or circumference measurements. Patients agreed to return for sequential treatments, if indicated, and were advised that 2 to 4 injection sessions were recommended for optimal outcome. An interval of 4 to 8 weeks was maintained between injection sessions.

At the time of treatment, patients were asked to make preliminary markings around the areas they wanted treated; these were modified with the patient's consent. A grid was used to mark injection points, 1.5 cm apart in the broader areas, and 1.0 cm apart in the smaller or more densely thick areas. When treating cellulite or other skin deformities, the tighter grid was used.

Injection depth varied according to the desired goal. If there was a thick fat pad, a 13-mm 30 10 32 gauge needle was used to inject 0.4 mL of solution per grid mark. If skin retraction or smoothing was the primary goal, a 6-mm needle with a 1-cm grid was used to obtain subdermal fat loss with subsequent skin retraction. In most patients, a deeper, midlevel subcutaneous injection with a more superficial injection was used to target both fat loss and skin tightening. Great care was taken to avoid excessively deep injections that might damage adjacent tissues.

Technique

The proper injection technique is critical in achieving fat loss in the target area. The injections must never be placed too deeply, since that will not only minimize results but may also damage adjacent fascia or muscle. A good injection technique may be compared with good lipoplasty technique, in that the practitioner must have the sense of suctioning within the fat layer in the targeted level. A good injector can also sense fat versus fascia or muscle and will evaluate the needle-tip location before pushing the plunger.[14]

In larger surface areas, using a 1.5-cm grid will achieve safe and effective clinical results while limiting the dosage of PPC. The current maximal safe dose is 100 mL of PPC, 2500 mg PPC. In treating smaller surface areas, or if more skin retraction is desired, a 1.0-cm grid can be used. If fat loss is the primary goal, the first injection is done at the 10- or 13-mm level, followed by a 6-mm injection level for the second treatment. When skin

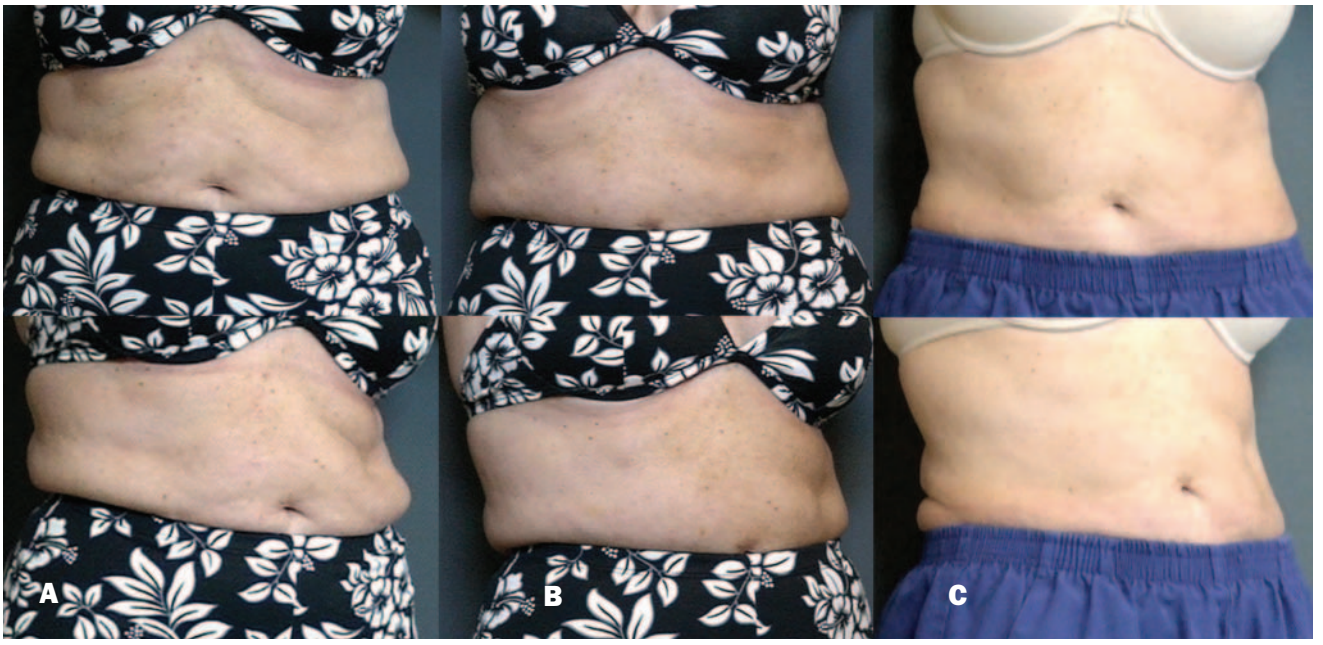

Figure 1. A, *Pretreatment view of a 51-year-old woman who complained of skin laxity in the epigastric region. She was injected in 2 sessions, using the standard Lipodissolve formula.* **B,** *Significant improvement is shown following the first injection.* **C,** *Four weeks after the first injection session, she underwent a second treatment in the same area. She received a more superficial injection technique resulting in a much more dramatic improvement in skin retraction.*

