Modification of Subcutaneous Adipose Tissue by a Methylxanthine Formulation: A Double-Blind Controlled Study

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BACKGROUND. **Excessive subcutaneous adipose tissue is typically treated by physically removing the fat through liposuction, but cost and accessibility have popularized alternative treatments for reducing adipose tissue thickness.**

OBJECTIVE. **The purpose of this study was to test the absolute and relative effectiveness of a liposome-encapsulated caffeine-based cream in modifying subcutaneous adipose tissue.**

METHODS. **Forty-one patients consented and completed the double-blind, single-center, placebo-controlled study. Caliper measurements, tape measurements, and photographs were taken over a 2-month period.**

RESULTS. **Both concentrations of the cream were found to significantly reduce the thickness of the adipose tissue in all areas of the body. In addition, the more concentrated cream was significantly more effective than the less concentrated cream in the areas of the hips and the triceps.**

CONCLUSION. **The caffeine-based liposome-encapsulated cream significantly reduced the thickness of the subcutaneous fat over a 2-month period.**

EXCESSIVE SUBCUTANEOUS FAT can cause irregular physical contours in specific areas of the body that are popularly perceived as being unsightly and unhealthy.[1–3] Typical treatments include physical removal of the excess fat through surgical liposuction or ultrasound liposuction.[4] Recently a mechanical system for contouring the subcutaneous fat has gained popularity and been shown to be effective in reducing the thickness of subcutaneous adipose tissue.[5]

The use of topical creams for modifying subcutaneous fat has been heavily marketed in recent years. However, the actual efficacy of these products has not been scientifically proven.[6] Many of the products that have been available are based on aminophylline, which is a methylxanthine, and though some of the research is encouraging,[7] there is little conclusive data pointing to a significant reduction in adipose tissue thickness from the use of these products.[8] More recently, several products have become available that are based on caffeine, another methylxanthine.

The mechanism by which methylxanthines such as aminophylline and caffeine modify subcutaneous layers has not been systematically illustrated. However, there is research to show that methylxanthines cause lipolysis or hydrolysis of adipose tissue into free fatty acid chains.[9] It is also believed that the endocytotic process by which caffeine is absorbed into the cell stimulates the sodium pump to release sodium into the extracellular fluid, causing intracellular dehydration.[9,10] In addition, the inability to ensure that the methylxanthines are delivered to the appropriate subcutaneous layer has most likely contributed to the poor results seen in the past with aminophylline and caffeine-based creams. Encapsulating the ingredients in a liposome may ensure delivery of the methylxanthines to the appropriate layer, as encapsulated liposomes have been shown to be effective in delivering higher concentrations of ingredients to the subcutaneous layers of the skin.[11]

The purpose of this study was to scientifically study in a double-blind format the dose response action of a liposome-encapsulated caffeine-based formulation on subcutaneous fat. In addition, the relative efficacy of two different concentrations of caffeine was tested.

Materials and Methods

A single-center, double-blind, randomized, bilateral, placebo-controlled study enrolled 49 patients, 41 of whom completed the study. The eight who did not complete the study were unable to be contacted as to the reason for their incompletion. Patients were approved to participate in the study by a number of criteria. Both men and women were accepted if they had slight to moderate amounts of subcutaneous adipose tissue in the hips, thighs, abdomen, or upper posterior arm area. The patients had to be in generally good health and between the ages of 18 and 65. Patients were ex-

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cluded if they were pregnant, if they had experienced recent excessive (20 lb/month) weight gain or weight loss, if they were on any hormone therapy excluding birth control or estrogen replacement, or if they had a coincidental rash in the area of application. The patients were also excluded if they had ever had liposuction or a surgical tuck, if they had been treated with a mechanical body contouring device within the last year, or if they had taken any weight loss medications in the last 6 months.

The creams were made of a novel combination of the following ingredients: purified water, cetyl alcohol, safflower oil, PEG-40 stearate, isopropyl myristate, lecithin, triethanolamine, butylene glycol, dimethicone, cyclomethicone, polysorbate 80, caffeine (in different percentages for each cream), glycolic acid (70%), carbomer, panthenol, imidazolidinyl urea, quaternium 15, tocopheryl acetate, methylparaben, propylparaben, and fragrance.

