

## Obesity Treatment

# Mesotherapy for local fat reduction

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Received 18 February 2013; revised 9 April 2013; accepted 6 May 2013

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### Summary

Mesotherapy, which is the injection of substances locally into mesodermally derived subcutaneous tissue, developed from empirical observations of a French physician in the 1950s. Although popular in Europe for many medical purposes, it is used for local cosmetic fat reduction in the United States. This paper reviews manuscripts indexed in PubMed/MEDLINE under 'mesotherapy', which pertains to local fat reduction. The history of lipolytic mesotherapy, the physiology of body fat distribution, the mechanism of action of different lipolytic stimulators and their increased efficacy in combination are reviewed. Mesotherapy falls into two categories. Lipolytic mesotherapy using lipolytic stimulators requires more frequent treatments as the fat cells are not destroyed and can refill over time. Ablative mesotherapy destroys fat cells with a detergent, causes inflammation and scarring from the fat necrosis, but requires fewer treatments. The historic and empiric mixing of sodium channel blocking local anaesthetics in mesotherapy solutions inhibits the intended lipolysis. Major mesotherapy safety concerns include injection site infections from poor sterile technique. Cosmetic mesotherapy directs the area from which fat is lost to improve self-image. Studies were of relatively small number, many with limited sample sizes. Future research should be directed towards achieving a Food and Drug Administration indication rather than continuing expansion of off-label use.

**Keywords:** Cosmetic, fat necrosis, lipolysis.

**obesity reviews** (2013) **14**, 780–791

### Introduction

Mesotherapy was introduced by Michel Pistor who treated a man with asthma in France using intravenous procaine during the 1950s. The asthma did not improve, but the man's deafness did. Dr Pistor concluded that injections of procaine into the subcutaneous tissues would give many health benefits. As these tissues were of mesodermal origin, he called his treatment mesotherapy (1). Although mesotherapy is used for many indications in France, it is primarily used in the United States for cosmetic indications to induce local fat reduction and smoothing of the skin. Mesotherapy techniques, including a novel syringe with multiple needles that can be actuated like a gun, were brought to this country by physicians who travelled to France to train

under Dr Pistor. Mesotherapy also spread to Italy, where the Italian Society of Mesotherapy recently issued a consensus report on the definition of mesotherapy and its rationale and clinical use (2). This report, which called for clinical trial research, addressed issues such as pain control, venous and lymphatic insufficiency, oedematous fibrosclerotic panniculopathy, facial ageing and vaccination.

This review, using the term 'mesotherapy' to search PubMed/MEDLINE, also includes references found in the bibliographies of those indexed articles. Although there are articles that refer to other applications of mesotherapy such as skin rejuvenation, the treatment of back pain and hair restoration, this review is limited to local fat reduction and the cosmetic aspects of mesotherapy. This review describes the two different types of mesotherapy used for cosmetic

fat reduction, their efficacy and reported safety concerns. One form of mesotherapy for local fat reduction is based on stimulation of lipolysis in fat cells, and the other is based on destruction of fat cells using a detergent. This preferential melting of fat, sometimes referred to as body contouring or body sculpting, remains controversial despite the research that will be reviewed. Nevertheless, it is joining other therapies, such as botulinum toxin injections, as a common and popular cosmetic procedure. Thus, it is important for those interested in the treatment of obesity to be familiar with mesotherapy, how it works, its benefits and its safety concerns.

### Lipolytic stimulation

Lipolytic mesotherapy is based on the activation of lipolysis in fat cells. Mesotherapy for lipolytic stimulation was initially based on empirical observations. More recently, *in vitro* experiments using the different lipolytic stimulators that mesotherapists commonly employ have been performed. *In vivo* studies with lipolytic mesotherapy can be further subdivided based on body location.

Women have complained that fat on the hips and thighs is more difficult to mobilize, but these empirical observations were not initially given credence by the scientific community. These observations are now scientifically confirmed (3,4) and it is understood that a person's fat distribution is determined by the relative lipolytic thresholds of fat cells in different body locations. We now know, e.g. that a greater number of  $\alpha$ -2 adrenergic receptors are found on fat cells of women's hips and thighs, and that these  $\alpha$ -2 adrenergic receptors inhibit lipolysis. Oestrogen increases the number of  $\alpha$ -2 receptors in these locations, accounting for a woman's gynoid fat distribution.

Because of this elevated lipolytic threshold, women have greater difficulty losing fat from their hips and thighs as compared to their abdomen and breasts where the lipolytic threshold is relatively lower (3,5).

Preferential fat reduction in a given body area is not possible under normal conditions because the endogenous lipolytic stimulators, such as catecholamines, reduce all body lipolytic thresholds to the same degree without creating any relative change between depots. A  $\beta$ -adrenergic stimulator such as isoproterenol, however, can be locally injected into a specific fat depot, reduce the lipolytic threshold in the area and cause accelerated differential fat loss from that targeted depot.

The biochemical process of lipolysis has been defined in the past 20 years. More recent studies have evaluated factors that regulate and affect this lipolytic process. There are at least three general mechanisms by which lipolysis can be increased: (i) inhibition of phosphodiesterase or the adenosine receptor (5,6); (ii) activation of the  $\beta$ -adrenergic

receptor or (iii) inhibition of the  $\alpha$ -2 receptor. Aminophylline, isoproterenol or forskolin, and yohimbine are thought to act on the three different lipolytic signalling pathways correspondingly (7) (Fig. 1).