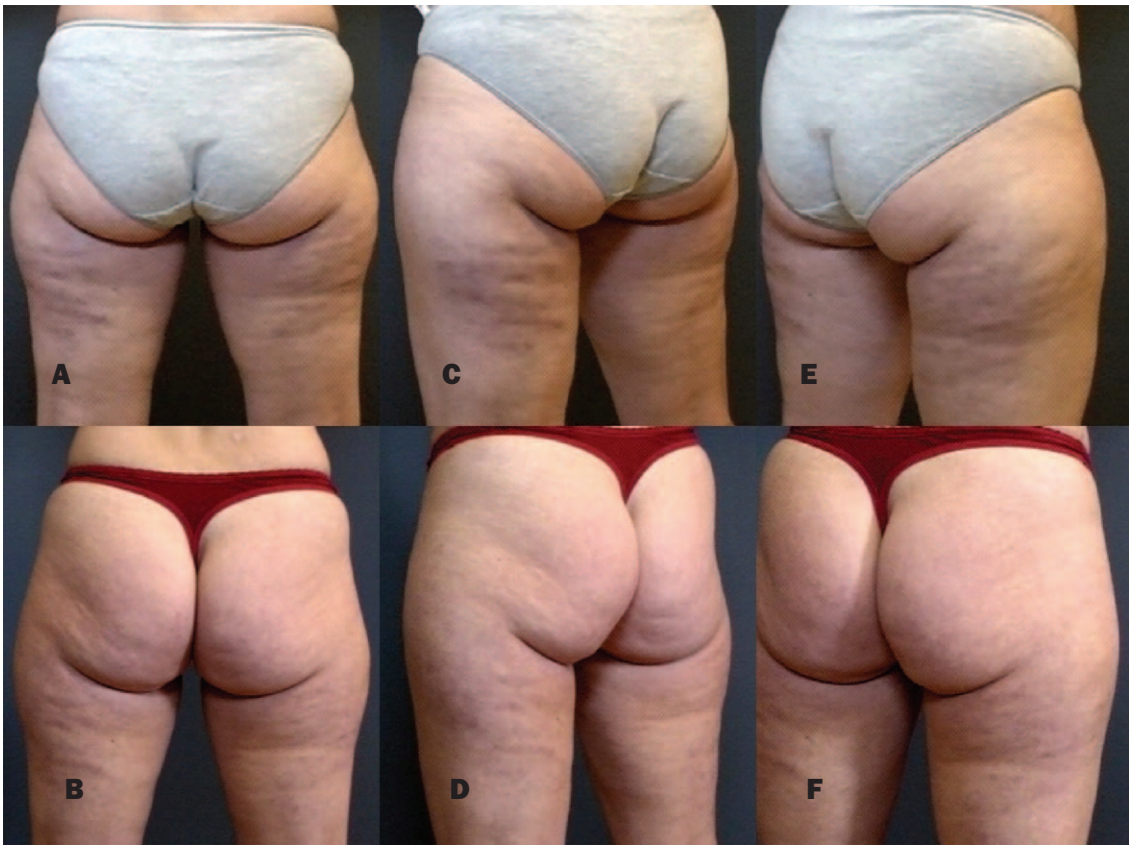

Figure 2. A, C, E, *Pretreatment views of a 32-year-old woman complaining of cellulite and saddlebags.* **B, D, F,** *Posttreatment views 6 weeks after undergoing 3 sessions of Lipodissolve injections in her outer thighs (saddlebags) and posterior thigh (cellulite). Significant improvement was noted in both areas.*

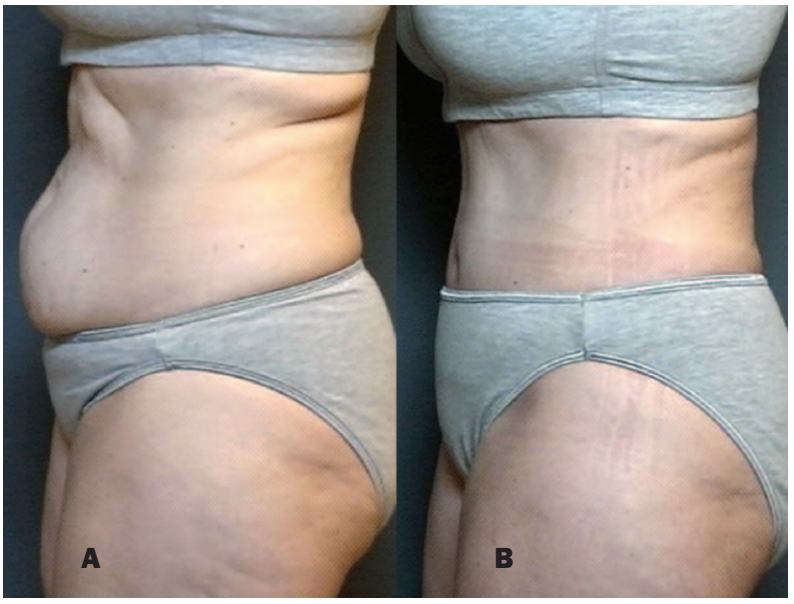

Figure 3. A, *Pretreatment view of a 53-year-old woman who was undergoing abdominoplasty and wished to improve her overhanging back roll.* **B,** *Posttreatment view following abdominoplasty. Fifty mL of Lipodissolve was injected bilaterally during one session. Dramatic reduction in the fat deposit was accompanied by smooth skin retraction.*