Informed consent was obtained and the patients were randomized into two groups. One group consisted of 23 patients who were given the control cream and the 2% active ingredient cream. The other consisted of 18 patients who were given the control cream and the 1% active ingredient cream. The side of the body to which the active cream was applied was individually randomized. The patients were then instructed as to the use of the creams. They were told to apply the creams twice a day to the tricep area, the hip area, the lateral abdomen area, and the lateral and posterior thigh area. Some patients did not have measurable amounts of subcutaneous fat in all of these areas. These patients were instructed to apply the cream to only the measurable areas. They were told not to use the same hand when applying both creams, they were told to thoroughly massage the creams into the skin, and they were reminded to consistently apply the creams to the designated side of the body twice a day.

The patients applied the creams as instructed for 1 month. They then visited the office to undergo an examination and to receive more of the cream, if necessary. After another month of cream application, they were examined for a final time.

During each visit, unilateral measurements of circumference were taken using a tape measure. The arms were measured at 3 cm distal to the acromion point of the shoulder and 3 cm medial to the ulnar process of the elbow. The thigh was measured at 7 cm below the lateral illeal crest and 4 cm above the lateral superior knee. The abdomen and the hips were measured for baseline and change. The hips were measured at the illeal crest and the abdomen was measured at the umbilical level.

Caliper measurements were used to quantify changes in the thickness of the subcutaneous tissue. The arms were measured at the midpoint of the tricep area 3 cm distal to the acromion of the shoulder and 3 cm medial to the ulnar process of the elbow. The thighs were measured in the lateral and posterior areas 4 cm below the inguinal ligament and 4 cm above the knee. The abdomen was measured 15 cm on either side of the umbilicus, and the hips were measured 3 cm below the lateral illeal crest.

In addition to quantitative measurements, the dermatologist made an evaluation of each of the areas with respect to the appearance of cellulite, the tone of the skin, the appearance of lesions including stretch marks, and the tension of the skin. The changes in each of the areas of the body for each evaluative parameter were scored on a -3 to $+3$ scale (-3 = severe worsening to $+3$ = marked improvement; 0 = no change). General body photos and photos of specific areas were taken for each patient at each visit using a 100 mm macro lens.

Results

The patients were predominantly women (40 of 41), 21–65 years old, with measurable amounts of subcutaneous fat in either the hip, abdomen, tricep, lateral thigh, or posterior thigh area. We performed a Student's *t*-test after compiling our initial data and determined that there was not a significant difference between the measurements obtained for the placebo side of the body and those obtained for the active side. At the conclusion of 2 months, both the 2% cream and the 1% cream resulted in a significant decrease in subcutaneous fat thickness as measured by calipers in all of the areas tested.

Table 1. The Change Over Time of Subcutaneous Adipose Tissue Thickness due to Use of 2% Cream versus the Placebo

	Placebo				*Active*			
	0 months	*1 month*	*2 months*	*Total*	*0 months*	*1 month*	*2 months*	*Total*
Abdomen (n = 22)	30.5	29.8	29.9	0.6 SD = 1.1	31.2	29.5	28.2	3.0 SD = 2.6
Triceps (n = 15)	31.4	31.2	30.9	0.5 SD = 0.8	32.1	30.3	28.8	3.3 SD = 1.6
Lateral thighs (n = 23)	45.1	44.4	43.9	1.2 SD = 2.5	44.5	42.6	40.6	3.9 SD = 2.4
Posterior thighs (n = 22)	43.5	42.9	42.5	1.0 SD = 1.2	41.5	40	38.3	3.2 SD = 2.1
Hips (n = 21)	46.3	45.7	45.2	1.1 SD = 1.9	46.1	42.8	40.7	5.4 SD = 1.9

All of the measurements are in millimeters using calipers. Note the large degree of change on the active side as compared to the placebo, especially in the hip area.