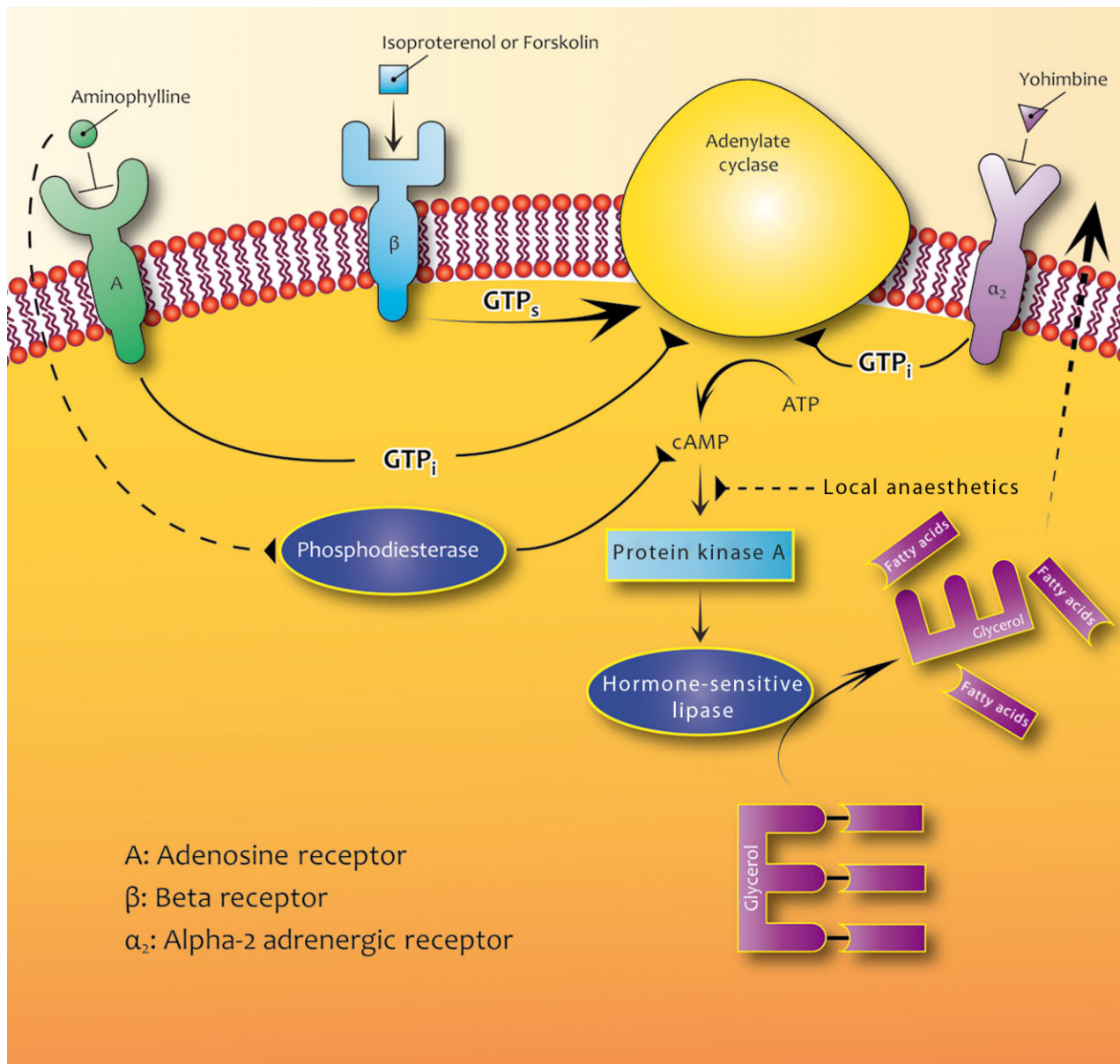
### Aminophylline

Experiments with cultured human adipocytes demonstrated that  $10^{-4}$  M aminophylline increases lipolysis by increasing glycerol generation by 1.5-fold compared with the non-stimulatory buffer control ( $P < 0.001$ ) (8).

In a proof-of-concept study, a 10% aminophylline ointment was applied to one thigh and the ointment base to the other thigh by a blinded individual 5 d a week for 4 weeks in five obese women. In order to maximize lipolysis, participants were placed on an 800-kcal  $d^{-1}$  diet, were encouraged to walk and their thighs were wrapped in towels soaked in warm hypertonic (600–900 mOsm  $L^{-1}$ ) magnesium sulphate solution for 30 min prior to the ointment application. There was a  $1.5 \pm 0.77$  cm greater loss of girth from the aminophylline-treated thigh compared with the control thigh ( $P < 0.02$ ). Thigh girth measurements were made two-thirds of the way from the knee to the greater trochanter, with weight supported on the measured leg which created a reproducible amount of muscle tension and reduced variability. A heat rash from the hypertonic warm wraps was seen in one subject and was the only adverse reaction noted (9).

Other blinded and controlled human studies with larger sample sizes confirmed the effectiveness of topical aminophylline in both ointment and cream forms applied to the thigh. One experiment involved multiple studies each using a different concentration of aminophylline cream. The experiment was double-blinded and several of the studies used warm hypertonic soaks, diet or exercise. Fifty-one subjects were included in these studies, and the results demonstrated statistically significantly greater losses of thigh girth from the aminophylline-treated thigh compared with the control thigh. One patient developed a rash when exposed to 2% aminophylline cream. The rash resolved after discontinuation of the cream. A greater girth loss was seen using 0.5% aminophylline cream, and the same woman did not have a recurrence of the rash (5).