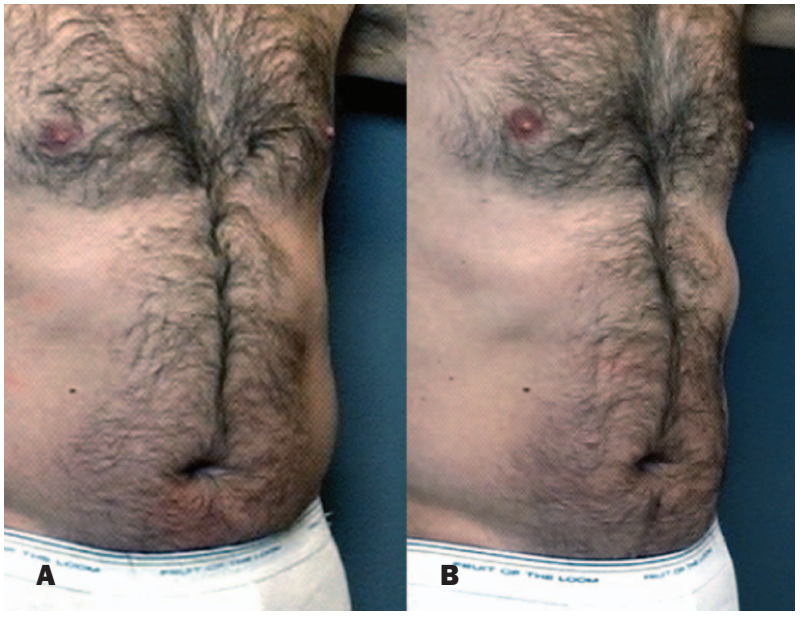

Figure 4. A, *Pretreatment view of a 52-year-old man who complained of periumbilical abdomen and flank excess despite workouts and dietary modification.* **B,** *Posttreatment view after one injection with 78 mL of Lipodissolve. Definite improvement in the laxity and overhang of the abdomen and a change in vertical measurement between the pubic fold and umbilicus can be seen.*

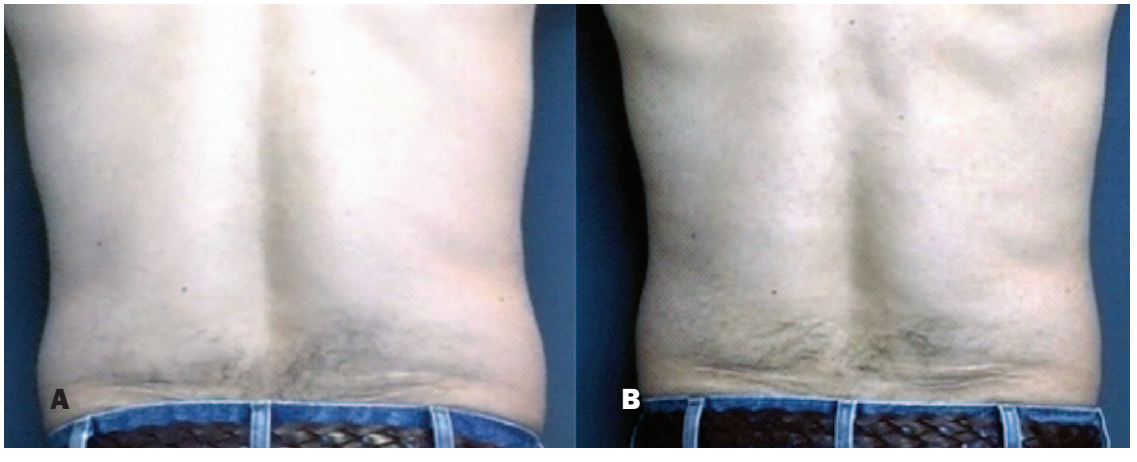

Figure 5. A, *Pretreatment view of a 52-year-old man.* **B,** *Posttreatment view 6 weeks after 2 injection sessions demonstrates reduction in the flank area.*

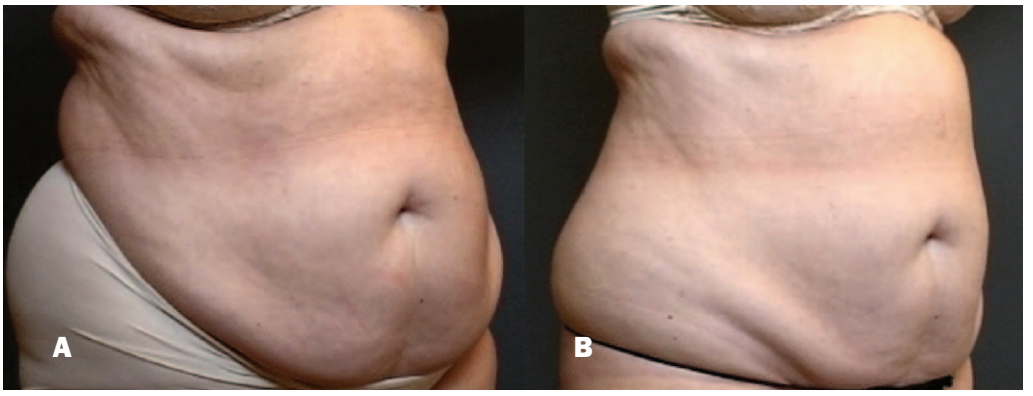

Figure 6. A, *Pretreatment view of a 56-year-old woman who persisted in her request for abdominal Lipodissolve injections even though she was advised that she needed an abdominoplasty to get the best results. She was counseled that she did not fit into the recommended treatment protocol, and, if injected, her expectations would probably not be met.* **B,** *Posttreatment view shows her appearance 6 weeks after 3 treatment sessions.*