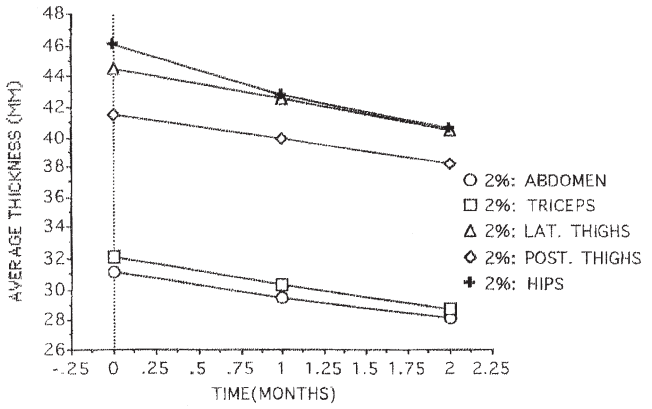

Figure 1. Average change in thickness of subcutaneous adipose tissue due to the use of the 2% cream.

Caliper Measurements

The differences between the initial and final caliper measurements were tested for significance using a two-tailed *t*-test. The 2% cream showed a significant change in all of the areas measured ($P = .001$ for all areas). The caliper measurements for the active cream demonstrated a decrease in the average thickness of the abdominal subcutaneous fat of 3.0 mm (SD = 2.6) versus 0.6 mm (SD = 1.1) for the placebo. The tricep area decreased by an average of 3.3 mm (SD = 1.6) for the active cream and 0.5 mm (SD = 0.8) for the placebo. The active cream resulted in a 3.9 mm (SD = 2.4) average decrease in the lateral thighs, while the placebo decreased the thickness of the subcutaneous fat in the lateral thighs by 1.2 mm (SD = 2.5). The posterior thighs decreased by an average of 3.2 mm (SD = 2.1) for the active cream and 1.0 mm (SD = 1.2) for the placebo. Finally, the hips showed the greatest improvement, decreasing by an average of 5.4 mm (SD = 1.9) versus 1.1 mm (SD = 1.9) for the placebo. All of these areas demonstrated a significant ($P = .001$) decrease in subcutaneous fat thickness with the application of the 2% cream (Table 1 and Figure 1).

The 1% cream also significantly reduced the thickness of the subcutaneous fat ($P = .005$ for the triceps and .001 for all other areas). There was an improvement in the abdomen area: the active cream decreased the thickness of the subcutaneous fat by an average of 2.2 mm (SD = 2.2) versus 0.5 mm (SD = 2.0) for the placebo. The tricep area decreased by an average of 2.1 mm (SD = 2.2) for the active cream versus 0.1 mm (SD = 1.2) for the placebo. The lateral thighs decreased by an average of 3.5 mm (SD = 1.7) for the active cream and 0.5 mm (SD = 1.1) for the placebo. The posterior thighs showed an average decrease in subcutaneous fat thickness of 3.3 mm (SD = 1.6) for the active cream versus 0.1 mm (SD = 0.8) for the placebo. The hips showed a decrease in average thickness of 3.4 mm (SD = 1.7) for the active cream and 0.3 mm (SD = 1.3) for the placebo (Table 2 and Figure 2).

In addition to testing the differences between initial and final caliper measurements, the differences between the active and placebo groups were tested for significance at the end of 2 months. A two-tailed *t*-test was performed for both the 2% cream versus the placebo and the 1% cream versus the placebo. The differences between the two were found to be significant in all of the areas except the hips treated with the 1% cream. For the 2% cream, the abdomen ($P = .009$), the triceps ($P = .001$), the lateral thighs ($P = .001$), the posterior thighs ($P = .001$), the hips ($P = .001$) showed a significant difference between the final caliper measurements on the placebo side versus the active side. For the 1% cream, the abdomen ($P = .001$), the triceps ($P = .002$), the lateral thighs ($P = .001$), and the posterior thighs ($P = .001$) showed a significant difference between the active and the placebo side at the end of the study period. Only the hips treated with the 1% cream did not show a significant difference between sides at the end of the treatment period ($P = .059$).