Another human study applied 0.5% aminophylline cream to the waist of 25 middle-aged subjects and compared the girth loss during a weight loss programme to another 25 middle-aged people who received no aminophylline to the waist. This study confirmed that the ability of aminophylline cream to cause local fat reduction was not limited to the thigh. Participants in the study were placed on a 1,200-kcal  $d^{-1}$  diet and an exercise programme to decrease their systemic lipolytic threshold. The group of 25 subjects treated with the aminophylline cream and the 25



**Figure 1** Aminophylline, isoproterenol, forskolin and yohimbine all activate lipolysis by increasing concentrations of cyclic adenosine monophosphate (cAMP). These compounds do this either by increasing the activity of adenylate cyclase or inhibiting cAMP degradation. Increased levels of intracellular cAMP activates protein kinase A, which increases the activity of hormone-sensitive lipase, resulting in the degradation of triglycerides and the release of fatty acids and glycerol from the cell (83).

As a medication, aminophylline is a short-acting, weak bronchodilator used to treat asthma. Intracellularly, aminophylline is a phosphodiesterase inhibitor and a non-selectively adenosine receptor blocker. Phosphodiesterase inhibition causes cAMP levels to rise by inhibiting its degradation.

A blocked adenosine receptor prevents it from inhibiting adenylate cyclase via inhibitory G proteins (84).

As a medication, isoproterenol increases cardiac output and is used to treat bradycardia and atrioventricular block. Intracellularly, isoproterenol is a direct acting synthetic catecholamine, similar to epinephrine, which activates  $\beta$  receptors non-selectively. This increases the activity of adenylate cyclase via stimulatory G proteins (85).

Forskolin is an herbal extract used as a vasodilator. It is sometimes used to treat hypertension, asthma and glaucoma. Intracellularly, forskolin is a  $\beta$  receptor activator that activates adenylate cyclase similar to isoproterenol (5).

As an over-the-counter dietary supplement, yohimbine increases peripheral blood flow and is used to treat impotence. Intracellularly, yohimbine preferentially blocks  $\alpha_2$  receptors, which prevents inhibition of adenylate cyclase via inhibitory G proteins (86).

Local anaesthetics uncouple adenylate cyclase from activating hormone-sensitive lipase (8).

untreated control subjects had a significant overall body mass index loss with no statistical difference between the two groups. The experimental group lost approximately 5 cm more in waist circumference vs. the control group after 12 weeks of treatment ( $P < 0.001$ ). No side effects were observed (6).

### Isoproterenol

An early study concluded that isoproterenol stimulates the  $\beta$ -adrenergic pathway through a mechanism similar to endogenous catecholaminergic stimulators. This study involved treating fat biopsies of trained marathon runners and sedentary males with epinephrine, isoproterenol and propranolol (10). Another study confirmed these findings using cultured human adipocytes and demonstrated that isoproterenol-treated fat cells increased their lipolytic rate measured by glycerol generation compared with untreated controls. Isoproterenol increased lipolysis more than 1.5-fold compared with the control ( $P < 0.002$ ) (8). A separate study found that the dose response for isoproterenol was U-shaped and the greatest lipolysis occurred at a concentration of  $10^{-6}$  M. The lipolytic effects of isoproterenol were also augmented by twofold when combined with  $10^{-6}$  M prednisolone, which reduced lipolytic down-regulation that occurs with isoproterenol alone (11–13) (Fig. 2).

In a study of five women who were given daily  $10^{-5}$  M isoproterenol injections around the circumference of the thigh 3 days per week for 4 weeks, isoproterenol reduced thigh girth. The study was double-blinded and the control was saline injections around the circumference of the patient's alternate thigh. The women were placed on a 600-kcal  $d^{-1}$  diet and were encouraged to participate in a walking programme to decrease their systemic lipolytic threshold. There was a reduction in the girth of the isoproterenol-treated thigh of  $1.8 \pm 0.89$  cm greater than the control thigh injected with saline ( $P < 0.05$ ). There were no side effects (9).

Another study treated lipomas in 10 middle-aged subjects with injections of  $10^{-6}$  M isoproterenol combined with  $10^{-6}$  M prednisolone. The lipomas included in the study were at least 2.5 cm and were treated five times a week for 4 weeks. The lipomas decreased by 50% in volume with a large variance. Microdialysis confirmed that the lipolysis of both subcutaneous fat and lipomas responded better when pretreated with prednisolone, as suggested by earlier *in vitro* studies (11).