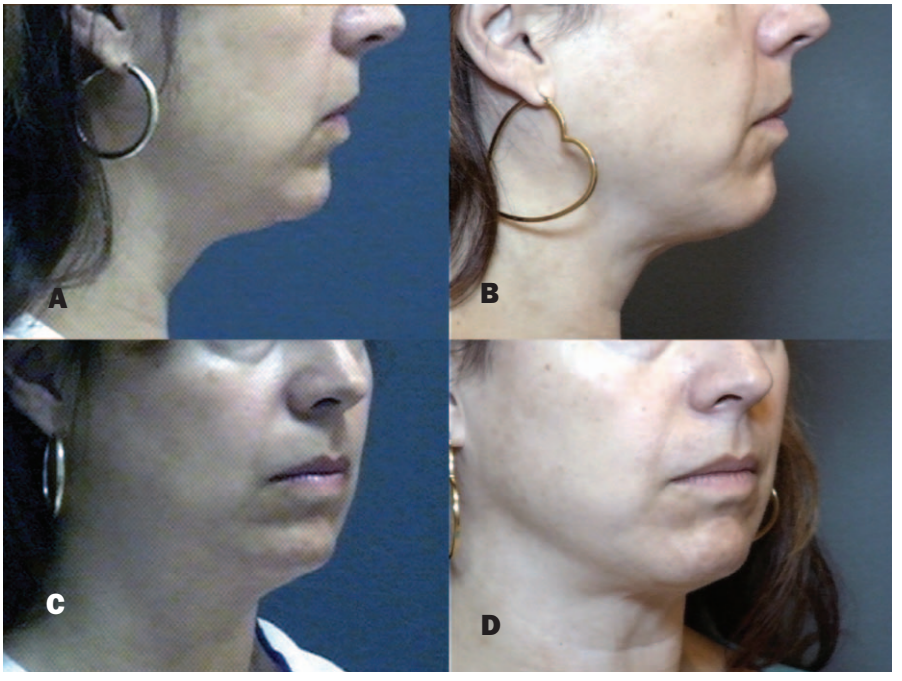

Figure 7. A, C, *Pretreatment views of a 48-year-old woman.* **B, D,** *Facial injections were performed in the area of the jowls, submental chin, and submandibular jawline. Great care must be taken in treating theses areas because the fat layer is very thin. Superficial injections precisely placed are the key to success in the face.*

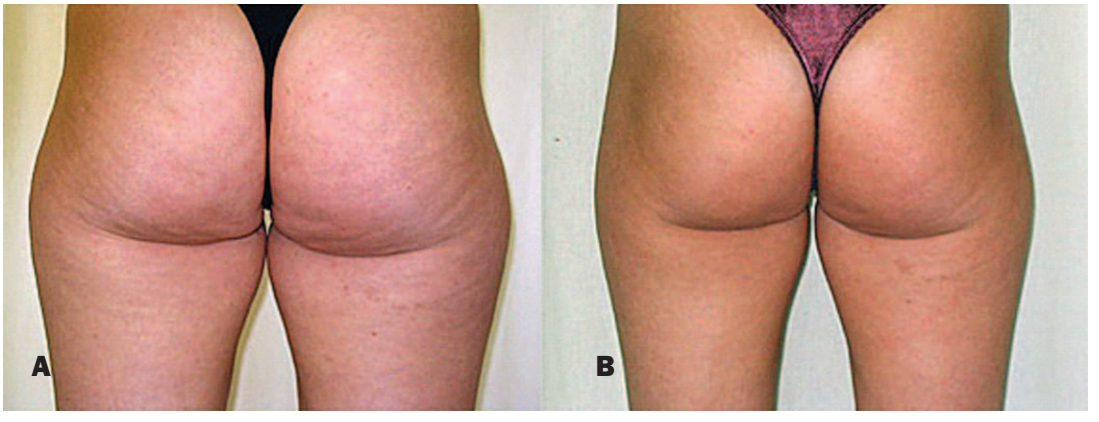

Figure 8. A, *Pretreatment view of a 28-year-old woman who requested treatment for rippling in the thigh area following lipoplasty; she had no real residual fat, just skin contour irregularities.* **B,** *Some improvement was seen in the treated areas after 2 sessions.*

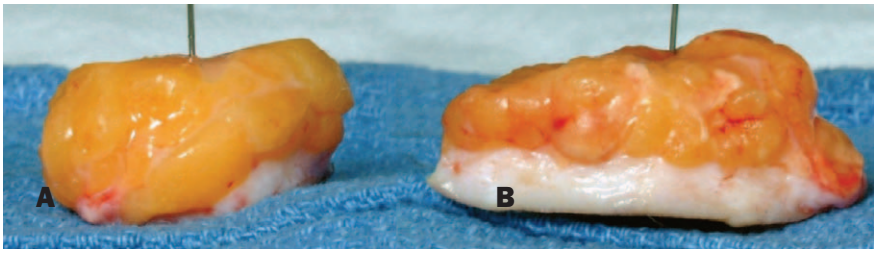

Figure 9. A, *Untreated view.* **B,** *Posttreatment view after injection with standard Lipodissolve formula demonstrates visible small white nodules of fat necrosis in the superficial fat, accompanied by threadlike strands of scar tissue.*