Table 2. The Change Over Time of Subcutaneous Adipose Tissue Thickness due to the Use of 1% Cream versus the Placebo

	Placebo				*Active*			
	0 months	*1 month*	*2 months*	*Total*	*0 months*	*1 month*	*2 months*	*Total*
Abdomen ($n = 15$)	31.3	31.1	30.8	0.5 SD = 2.0	30.9	29.1	27.1	2.2 SD = 2.2
Triceps ($n = 15$)	28.6	28.5	28.5	0.1 SD = 1.2	28	26.9	25.9	2.1 SD = 2.2
Lateral thighs ($n = 17$)	43.2	42.8	42.7	0.5 SD = 1.1	43.2	41.6	39.7	3.5 SD = 1.7
Posterior thighs ($n = 17$)	41.3	41.4	41.2	0.1 SD = 0.8	41.2	39.6	37.9	3.3 SD = 1.6
Hips ($n = 17$)	42.1	42.1	41.8	0.3 SD = 1.3	43.3	41.3	39.9	3.4 SD = 1.7

All of the measurements are in millimeters using calipers.

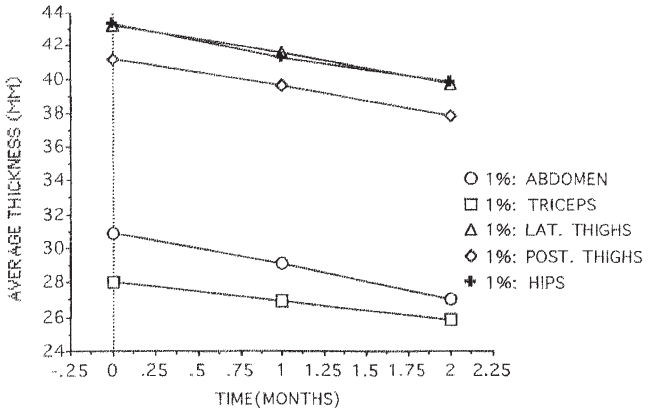

Figure 2. Average change in thickness of subcutaneous adipose tissue due to the use of the 1% cream.

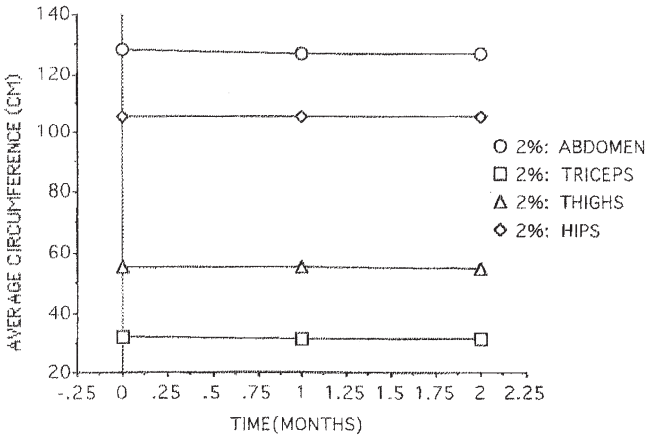

Figure 3. The average change in circumference of each area of the body due to the use of the 2% cream.

Both of the creams showed a significant decrease in the thickness of the subcutaneous fat in each of the areas of the body. For each of the areas and for each cream, a two-tailed *t*-test was used to compare the decrease in thickness from the active cream use versus the decrease from placebo use. All of the areas for each concentration of cream showed a highly significant decrease ($P = .001$ for all areas except 1% triceps = .005) in subcutaneous fat thickness. Because of the relatively small number of people involved in the study, a regression analysis was performed to determine if the results were significantly affected by any unusual results. Only the lateral ($P = .019$) and posterior ($P = .009$) thighs demonstrated any significant regression effect. The regression effect had an 11.9% effect on the results obtained for the lateral thighs and a 2.2% effect on the results obtained for the posterior thighs. There was no significant regression effect for any of the other areas.