### Yohimbine

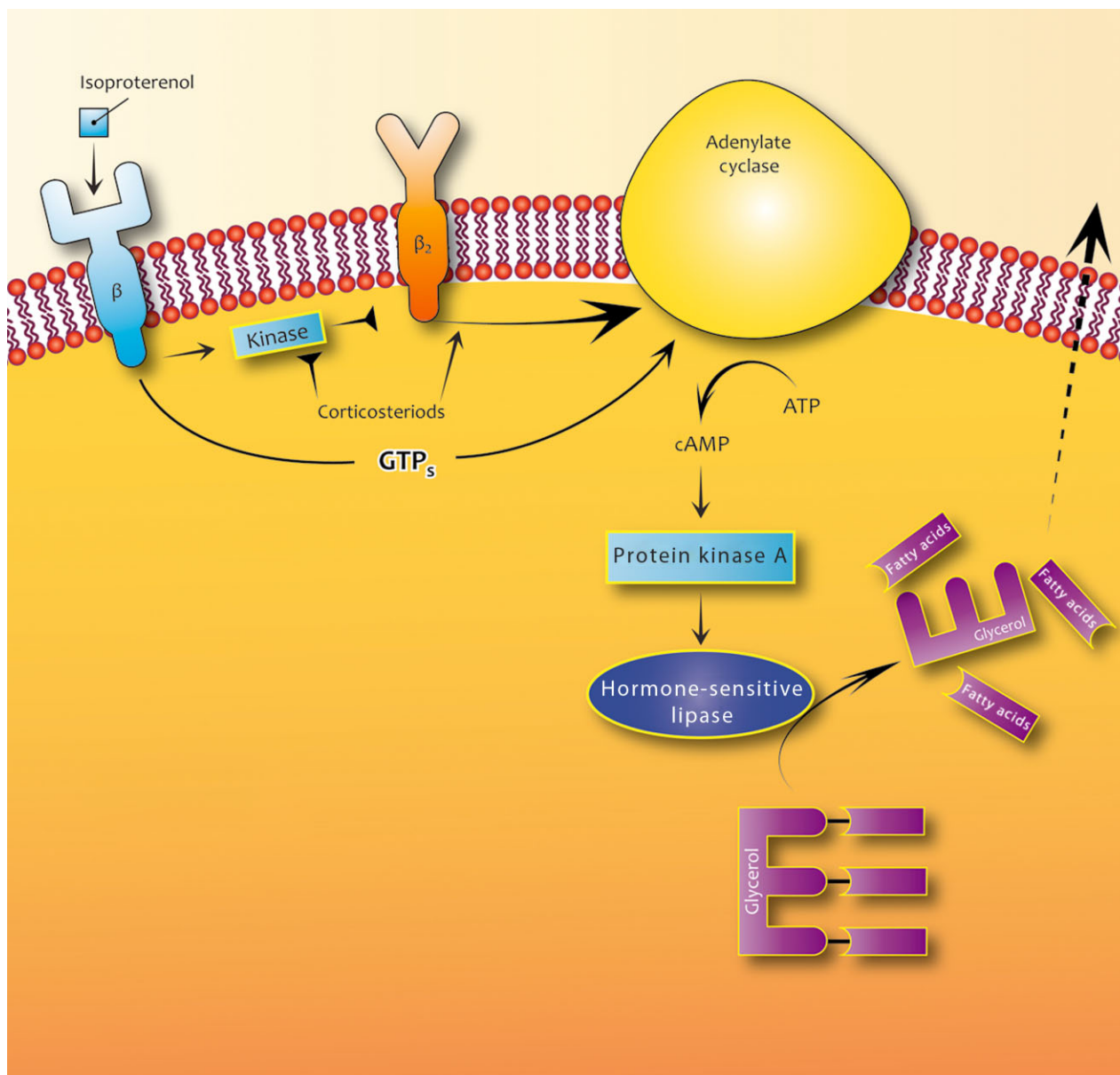
The effect of yohimbine on lipolysis was studied in several experiments. Cultured human adipocytes treated with yohimbine were compared to human adipocytes treated

with a buffer control. There was a twofold increase in lipolysis expressed as glycerol generation with yohimbine compared with the buffer control ( $P < 0.002$ ) (8). A human study using yohimbine ointment on the thigh found a  $0.75 \pm 0.35$  cm greater decrease in the girth of the treated thigh compared with the ointment base-treated control thigh, but the results were not statistically significant because of the small sample size and problems with measurement technique (5,9). During these experiments, it was appreciated that the variability of thigh measurement could be minimized by having the subject support weight on the measured thigh, making the muscle tension more reproducible. Future experiments consistently measured thigh girth with weight supported on the measured thigh, and these studies have given statistically significant results despite similar mean changes due to the reduced variability.

### Combinations

Isoproterenol, aminophylline and yohimbine should have additive effects as they act at different points in the same physiological pathway. Lipolysis in human adipocytes treated individually with isoproterenol or aminophylline was therefore compared to lipolysis in human adipocytes treated with the combination of isoproterenol and aminophylline. There was a 30% increase in lipolysis using the combination compared with lipolytic stimulation by the individual components (8).

The conclusions of these cell culture experiments were confirmed in a clinical trial in which a topical combination ointment gave greater thigh girth reduction than the individual components. In this set of experiments, five women were treated with an ointment containing a combination of  $2.5 \times 10^{-4}$  M forskolin,  $5 \times 10^{-4}$  M yohimbine and  $1.3 \times 10^{-2}$  M aminophylline ointment for 6 weeks. The subject's alternate thigh was used as a control, with a similar ointment not containing the active compounds investigated for comparison. Their girth loss was also compared to a similar number of women who were treated with these compounds individually. Women who were treated with the combination lost  $2.03 \pm 1.36$  cm more girth from their treated thigh as compared with their alternate control thigh. Women treated with individual forskolin ointment lost  $1.0 \pm 0.61$  cm more girth similarly, and women treated with yohimbine ointment lost  $0.75 \pm 0.35$  cm girth similarly. Those treated with aminophylline ointment also lost  $1.5 \pm 0.77$  cm more girth as compared with their alternate control thigh. Based on these studies, it was therefore concluded that women treated with a combination ointment lost more thigh girth compared to treatment with the individual compounds, and ingredients working



**Figure 2** Low-dose corticosteroid pre-treatment, such as prednisolone, in cultured human adipocytes prevents isoproterenol-induced  $\beta_2$  down-regulation by  $\beta$ -adrenergic receptors involved in lipolysis. The resulting increased lipolysis is expressed as glycerol fold induction over baseline ( $n = 8$  replicates of wells in a 96-well plate).