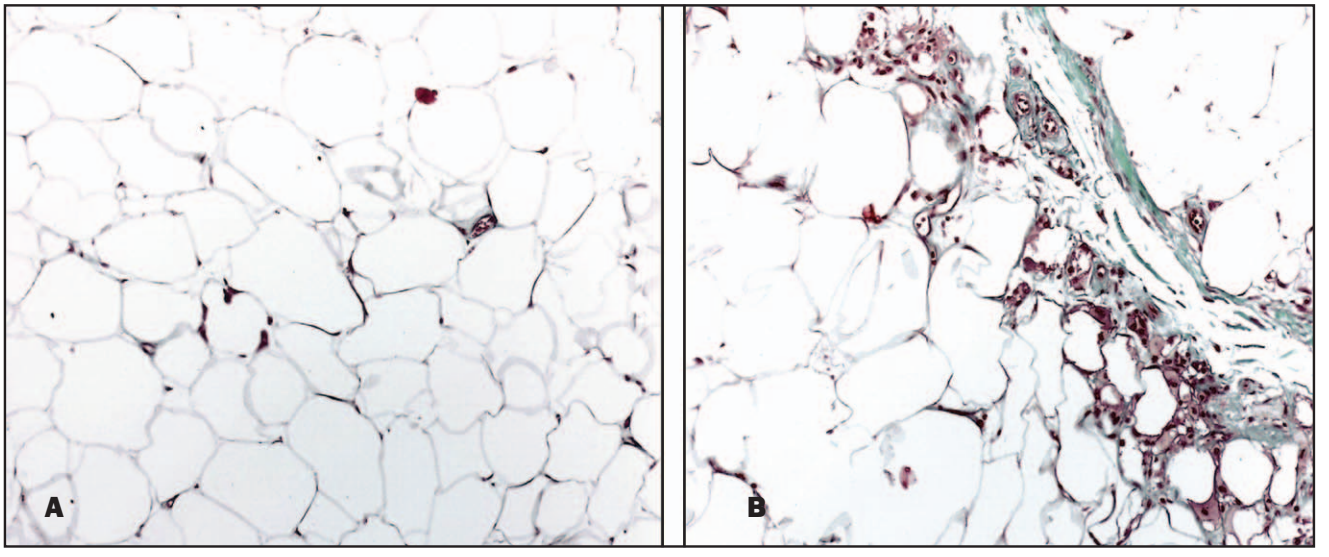

Figure 10. A, *Trichrome stain shows normal architecture and intact adipocyte cell walls in the untreated control specimen.* **B,** *Trichrome stain, specific for collagen, shows new collagen formation along the track of the injection site. Inflammatory cells are present in a laminate along the needle track, along with adipocytes showing reduced cell volume. The periphery shows a localized region of nonviable adipocytes with cell wall disruption.*

character alteration is the primary goal, the immediate subdermal fat layer is targeted with a 6- to 8-mm injection depth. Skin retraction and smoothing will vary according to skin type with thinner skin being more responsive.

Results

Of the 43 patients treated, 13 patients reported dramatic improvement of their localized fat deposits, and 29 saw mild to moderate improvement. One nonresponder had little visible change. There were no complications such as hematoma, allergic reaction, infection, skin contour irregularity, or need for surgical or injection revision. With higher dosages and larger treatment areas, minor side effects included transient nausea or diarrhea for less than 24 hours. Itching, burning, erythema, bruising, and swelling, all viewed as part of the treatment process, were seen from 3 to 10 days.

Three patients reported prolonged sensitivity in the treatment areas for about 1 month following their injections. About 13% of patients reported that their improvement was less than what they had hoped for. Documented reduction in localized fat deposits and/or accompanying skin retraction was seen in 42 of the 43 treated patients.

As with other studies, results varied from patient to patient.[15-17] The best results were achieved in patients who were closest to their ideal weight and needed improvement in a small, focused area. Soft fat was more responsive than fibrotic fat. When used primarily for skin retraction, surprisingly good results were obtained in patients who had a combination of subcutaneous fat and skin laxity. Smooth skin retraction without rippling, creases, or local indentations was observed in all patients treated (Figures 1 through 8).

In Vivo Human Histology

There are several theories regarding the exact mechanism of action of the PPC-based compounds used in subcutaneous fat reduction.[18] To provide a sample of in vivo human histology, the author injected a volunteer with standard Lipodissolve formula in the left lower abdomi-

Benefits of PPC

Since 1955, when large intravenous doses of the compound were used to treat fat embolism,[42] many other disease conditions have been improved with the intravenous or oral administration of PPC. Benefits of treatment have been reported in cardiac disease,[43] hypertriglyceridemia,[44] elevated serum cholesterol,[45] and gallstone development.[46] Three liver conditions (fatty liver, alcoholic cirrhosis, and viral fibrosis due to hepatitis A, B, and C), have been shown to improve with intravenous administration of the soy-derived PPC compound.[47]

Bobkova et al[1] reported on the metabolic effect of Lipostabil in improving coronary atherosclerosis, hypothyroidism, and insulin resistance. They also reported an average decrease of 32% in serum triglyceride levels in cardiac patients treated with the compound.[1] Lipostabil and Essentiale (Natterman, Cologne, West Germany) are PPC preparations that are currently commercially available in several European countries.[48] Documented cardiac benefits include dissolution of atherosclerotic coronary artery plaques, decrease in LDL, triglycerides, and VLDL, and an increase in serum HDL values. PPC has also been shown to inhibit platelet aggregation.[49]

There is also a marked hepatoprotective effect. When given to baboons on a high alcohol diet, PPC appeared to prevent cirrhosis and fibrosis. Several studies document the dramatic clinical improvement of patients with cirrhosis and viral fibrosis caused by hepatitis A, B, and C.[50] Since choline itself has no hepatoprotective effect, it has been postulated that unsaturated free fatty acids are the mechanism of action due to their effect on inducing hepatic collagenase.[51] Neurologic effects of PPC have been addressed in clinical trials for treatment of both Alzheimer's syndrome and bipolar depression. Oral doses of 800 to 1200 mg/day seem to improve cell membrane fluidity and, thus, improve signal transduction.

nal area. The injection area was tattooed to serve as a marker for future biopsy. As a control, a mirror image biopsy of untreated fat in the right lower abdomen was performed. One month later, a 2 × 3-cm ellipse of skin and subcutaneous tissue was harvested at the tattoo site. Visible firmness and localized skin retraction were noted at the treatment site. Gross examination showed visible small white nodules of fat necrosis in the superficial fat, accompanied by threadlike strands of scar tissue (Figure 9). Neither of these findings was visible in the normal fat specimen (control). Microscopic examination of the untreated fat sections demonstrated normal adipocyte architecture. No cell-wall disruption, inflammation, or focal scarring was seen. Two methods of tissue staining were used: standard hematoxylin and eosin, and a special trichrome stain that is specific for collagen. The treated tissue appeared markedly different from the control. Both treated specimens showed cell-wall disruption, focal inflammation, and strands of collagen deposition aligned with a palisade of fat cells with marked reduction in diameter (Figure 10).

These findings suggest that the mechanism of action of the PPC solution is 4-fold: (1) cell-wall disruption; (2) enzymatic and lipoprotein transport of triglycerides and fatty acids out of the adipocyte, resulting in a smaller adipocyte; (3) inflammation, causing tissue retraction; (4) new collagen formation in the subdermal plane, causing skin retraction and a denser, firmer skin character.