In addition to the differences between initial and final measurements, we compared the decreases demonstrated by the 2% and 1% creams to ascertain if there was a significant difference between the two concentrations. An ANOVA test was performed using the active and placebo groups as one factor and the concentration of the cream as the other factor. The two different concentrations of caffeine in the creams showed a significant difference between their effect on subcutaneous fat thickness only in the tricep and hip areas. The 2% cream was significantly more effective at decreasing tricep fat thickness ($P = .046$) and hip fat thickness ($P = .001$). None of the other areas showed a significant difference between the effects of the two creams.

Tape Measurements

The tape measure did not show a significant change for any of the areas of the body for either cream. For the 2% cream, the circumference of the abdomen decreased by an average of 1.0 cm (SD = 1.7). The girth of the arms decreased by an average of 0.5 cm (SD = 1.1) for the active cream versus a decrease of 0.3 cm (SD = 0.8) for the placebo. The circumference of the thigh to which the active cream was applied decreased by an average of 0.4 cm (SD = 1.1), while the thigh to which the placebo was applied showed no change (SD = 1.2) in circumference.

Table 3. The Change Over Time of Circumference for Each Area of the Body due to the Use of 2% Cream versus the Placebo

	Placebo				*Active*			
	0 months	*1 month*	*2 months*	*Total*	*0 months*	*1 month*	*2 months*	*Total*
Triceps ($n = 15$)	31.7	31.4	31.4	0.3 SD = 0.8	31.7	31.3	31.2	0.5 SD = 1.1
Thighs ($n = 23$)	56.3	56.3	56.3	0 SD = 1.2	55.4	55.2	55	0.4 SD = 1.1
Abdomen ($n = 22$)	128	127	127	1.0 SD = 1.7				
Hips ($n = 23$)	105	105	105	0 SD = 1.2				

All of the measurements are in centimeters using a tape measure. Please note that the tape measurements for hips and abdomen are circumference measurements and are therefore not useful for relative measurements of placebo versus active cream, only for relative change over time.

Table 4. The Change Over Time of Circumference for Each Area of the Body due to the Use of 1% Cream versus the Placebo

	Placebo				*Active*			
	0 months	*1 month*	*2 months*	*Total*	*0 months*	*1 month*	*2 months*	*Total*
Triceps (n = 16)	29.3	29.3	29.3	0 SD = 0.9	29.3	29.3	29.3	0 SD = 0.6
Thighs (n = 17)	55.8	55.6	55.5	0.3 SD = 0.9	55	55.1	54.9	0.1 SD = 1.1
Abdomen (n = 15)	86.9	87.1	86.9	0 SD = 1.7				
Hips (n = 17)	102	102	101	1.0 SD = 1.6				

All of the measurements are in centimeters using a tape measure. Please note that the tape measurements for hips and abdomen are circumference measurements and are therefore not useful for relative measurements of placebo versus active cream, only for relative change over time.

The hips showed no measurable change (SD = 1.2) in circumference (Table 3 and Figure 3).

The 1% cream did not show any decrease in girth in either the abdomen (SD = 1.7) or the tricep areas (SD = 0.6 for active, 0.9 for placebo). There was a slight decrease in the girth of the thighs for the active cream, which lost an average of 0.1 cm (SD = 1.1). But the thigh to which the placebo was applied showed an average decrease of 0.3 cm (SD = 0.9). The circumference of the hips showed a decrease of 1.0 cm (SD = 1.6) (Table 4 and Figure 4).

Physician's Evaluation

The physician's evaluation pointed to an improvement in cellulitic appearance, skin tone, and skin tension. There was very little change in the appearance of skin lesions or stretch marks. Each area of the body showed an improvement with respect to cellulitic appearance, skin tone, and skin tension (Tables 5 and 6).

The physician's evaluation demonstrated the visible improvement in the appearance of the skin that resulted from the use of the cream. The significant decrease in the thickness of the subcutaneous adipose tissue shown by the caliper measurements correlated with the clinical improvement in skin tension and smoothness. The improvement was visibly apparent in all of the areas of the body with respect to skin tone, skin tension, and skin smoothness.