Low-dose corticosteroids, such as prednisolone, increases efficiency of coupling between the  $\beta_2$  receptors and the adenylate cyclase system (11).

by different mechanisms in the same physiological pathway are indeed additive (5,9).

### Other studies

In contrast to all of the above-mentioned experiments, two studies performed in South Korea drew different conclusions. One of these studies analysed rats after aminophylline injection to the abdomen and found no fat-reducing effects (14). Another study analysed aminophylline injec-

tion on human thighs and found no statistical reduction in thigh girth. This latter study was performed on 20 women less than 40 years of age who had localized obesity on their thighs. The study was double-blinded, and the other untreated thigh was used as a treatment control. The authors noted many possible explanations for their contradictory findings but failed to appreciate that the lidocaine given with the injected aminophylline cocktail was a lipolytic inhibitor. The importance of lipolytic inhibition by lidocaine is explained in the following section (15).

### Effects of local sodium channel blocking anaesthetics

Several experiments have concluded that lipolysis is inhibited by local anaesthetics that inhibit sodium channels in the nerves. A study in cultured human adipocytes compared the effects of isoproterenol and aminophylline with and without lidocaine. Another study compared the effects of isoproterenol, aminophylline and yohimbine in cultured human adipocytes with and without lidocaine. Both these studies demonstrated that lidocaine dramatically reduced lipolysis measured by glycerol generation to a level that was not statistically different from the buffer-treated control (8). Other experiments involving lidocaine (16), procaine (7) and prilocaine drew similar conclusions. This supports the conclusion that sodium channel inhibiting local anaesthetics, as a class, inhibit lipolysis in fat cells (17). As the original observations by Pistor were made with procaine, topical anaesthetics have been routinely included in mesotherapy solutions. The inclusion of sodium channel inhibiting anaesthetics uncouples adenylate cyclase from hormone-sensitive lipase, an enzyme responsible for lipolysis in the fat cell and should therefore not be used in mesotherapy preparations (17) (Fig. 1).

### Ablative mesotherapy

In contrast to lipolytic stimulation to enhance lipolysis, the second type of mesotherapy for cosmetic fat reduction is based on the destruction of fat cells using a detergent. This technique, termed ablative mesotherapy, is usually performed using a phosphatidylcholine and deoxycholate formulation, or more recently deoxycholate alone. Other terms for ablative mesotherapy include lipodissolve, adipolysis, adipocytolysis, adipocyte lysis, adipolytic therapy and fat necrosis (18,19).

There is no standard protocol for ablative mesotherapy. Most recommendations are given by individual researchers and are based on their own clinical experience. Some researchers recommend injection depths of 4 mm, while others recommend injection depths as deep as 13 mm in order to penetrate the mid-layers of the subcutaneous fat in those who have thick fat pads. Some researchers also recommend that the distance between injections be 1–4 cm, while others advocate the use of a grid pattern at 1- to 1.5-cm intervals. The recommended frequency of repeat injections varies from 1-week intervals, with approximately 4–15 sessions, to 4- to 8-week intervals, with only 1–4 sessions. The volume of the injections is usually 0.4–0.5 mL and can be administered with a needle and syringe (19–21). This section will focus on injectable phosphatidylcholine and deoxycholate, the major components used in ablative mesotherapy.

### Phosphatidylcholine

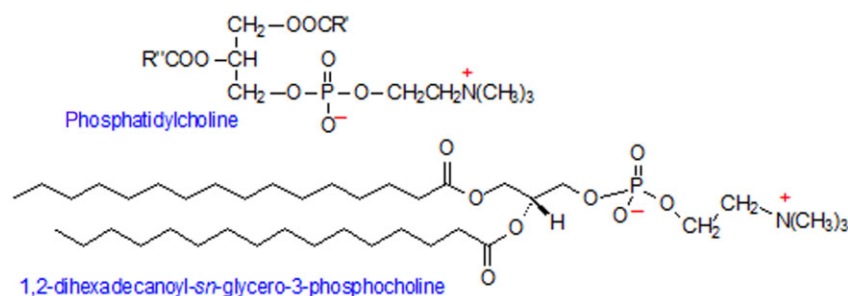
The belief that phosphatidylcholine is the active component in ablative mesotherapy was first popularized by Patricia Rittes, a Brazilian dermatologist who reported a reduction in infra-orbital fat using a commercially available solution. As phosphatidylcholine is a very viscous lipid, it requires a detergent to solubilize it sufficiently for use as an injectable preparation. Deoxycholate is often used for this purpose and was included in the commercially available solution used by Dr Rittes (22).

Phosphatidylcholine can exist in an aqueous environment as a lipid bilayer, a vesicle with a hydrophilic centre, or in higher concentrations, as a micelle with a hydrophobic core. The form of phosphatidylcholine is important because triglycerides released from disrupted fat cells can only be transported by the micelle and lipid bilayer forms. Presently, mesotherapists use different concentrations of the phosphatidylcholine, making it difficult to determine from the literature which form is being investigated (23).