These findings are supported by Rose,[19] who reported similar findings when injecting a patient's flank. He performed a biopsy 1 week later and noted a prominent inflammatory response. Rose felt that there could be 2 mechanisms of action—a release of triglycerides and fatty acids from within the adipocytes, and frank cell destruction. He reasoned that the new collagen that formed as a result of the injury could cause skin retraction.

The author's histologic evidence supports the idea that several bioactive events occur over a period of about 8 to 10 weeks. The work of Rotunda et al[11] suggests that the "detergent effect" of deoxycholate causes cell disruption; however, the injections remained in the in vitro porcine specimen for only 1 to 4 hours. A human in vivo biopsy with a longer duration of action would be necessary to better understand the compound's effect on subcutaneous fat over a 1-month time period.

Rotunda et al[11] postulate that sodium deoxycholate is the primary cause of fat cell destruction. Ablon and Rotunda's[20] clinical trial involving the use of sodium deoxycholate only was marred by patients dropping out of the study because of the intense pain and persistent numbness accompanying injections. One possibility of the failure of the Brazilian formula was the very high concentration of benzyl alcohol. Vickbjerg et al[22] feel that a high concentration of solvent in a phospholipid formula is a factor having a strong negative effect on recovery.[21,22]

Others feel that there is a synergistic process; the compound containing PPC, sodium deoxycholate, and

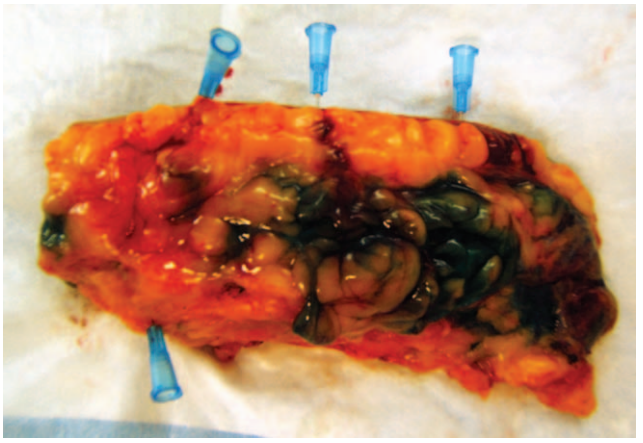

Figure 11. *Dispersion studies show the effect of spacing of injections. The top left needle indicates a 1.5-cm spacing with no coalescence of formula. The central needle shows the effect of a l.0 cm spacing, with good confluence. The far right needle shows the effect of a 0.75-cm spacing, with dense coalescence and upward migration.*

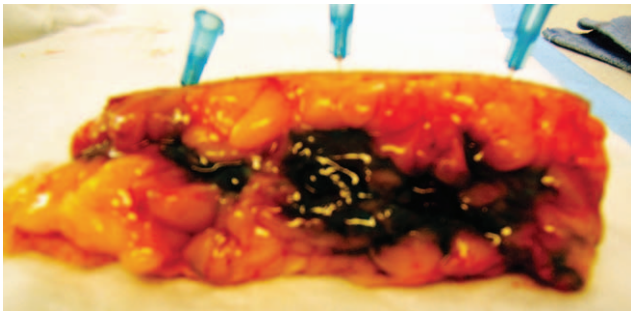

Figure 12. *Dispersion studies show the depth of injection. A superficial injection of 6-åmm (top left needle) remains in the superficial fat layer at 1 hour. The central needle shows a 10-mm injection depth in which the formula disperses at the level of Scarpa's fascia. The deeper 13-mm injection level (needle, far right) shows deep migration. Unless the fat pad is very thick, deep injections should be avoided.*

benzyl alcohol initially causes cell membrane disruption. Once injected into the subcutaneous layer, PPC causes a chain of reactions over an 8- to 10-week period. The subsequent inflammatory reaction causes an enzymatic cascade[23,24] and hydrolysis of the phospholipids-rich adipocyte cell membrane. Mathur et al[25] describes a critical concentration of 250-mmol PPC that is necessary to destabilize the adipocyte cell fatty acyl chain on the PPC molecule. This change in the physical properties of the cell membrane then causes a stimulation of apolipoprotein-B lipoproteins, which activates lipoprotein lipase.[26] Other reactions in the enzyme cascade include the release of endothelial lipase,[27] which initiates hydrolysis of the sn-1 fatty acyl chain on the PPC molecule. A subsequent deacylation of the sn-2 fatty acid releases both unsaturated fatty acids, for either oxidation and energy production, or liponeogenesis. Hormone-sensitive lipase has a broad substrate specificity and will hydrolyze triacylglycerols, diacylglycerols, and monoacylglycerols, as well as cholesterol esters,[28] thus breaking down the cytoploasmic components of adipocytes.

Another important pathway is the activation of lecithin cholesterol acyl transferase (LCAT), the primary mechanism of PPC dissolution in atherosclerotic plaque, which occurs, in part, by activating phospholipase A2.[29] Ng et al[30] showed that LCAT deficiency correlates with elevated triglyceride levels. Several studies confirm the effect of PPC on LCAT stimulation. Morgan[31] demonstrated another lipase, phospholipase B, that enzymatically removes both fatty acyl chains from PPC, also producing water soluble glycerophosphorylcholine. Caiazza et al[32] show that endothelial lipase, a newly identified member of the triglyceride lipase family, hydrolyzes HDL type phospholipids. They demonstrate that the apolipoproteins regulate the kinetics of EL-mediated hydrolysis of phospholipids.

Another important mechanism of fat cell death is described by Peckitt.[33] He demonstrates the destabilization of the adipocyte cell membrane following injection of a critical concentration of PPC, which produces asymmetric phospholipid dynamics. A rapid apoptotic caspase cascade then causes cell death. If the critical concentration is not reached, an unstable cell membrane causes gaps or pore formation in the plasma membrane, allowing efflux of some of the cytoplasmic contents. This mechanism accounts for the reduction in viable fat cell diameter present in human histologic sections. Peckitt warns that aspirin stops adipocytes from bursting open, so strict avoidance of aspirin during treatment with Lipodissolve is advisable.