Discussion

Excessive levels of fat in the subcutaneous layers of the skin can be both unsightly and unhealthy.[1–3] The superficial irregularities that result from this excessive fat are most likely caused by altered structures of fat lobules that are excessive in size and abnormally shaped. The use of a cream to modify these layers of subcutaneous adipose tissue has been negatively received because of the lack of scientific evidence.[6,8] There have been a number of products that have claimed effective treatment with questionable substantiation.[7] The study presented here demonstrates that a specific formulation that combines the use of caffeine with a specialized lipoceutical liposome can effectively decrease the thickness and irregularity of the subcutaneous fat layers and thereby reduce the visible signs of the excessive fat (Figure 5).

The lipoceutical liposome is a specialized, multilamellar liposome that has been shown to be effective at delivering ingredients to the subcutaneous and dermal layers of the skin. Specific in vivo studies by Mezei[11] using guinea pigs and rabbits demonstrated that econazole, retinoic acid, minoxidil, and "cortisone" were deposited in significantly higher concentrations in the epidermis (up to 872% higher concentration), dermis (up to 482% higher concentration), and subcutaneous tissue (up to 1036% higher concentration) compared to the same ingredients not encapsulated in liposomes. Of interest, blood levels, tissue samples, and urinary data demonstrated that there was a significantly lower systemic uptake of the drug when it was liposome en-

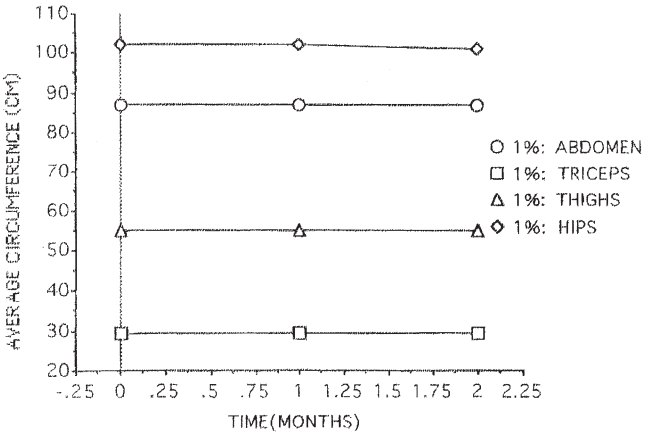

Figure 4. The average change in circumference of each area of the body due to the use of the 1% cream.

Table 5. Dermatologist Evaluation of the Change from Initial to Final Visit on the Active versus the Placebo Side of the Body due to the Use of 2% Cream

	Placebo				*Active*			
	Cellulitic Evaluation	*Lesions (including striae)*	*Skin Tone*	*Skin Tension*	*Cellulitic Evaluation*	*Lesions (including striae)*	*Skin Tone*	*Skin Tension*
Abdomen (n = 22)	0 SD = 0	0 SD = 0	0 SD = 0	0.05 SD = 0.58	0.50 SD = 0.60	0 SD = 0	0.77 SD = 0.75	1.32 SD = 0.72
Triceps (n = 15)	0 SD = 0	0 SD = 0	0 SD = 0	0 SD = 0	0.25 SD = 0.45	0 SD = 0	0.38 SD = 0.49	0.63 SD = 0.50
Lateral thighs (n = 23)	0 SD = 0	0 SD = 0	0.04 SD = 0.21	0 SD = 0	0.83 SD = 0.39	0.04 SD = 0.58	1.17 SD = 0.58	1.26 SD = 0.48
Posterior thighs (n = 22)	0 SD = 0	0 SD = 0	0.05 SD = 0.21	0 SD = 0	0.86 SD = 0.47	0.05 SD = 0.71	1.27 SD = 0.63	1.45 SD = 0.60
Hips (n = 21)	0 SD = 0	0 SD = 0	0.04 SD = 0.21	0 SD = 0	1.00 SD = 0.60	0.04 SD = 0.58	1.48 SD = 0.67	1.48 SD = 0.60

Note the large change in skin tone and tension in the thigh and hip areas. The scale used for these went from −3 = severe worsening to +3 = marked improvement with 0 = no change.

capsulated despite the relatively high concentrations in the dermis and the subcutaneous tissue.[11,12–14] Therefore, the lipoceutical liposomes target the skin areas of interest with less potential systemic toxicity or systemic effects.