Early experiments treating infra-orbital fat with 50 mg mL<sup>-1</sup> phosphatidylcholine relied upon subjective measures of success (22,24). Later studies emphasized the weakness of relying on patient reported outcomes and the importance of using blinded observers to evaluate success (25). The next step in advancing ablative mesotherapy was a study of 441 patients injected at multiple body sites with a phosphatidylcholine and deoxycholate mixture. This study demonstrated that ablative mesotherapy could be used to treat localized fat deposits in the abdomen, hips, thighs, upper arms and face, in addition to the lower eyelid, and changed the belief that ablative mesotherapy had to be reserved for use in small, well-defined zones resistant to diet and exercise (19,26–29). A subsequent study suggested that optimal results were seen in those closest to their desirable weight, emphasizing the cosmetic nature of ablative mesotherapy (19).

Physiologically, phosphatidylcholine acts in the body in three important ways: (i) to emulsify dietary fat in bile as part of the digestion process; (ii) to act as a component of apolipoproteins that are essential for cholesterol metabolism and (iii) to act as an essential component of cell membranes. Phosphatidylcholine is a dietary compound from which the body makes acetylcholine and surfactant for the lung alveoli. Gall stone formation, fatty liver disease and fibrosis are also attributed to phosphatidylcholine (30–39). In addition, preliminary evidence suggests that it may play a role in neurological, endocrine and psychological disorders (40–42). The important physiological roles of phosphatidylcholine led mesotherapists to attribute fat cell destruction to it as well, without any mechanistic rationale for doing so (Fig. 3).

Later on, the idea that phosphatidylcholine was the active moiety in fat cell destruction caused several potential

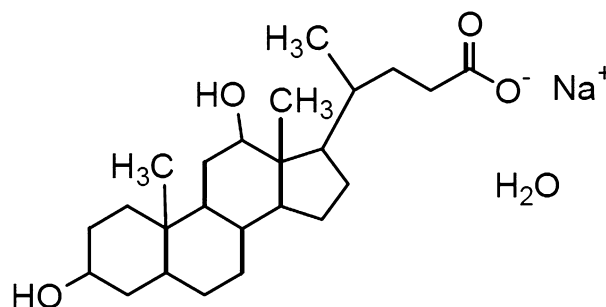


**Figure 3** Phosphatidylcholine is a naturally occurring phospholipid with a glycerol backbone esterified to choline and contains two long-chain fatty acids with both polar and non-polar components.

mechanisms to be proposed, including apoptosis and activation of hormone-sensitive lipase (26,43–45). Eventually, by taking fat biopsies before and after treatment with phosphatidylcholine, which was solubilized with deoxycholate, it was established that cell walls were disrupted and inflammation was created, resulting in scar tissue formation (19).

Although a study in 2004 demonstrated that deoxycholate alone and two other detergents lysed human keratinocytes, fat cells and muscle cells in culture, the field was slow to accept the pivotal role of deoxycholate (19,46–48). The slow acceptance of deoxycholate as the critical component of the mixture was partly due to the insolubility of phosphatidylcholine, which precluded its evaluation alone on cell membranes in living humans (28). The definitive study addressing the controversy over the active ingredient was carried out in 2010. Phosphatidylcholine was dissolved in inert mineral oil, and cytotoxicity on cultured adipocytes was measured using oil red O and levels of lactate dehydrogenase. This study convincingly demonstrated that sodium deoxycholate was the active agent and that phosphatidylcholine alone did not cause cell lysis (45,49).

There seems to be a beneficial role for phosphatidylcholine in the combined formulation, however. Phosphatidylcholine reduces the intensity and severity of the fat necrosis, as well as reducing scar formation (49,50). Although the mechanism by which phosphatidylcholine achieves these beneficial effects is unknown, hypotheses include (i) phosphatidylcholine acting as a buffer for deoxycholate as the pH of the deoxycholate-phosphatidylcholine solution is closer to human tissue pH than the pH of deoxycholate solution alone; (ii) phosphatidylcholine acting as a drug delivery system by creating non-covalent bonds with deoxycholate to permit the briefly inactivated deoxycholate detergent to diffuse beyond the injection site or (iii) phosphatidylcholine acting as a regulator to attenuate the intensity and degree of fat necrosis (50). Based on these considerations, deoxycholate alone is recommended for use in small localized fat deposits with a phosphatidylcholine and deoxycholate combination reserved for larger treatment areas (45). The observation that post-injection resolution of inflammation is faster with the phosphatidylcholine and deoxycholate mixture compared to deoxycholate alone supports these recommendations (51).



**Figure 4** Deoxycholate is a mild detergent commonly used to solubilize phosphatidylcholine.

## Deoxycholate

In contrast to phosphatidylcholine, deoxycholate is a water-soluble compound. In the body, it acts as a bile acid in the intestine to emulsify fat and is also a metabolic by-product of intestinal bacteria. As an exogenous chemical, deoxycholate acts as a mild detergent to solubilize phosphatidylcholine. Its structure is shown in Fig. 4. From a chemical perspective, deoxycholate can exist in four forms – micelles, vesicles, monomers and crystals. Deoxycholate in a monomer or a crystal form leads directly to cell damage, but as a micelle, deoxycholate mobilizes fats released from adipocytes. In ablative mesotherapy, the form in which deoxycholate exists depends mostly on its concentration (23,31).