Many European Network Lipodissolve (ENL) physicians incorporate low-amplitude ultrasound as an adjunct to Lipodissolve. This[34] causes cavitation in the treated area as long as third-spaced fluid is present. Further fat necrosis, a confluent localized reaction, and the formation of a fishnet-like network of collagen fibers just under the skin result in apparent skin retraction. Interestingly, in many cases there is noticeable reduction of subcutaneous fat in areas not injected, but near the injected region. Several other practitioners have noted a similar effect in their patients, but currently, the mechanism remains unknown.

Dispersion Studies

To study flow characteristics and dispersion techniques, the author performed an in vivo study, injecting abdominoplasty specimens from 3 volunteers with Lipodissolve. The goal was to assess where the solution

settles following injection, assuming it does settle, and to determine whether migration of PPC solution, which theoretically might damage adjacent tissues, occurs.

Technique

A line was drawn dividing the lower abdominal skin in half. A grid pattern was applied with standard 1.5-cm spacing on the left and spacing variations of 1.5-, 1.0-, and 0.75-cm on the right. The depth of injection was varied on the left side to find the optimal depth that would target the mid level of the fat deposit without penetrating too deeply. On the right, injections were performed at the same depth, but spacing was varied to assess how closely injections should be placed to achieve confluence without pooling. The Lipodissolve solution was limited to 40 mL per abdomen and mixed with 1 mL of methylene blue so that dispersion and flow characteristics could be tracked.

The first specimen was injected after it was resected, and the other 2 were injected in vivo. The solution was left in position for 1 hour. The lower abdominal specimens were then resected and transected along the injection points to assess depth of penetration, confluence of the solution, and upward or downward migration. In the first half of the specimen, needle depth was addressed. One segment was injected with 0.4 mL of Lipodissolve solution per grid mark to a 13-mm depth, the next area injected to a 10-mm depth, and the third, to a 6-mm depth.

After 1 hour, the underside of the specimen demonstrated visible tracking through the suprafascial surface with the longest needle (Figure 11). The specimen was then transected along the injection sites. As expected, the more superficial needle, 6-mm 32-gauge, delivered the solution near the subdermal level. The mid-range 10-mm injections provided solution to the level of Scarpa's fascia. The longer 13-mm needle delivered solution in the lower third of the fat layer, too deeply for safety or the best visible effect.

The right side of all 3 specimens was injected with 0.4 mL of Lipodissolve solution using spacings of 1.5, 1.0, and .75 cm. The transected specimen showed a somewhat columnar injection pattern in the 1.5-cm spacing area, with some downward tracking. The 1.0-cm spacing showed good confluence. The 75-cm area appeared to have so much solution that pooling and migration were evident (Figure 12).

Results

After some initial dispersion, the 0.4-mL dose of Lipodissolve (per injection site) seemed to settle in a localized distribution. Factors that could negatively affect precise placement of the solution might include: (1) using too great a volume per injection site, (2) using too much pressure to inject, (3) causing downward tracking, and (4) using a needle that is too long or has too large a gauge. The most significant factor, both in the dispersion studies and in clinical trials, appears to be the depth of injection.

Proper technique is critical in maintaining formula position in the target tissues. As with botulinum toxin injections, 4 variables affect dispersion of the formula and flow characteristics: concentration of the formula (viscosity), the volume injected, the pressure under which it is injected, and the depth of injection.[35]

Dr. Wojcech Norek[36] recently performed serial ultrasonograms on injected areas over a 10-week period. The injected fluid was found to remain within the subcutaneous fat compartment. Localized swelling and progressive changes were seen for 8 weeks, and then the subcutaneous layer, measurably thinner, appeared to stabilize.

Discussion

Phosphatidylcholine (PPC) is a major component of all cell membranes.[37] Its functions include fluidization of the cell membrane, signal transduction within the cell, and the formation of cellular energy.[38] A choline deficiency can contribute to liver disease, neurological malfunction (including Alzheimer's syndrome), and bipolar depression and has been implicated in some cancers and early cell death.[39-41] The benefits of PPC have been documented for 50 years (see sidebar for Benefits of PPC).

Ongoing studies by the ENL include the effect of PPC on adipocytes, animal trials on pigs and rabbits, studies on blood values after lipolysis, ultrasonic measurements of fat reduction following treatment, optimal treatment regimens, formula and dosage, combined use with lipoplasty, facial injections, treatment of cellulite, reduction of pain, side effects, ethics, and safety issues.[52]

The largest series of patients to date was treated by co-author Franz Hasengschwandtner from 2003 to 2005. He performed more than 3500 injections in 1500 patients. In his series only 1.03% of patients were nonresponders. While 14% of patients were satisfied after a single injection session, 87% were satisfied after 3 sessions. Nonresponders tended to be obese, estrogen-dominant women with hypoactive thyroid function. He observed no long-term side effects and no complications requiring further treatment. The average response to abdominal Lipodissolve was a 4-cm waistline reduction.

Heinrich[53] reported an average of 2.7-cm circumference reduction per application. He reported no recurrence of localized fat in the treated area. Hexsel et al's[54] series of 213 patients also showed efficacy combined with safety. She says that, "The greatest obstacle to PPC use is the limited knowledge of its pharmacology in the subcutaneous tissue." Her other concern is the potential for overuse and overdosage.