The methylxanthine aminophylline has most commonly been the product ingredient of choice for reducing the amount of subcutaneous fat. On a physiological level, the action of methylxanthines such as aminophylline and caffeine in causing lipolysis is well known, documented, and substantiated. Methylxanthines inhibit the action of the enzyme cyclic 3′,5′-nucleotide phosphodiesterase. This enzyme causes the degradation of cyclic adenosine monophosphate (cAMP) into 5′-AMP. Inhibition of the enzyme thus results in relatively high levels of cAMP, which stimulates a protein kinase that converts the inactive enzyme triacylglycerol lipase into an active lipase. This causes hydrolysis of triacylglycerols and releases free fatty acids and glycerol into the interstitial fluid and plasma.[9]

The action of caffeine and aminophylline in causing cellular dehydration through the transport of sodium into the extracellular fluid is also well documented.[9,10] The thickness and irregularity of the subcutaneous fat

Table 6. Dermatologist Evaluation of the Change from Initial to Final Visit on the Active versus the Placebo Side of the Body due to the Use of 1% cream

	Placebo				*Active*			
	Cellulitic Evaluation	*Lesions (including striae)*	*Skin Tone*	*Skin Tension*	*Cellulitic Evaluation*	*Lesions (including striae)*	*Skin Tone*	*Skin Tension*
Abdomen (n = 15)	0 SD = 0	0 SD = 0	0 SD = 0	0 SD = 0	0.38 SD = 0.50	0.06 SD = 0.24	0.63 SD = 0.62	0.88 SD = 0.72
Triceps (n = 15)	0 SD = 0	0 SD = 0	0 SD = 0	0.07 SD = 0.26	0.27 SD = 0.45	0 SD = 0	0.40 SD = 0.51	0.47 SD = 0.52
Lateral thighs (n = 17)	0 SD = 0	0 SD = 0	0 SD = 0	0.06 SD = 0.24	0.65 SD = 0.61	0.06 SD = 0.24	1.12 SD = 0.70	1.18 SD = 0.73
Posterior thighs (n = 17)	0 SD = 0	0 SD = 0	0 SD = 0	0.06 SD = 0.24	0.826 SD = 0.81	0.06 SD = 0.24	1.06 SD = 0.66	1.29 SD = 0.85
Hips (n = 17)	0 SD = 0	0 SD = 0	0 SD = 0	0.06 SD = .024	0.65 SD = 0.61	0.06 SD = 0.24	1.12 SD = 0.70	1.41 SD = 0.80

Note the large change in skin tone and tension in the thigh and hip areas. The scale used for these went from −3 = severe worsening to +3 = marked improvement with 0 = no change.