Several studies *in vivo* and *in vitro* have tried to illuminate the effects of deoxycholate alone in ablative mesotherapy. One of these studies demonstrates that deoxycholate is the active ingredient causing cell lysis with cell death in ablative mesotherapy. Another study in lipomas demonstrated that the adverse events were dose-dependent and limited to local reactions (45,51–53). Studies using human adipocytes treated with increasing concentrations of deoxycholate gave a non-linear increase in glycerol, suggesting that the release of lipolytic enzymes with triglyceride during cell lysis stimulates lipolysis (49,50). These results were confirmed by histological studies using serial human fat biopsies. Additional cell

culture experiments demonstrated that deoxycholate lyses not only fat cells but also fibroblasts, endothelial cells and myocytes (50,53,54).

## Safety

### Infection

Infection is clearly the most commonly reported safety concern related to mesotherapy. We identified 16 separate reports of infection resulting from its use. The case reports and case series represent a total of 198 separate cases of mesotherapy-associated infection, all of which were caused by atypical mycobacteria. Some of the descriptions are particularly instructive. One series of 15 cases involved mesotherapy with procaine and lecithin, which would not be expected to give lipolysis due to procaine in the mixture (55). These subjects were exposed to the risk of infection without any reasonable hope of fat loss. Another case described disfiguring scarring due to the infection (56). A series of 16 cases was described in which six subjects received triple antibiotic therapy and eight received dual antibiotic therapy. The mean duration of treatment was 14 weeks with a range of 1–25 weeks. All of the patients recovered after 2 years after the infection, except one subject who was still infected. The average time to healing was 6.2 months (57).

Another case series described 39 women who developed atypical mycobacterial infections from mesotherapy at the same beauty salon. The number of lesions per patient varied from 3 to 20. The lesions were indurated, erythematous papules varying in size from 0.5 to 6 cm, some of which progressed to fluctuant boils with suppuration, fistulization and scarring (58). Another report of 16 cases came from an individual mesotherapy practice. It was determined that the PCR (polymerase chain reaction) fingerprint of the atypical mycobacterium from the patient's wounds was the same as the atypical mycobacteria grown from tap water in the examination room used for the injections. It was later concluded that when the automatic repetitive injector became soiled with injection products, it was cleaned with soap and tap water (59). Another outbreak in 35 patients arose from a training session in which the students learning mesotherapy injected each other. This setting would also be consistent with a possible breakdown in hygiene (60). A report from the U.S. Communicable Disease Center related atypical mycobacterial infections in 14 patients who received mesotherapy from a single unlicensed practitioner in Washington, DC. This report emphasized that all 14 patients reported breaches in hygiene and deviations from safe injection practices. None of the injected substances, except procaine, were approved for injection by the U.S. Food and Drug Administration (FDA). It was also pointed out in the report that in 2003, the

Brazilian government banned the use of phosphatidylcholine in mesotherapy for cosmetic fat reduction due to concerns about safety and efficacy (61).

Judging from the number of reports of atypical mycobacterial infections, one can easily get the impression that these infections are unique to mesotherapy. This does not seem to be the case. Of the four reports of atypical mycobacterial infections from one salon, one was due to mesotherapy and three were due to foot baths (62). Another report on the infections associated with laparoscopic procedures and mesotherapy in the city of Belem, Brazil, found that of 67 atypical mycobacterial infections, only 8 were associated with mesotherapy, and all were from procedures performed in a single clinic (63). Thus, although atypical mycobacterial infections are not unique to mesotherapy, they seem to be the most prevalent adverse event and can be eliminated with attention to proper hygiene and appropriate injection techniques.

### Non-infectious skin complications

There are reports of urticaria associated with mesotherapy, a report of urticaria pigmentosa triggered by mesotherapy and an urticarial reaction to the ethylenediamine in aminophylline used in a mesotherapy treatment (64–66). There is a report of a granulomatous cutaneous reaction to mesotherapy, a report of non-infectious granulomatous panniculitis and a report of mesotherapy-induced panniculitis responding to dapsone treatment (67–69). These reports are consistent with the use of deoxycholate, and its known detergent action of destroying fat cells and causing inflammation. Case reports exist of mesotherapy triggering psoriasis and granuloma annulare (70,71). We also found a report of self-injected lipase obtained from the Internet. The authors called for better regulation as the person was not a health professional, and lipase has no history of use in mesotherapy (72).

Patients seeking mesotherapy often have other cosmetic procedures. Twelve patients who had polyacrylamide gel implants for cosmetic purposes had them punctured during mesotherapy. This resulted in pain, swelling, redness and induration. Resolution over 1–2 weeks was obtained with anti-inflammatory agents, drainage and empiric antibiotic therapy (73). Thus, it is important for mesotherapists to avoid puncture of polyacrylamide gel implants. One patient is reported who had a large haematoma after the laceration of a vessel during mesotherapy. This was confirmed histologically when a 4-cm encapsulated nodule was surgically excised (74).

### Systemic complications

A case of acute psychosis was reported 8–12 h after mesotherapy in a woman with no personal or family history of



psychosis. The woman was taking no drugs and the psychosis resolved over 2 days of observation without specific intervention. The contents of the mesotherapy cocktail were unknown (75).

A case of ischaemic colitis was reported in a 39-year-old woman 8 days after the initiation of two days of mesotherapy in which she was injected daily with unknown doses of aminophylline, epinephrine and lidocaine. She was also given oral fluoxetine 10 mg, ephedrine 10 mg, caffeine 50 mg and green tea powder 250 mg per dose, but stopped taking these 6 days prior to reporting to the emergency room with haematochezia. The diagnosis was confirmed by colonoscopy and symptoms resolved over 2 days with management of fluids and antibiotics (76).