Safety Issues

There are 2 very significant safety issues. First and most worrisome is the current availability of Lipostabil and PPC compounds for direct purchase online without a prescription.[55] Despite multiple outreach to vendors by the ENL requesting that vendors at least require a prescription from a licensed physician, these compounds[56] remain available to the general public. In a few Internet sites, there are recommended general dosages for both intravenous and subcutaneous administration, as well as a description of injection techniques. The second safety issue is that untrained or self-taught licensed or paramedical personnel injecting these compounds will achieve poor results, or complications similar to those in Meissner's group.[57]

Lipodissolve is very safe when injected in appropriate candidates in small doses (no more than 0.5 mL per injection site), using a superficial to mid-layer fat target, placing injections no closer than 1.0 cm apart, and injecting no more than the recommended dosage of 2500 mg PPC per treatment. However, it is contraindicated in certain groups, certain anatomic areas, and in those with certain conditions, as follows:

- Pregnant or nursing women
- Minors or children
- Persons with allergy or sensitivity to soy products
- Patients with active or chronic infections
- Patients with diabetes, vasculitis, or circulatory disturbances
- In the presence of hepatic carcinoma or altered hepatic function
- In the presence of regional cancer in the area treated such as breast or skin cancer
- Any use in the female breast
- Autoimmune diseases such as pemphigus, SLE, dermatomyositis
- Obesity
- Extreme skin laxity

It is safe to use in Hashimoto's thyroiditis and in patients who are rheumatoid. However, it should be used cautiously in patients with compromised kidney function since there is a minor excretory role. Check creatinine clearance before proceeding.

ASAPS Position Paper Safety Issues

In 2004 and again in 2005,[58] the American Society for Aesthetic Plastic Surgery (ASAPS) posed questions directed to practitioners of mesotherapy. Although the Lipodissolve technique is not mesotherapy, the issues that underlie these questions pertain to any substance injected for the purpose of fat reduction.

- *How can we be sure that the appropriate amount of fat—neither too little–nor too much—is dissolved?*

This is an issue related to injection technique. Two recent in vivo studies using the Lipodissolve compound and following recommended dosages and techniques show limited and finite dispersion with the substance remaining within the subcutaneous fat compartment. The injector should always know where the needle tip is; the most frequent error of new injectors is injecting too deeply. Proper technique includes following the ENL recommendations for spacing, dose per injection, total dose, depth of injection, using the proper formulation at the proper concentration, and avoiding high pressure during injections. Untrained or self-taught injectors should strictly avoid this technique.

- *If fatty tissue is being dissolved, is other adjacent tissue affected? How is delivery limited only to target tissues?*

Other adjacent tissue is affected only if poor technique or incorrect dosage is used. Like lipoplasty, Botox, or filler injections, significant damage can be done if practitioners transgress the target area. While injecting Lipodissolve does not require the extreme precision of injecting Botox or fillers, hematomas, nerve injury, or intramuscular or fascial injections can easily occur if the injector does not know or respect the local anatomy. A sense of caution and good judgment, as well as careful patient selection, is recommended before proceeding.

- *What are the short-term and long-term side effects? Is there a possibility of cell damage or cell death?*

Short-term side effects include immediate erythema and localized burning at the injection site, lasting from 15 to 90 minutes on average. The severity varies from one patient to another. Later that day, most patients note bruising, swelling and, occasionally, the sense of a "jelly-like" consistency in the injected area. By day 3 to 7, the swelling has resolved considerably, but there may be some residual soreness. Facial swelling tends to persist a little longer. By day 10, early changes in body contour

may be seen. The biggest acceleration in contour change occurs at postinjection week 4 to 6 when a "push" of subcutaneous resolution can be seen on ultrasound. Most of the bioactivity is completed at 8 weeks. A small percentage of patients note prolonged sensitivity of the treated area for up to a month.

Systemic side effects, in some patients, include transient nausea and diarrhea in patients receiving maximal dose injections over a broad surface. No other adverse systemic side effects have been noted. In most studies, an average of 10% of patients reported weight loss in other areas with no change in diet or exercise. When blood values were checked, many patients noted a significant improvement in cholesterol and triglyceride values. One series reported a drop in serum triglycerides of up to 32%. The hepatoprotective, cardiac, and neurologic effects remain under study.

At the recent International Lipolysis Convention in Salzburg, June 18-19, 2005, the combined series of more than 1000 patients presented showed no infections, no large hematomas, no severe skin contour irregularities, no necrosis, no persistent numbness, and no skin induration, blistering, or long-term hyperpigmentation. The biggest complication reported in this global series was a 1% to 2.2% nonresponder rate, classified as a lack of visible or measurable response as determined by both patient and physician.

- *What problems might arise from adding an uncontrolled amount of the substance?*

The greatest concern of the ASAL and the ENL is use of this compound by the lay public or untrained practitioners. According to Hexsel et al,[54] Lipostabil was banned by the Brazilian National Health Vigilance Agency (ANVISA) in Brazil because of a lack of clinical studies and indiscriminate use in beauty salons and gymnasiums by lay persons. A similar concern was recently raised in the UK, which led to Lipostabil or PPC being unavailable to physicians. Meissner[57] recently reported a series of 15 self-injected patients who sought help for problems arising from injecting the wrong doses in the wrong sites. One patient injected the periumbilical region with an extremely high dose in a closely spaced, very superficial pattern and developed periumbilical skin necrosis. Several instances of vasculitis, blistering, cellulitis, and "dents" were noted in this series as well. Hyperpigmentation was also noted in some of these self-injectors.

Lipodissolve injections are a safe and effective method of achieving a measurable decrease in the thickness of localized fat deposits. Noticeable smooth-skin retraction in these small areas accompanies the fat dissolution, but medium to large areas of skin laxity do not respond as well. Good results depend on patient selection and the skill, experience, and judgment of the injector. The proper formula, injected in the correct location using the proper technique and dosage, is critical to the success of injection lipolysis. Lipodissolve is effective in treating small areas of fat deposition, cellulite, and postlipoplasty deformities. It will not replace traditional lipoplasty techniques, but is an excellent adjunct or alternative for those patients seeking minimally invasive treatment. ■

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