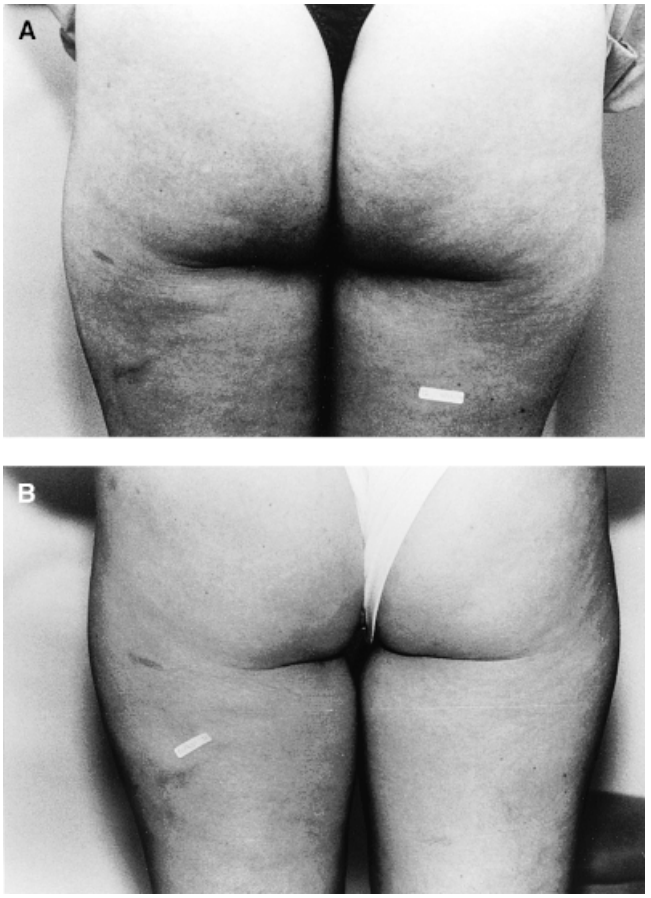

Figure 5. The improvement through use of the cream after 2 months. Note the improved skin tone and tension on the right leg, especially the decreased thickness in the upper thigh region.

layers can definitely be reduced by combining lipolysis with dehydration. Encapsulating the methylxanthine, in this case caffeine, in a liposome ensures that the active ingredient is delivered to the appropriate layers of the skin. We believe that this novel combination of product and delivery caused the significant changes that we have seen with the use of this cream.

Liposuction is indisputably the most effective and recommended treatment for removing excessive subcutaneous adipose tissue. Although the cream is certainly not as effective as liposuction, it may offer a less costly, albeit not as dramatic, alternative. Liposuction is often performed on areas of the body that are difficult to modify with alterations of exercise and diet. The hips, thighs, abdomen, and buttocks are the areas most often treated with liposuction, and the cream was shown to be effective at reducing the thickness of subcutaneous fat in these areas.

The new mechanical body contouring devices offer an additional alternative to liposuction surgery. They have been studied and were shown to be effective at reducing subcutaneous adipose tissue thickness.[5] Although liposuction is indisputably the most effective treatment for reducing the amount of subcutaneous fat, some patients will inevitably prefer not to undergo liposuction either because of its invasive surgical aspect or because of the cost. The body contouring device has recently become an alternative to liposuction, and we feel that the positive clinical results we have seen with caffeine-based creams provides yet another alternative to liposuction for the cosmetic surgeon.

It is the opinion of these investigators that using a tape measure for quantifying the smoothing of subcutaneous irregularities and the alteration in the thickness of subcutaneous adipose tissue is not appropriate for a study of this type. Daily fluctuations in physiological factors such as hydration will have a much more dramatic effect on circumference when measuring around an entire area of the body than it will when measuring a small section using calipers. In all of the areas tested, the calipers showed a significant decrease in the thickness of the subcutaneous adipose tissue while the tape measure showed no significant change. The immediate subcutaneous adipose tissue is the target tissue for the active cream, and measuring circumference to quantify changes in this tissue involves too many factors that could possibly interfere with consistently accurate measuring. These include muscular contraction, tightness of the measuring tape, and systemic fluid balance. Ideally the clinical use of creams for modifying cellulite and subcutaneous fat should be quantified with caliper measurements.

This study presents the best results that we know of for a cream designed to modify excessive subcutaneous adipose tissue. We realize that we have not tested the cream beyond 2 months of continuous daily use, and are therefore uncertain as to the permanency of the changes brought about by the use of the cream. However, the cream was effective at reducing the thickness of the subcutaneous adipose tissue in each of the areas of the body tested when used continuously.

This study demonstrates a clear and effective use of a cream formulation in modifying and improving the subcutaneous adipose tissue layers. It is difficult to control for many factors in a study of this type, including age, weight, body density, degree of physical activity, hydration of the skin, diet, handedness, and error in measurements. But with a randomized, correlated assignment to both cream concentration and treatment versus placebo, it is assumed that these variables are evenly spread among the different groups. Given that, the results indicate that the combination of caffeine as the active ingredient and the patented lipoceutical liposomes effectively deliver action to the subcutaneous tissue and improve the cosmetic appearance of skin with excessive subcutaneous adipose tissue.

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