A 32-year-old woman developed erythematous, indurated plaques and nodules at the site of mesotherapy injections and was subsequently diagnosed with Behcet's disease. Due to her history of oral aphthous ulcers for 2 years and abdominal pain for 2 months prior to the mesotherapy, it appears that the mesotherapy may have caused the diagnosis to be made, but the actual Behcet's disease may have preceded the mesotherapy (77).

Substances in the mesotherapy solutions can be responsible for systemic effects. A case is described in which thyrotoxicosis was induced by mesotherapy with triiodothyroacetic acid (78). Several patients who received mesotherapy with Chinese herbs for cosmetic purposes developed a nephropathy characterized by progressive fibrosis and tubular atrophy of the kidneys. The exact cause of the nephropathy was not discovered, and the herbs used in the mesotherapy were not approved to be safely administered by an injectable route (79). There is also a report of systemic lupus erythematosus after mesotherapy with acetyl-L-carnitine (80).

## Discussion

When asked, most people admit that they are concerned about their appearance. The reason for this is not entirely due to vanity. There is ample evidence that increased attractiveness directly translates to more wealth and a higher social status. Better looking people are more confident, perceived as more intelligent and have more social capital with which to make friends and assume leadership roles (81). One of the many factors affecting a person's appearance is their fat distribution. If diet and exercise fail in achieving the desired result, people often turn to plastic surgery or liposuction. Mesotherapy provides an alternative to this approach and has many advantages. In appropriate patients, mesotherapy is less invasive, less costly and has a quicker recovery time, while still providing benefits.

Although both types of mesotherapy are effective, the two procedures are mechanistically different, and several factors should be taken into account when deciding

which to use. An ablative mesotherapy treatment regimen involves fewer treatment sessions than lipolytic mesotherapy. Moreover, ablative mesotherapy is longer lasting because fat is destroyed and replaced with scar tissue. Disadvantages of an ablative mesotherapy approach predominantly include local symptoms such as inflammation, scar formation, transient pain and oedema.

In contrast, a lipolytic mesotherapy treatment regimen has far fewer local side effects and can be used in areas unsafe for ablative injection, such as the infra-orbital space. Disadvantages include more frequent treatment visits and the fact that lipolytic mesotherapy is fleeting because fat loss only lasts as long as the lipolytic threshold is reduced. When the injections are stopped, the normal lipolytic threshold resumes and fat distribution goes back to that which is characteristic of that person. In contrast to ablative mesotherapy which, like liposuction, causes any fat regained to be distributed into other fat cells that were not destroyed (82), lipolytic mesotherapy allows the fat to return to the distribution normal for that individual.

It must be emphasized that mesotherapy of both types is a cosmetic procedure to help re-contour the body. It is not a treatment for obesity. Therefore, the best results are seen in individuals that are near their desirable weight and seek removal of specific small areas of body fat. An additional use for lipolytic mesotherapy is to direct the areas of the body from which fat is preferentially lost during a weight loss programme. This is particularly useful in women who are pear-shaped with larger hips and thighs as these areas are resistant to fat mobilization. Women with this type of fat distribution typically have smaller breasts and become distressed when the breasts are the first place from which they notice fat mobilization during weight loss. By using mesotherapy to lower the lipolytic threshold in the hips and thighs, the fat these women lose during weight loss will be from these targeted areas. Although fat can be preferentially mobilized from the waist during weight loss, this is an area with an inherently lower lipolytic threshold, making fat loss from the abdomen less problematic than from the hips and thighs in women.

## Further research

There are several areas for future research. First, it must be stressed that no medication is approved for mesotherapy treatment for local fat reduction. Investigational studies have been performed that may result in approval of deoxycholate or lipolytic stimulators for cosmetic mesotherapy in the future, but at the time of this writing, mesotherapy for cosmetic fat reduction is an off-label treatment. In addition, some of the injections that are noted in this review are herbal products, which are not approved for injection. In view of the fact that off-label use is widespread and is becoming increasingly common, more clinical trials per-

formed under an investigational new drug number through the FDA should be performed to establish an optimal treatment regimen for subcutaneous injection. Parameters such as frequency, duration, concentration and technique should be established to achieve the greatest safety and efficacy. Follow-up studies evaluating the duration of the benefits of mesotherapy are also important. Because both methods of mesotherapy are partially effective for lipomas, more studies should be undertaken in this area using different lipolytic agents with longer durations of action to allow less-frequent injection regimens.

## Conclusion

Mesotherapy is capable of causing local fat reduction by two distinct mechanisms: fat ablation and lipolytic stimulation. The studies on which this review was based are relatively few in number and many were limited by small sample sizes. Although one might be tempted to equate mesotherapy to the use of Botox for cosmetic purposes, unlike Botox which is approved by the FDA, no mesotherapy product currently has an FDA approval as a cosmetic treatment. Due to the increasing off-label use of cosmetic mesotherapy, an emphasis should be placed on studies to demonstrate the safety and efficacy needed for such an approval, and further off-label use should be limited until FDA approval is obtained.

## Conflict of interest statement

Thomas Guillot and Lionel Bissoon performed mesotherapy treatments to patients in their professions. Frank Greenway is a consultant of Techenterprises, LLC for the development of a topical fat reduction cream and Lithera for the development of aesthetic products. Saman Jayasinghe has no conflict of interest to disclose.

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