# Topical Fat Reduction

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**Abstract**

**GREENWAY, FRANK L, GEORGE A BRAY AND DAVID HEBER. Topical fat reduction. *Obes Res.* 1995;3(Suppl 4):561S-568S.**

**The fat on women's thighs is more difficult to mobilize due to increased α–2 adrenergic receptor activity induced by estrogen. Lipolysis can be initiated through adipocyte receptor stimulation (β adrenergic) or inhibition (adenosine or α–2 adrenergic) or by inhibition of phosphodiesterase. Since many women desire regional thigh fat loss, a series of clinical trials were initiated using one thigh as a double-blinded control. Trial #1: Five overweight women had injections of isoproterenol at intervals around the thigh three times a week for 4 weeks with diet and walking. Trial #2: Five overweight woman had ointment containing forskolin, yohimbine and aminophylline applied to the thigh five times a week for 4 weeks after hypertonic warm soaks with a diet and walking. Trial #3: Eighteen overweight women were divided into three groups of six and trial #2 was repeated with each agent alone vs. placebo using forskolin, yohimbine or aminophylline in separate ointments. Trial #4: Thirty overweight women had 10% aminophylline ointment applied to the thigh five times a week for 6 weeks with diet and walking. Chemistry panel, theophylline level and patch testing were performed. Trial #5: Twelve women had trial #4 repeated with 2% aminophylline cream without a diet or walking. Trial #6: Trial #5 was repeated with 0.5% aminophylline cream. All trials except yohimbine ointment gave significantly more girth loss from the treated thigh ($p<0.05$ to $p<0.001$). Chemistry panel showed no toxicity. Theophylline was undetectable and patch testing was negative. We conclude that topical fat reduction for women's thighs can be achieved without diet or exercise.**

**Key words: obesity, adipocyte, aminophylline, lipolysis, adrenergic receptors**

## Introduction

Many people would like to selectively lose fat from a specific area of their body. The thighs and buttock area seem to be the area of most frequent concern for women. This desire for cosmetic change has been the basis for much popular and professional writing (10). Ronsard (13) popularized the term "cellulite" to describe the dimpling and orange skin look of the thighs (peau d'orange). Bayard (3) attributed it to the aging process. Regardless of the cause, these cosmetic concerns are widespread. As Ohrbach says, "Our images of womanhood are almost synonymous with thinness" (11).

The structure of the subcutaneous adipose tissue accounts for the development of the peau d'orange appearance. Fibrous connective tissue septae surround groups of fat cells and attach to the underside of the dermis. As fat cells enlarge, these septae are stretched and pull down on the overlying skin. The result of this process is an indentation or dimpling of the skin over the thigh and buttock area in women to which Ronsard has given the name cellulite (13). Although Ronsard has proposed treatment procedures for cellulite, no experimental evidence has been published to support the efficacy of her suggestions.

Several studies have examined spot reducing. Early studies suggested that massage might have effects on local fat distribution (5,14). A carefully controlled study by Kalb (7), however, demonstrated that massage was unable to achieve local fat reduction. In his study, 40 patients were placed on an 800 calorie diet with 20 subjects receiving massage and 20 subjects serving as unmassaged controls. All patients lost weight and their arms and legs became smaller, but there were no differences between the massaged group and the unmassaged control group in the loss of arm or leg fat.

Adipose tissue metabolism varies from one region of the body to another. Smith et al. (15), and Kral et al. (8), demonstrated that fat was absorbed more slowly in the femoral region than from the abdominal region in women losing weight after the jejuno-ileal bypass operation for severe obesity. These observations suggested regional differences in the lipolytic processes that might respond to the local application of lipolytic agents. The lipolytic process has been described in great detail in the past 20 years (16). Lipolysis, the process of hydrolyzing triacylglycerol into glycerol and fatty acids, is mediated by the enzyme hormone sensitive lipase. Hormone sensitive lipase is active in the phosphorylated form. This activation is produced by protein kinase-A which is activated by cyclic AMP. Membrane-bound adeny-

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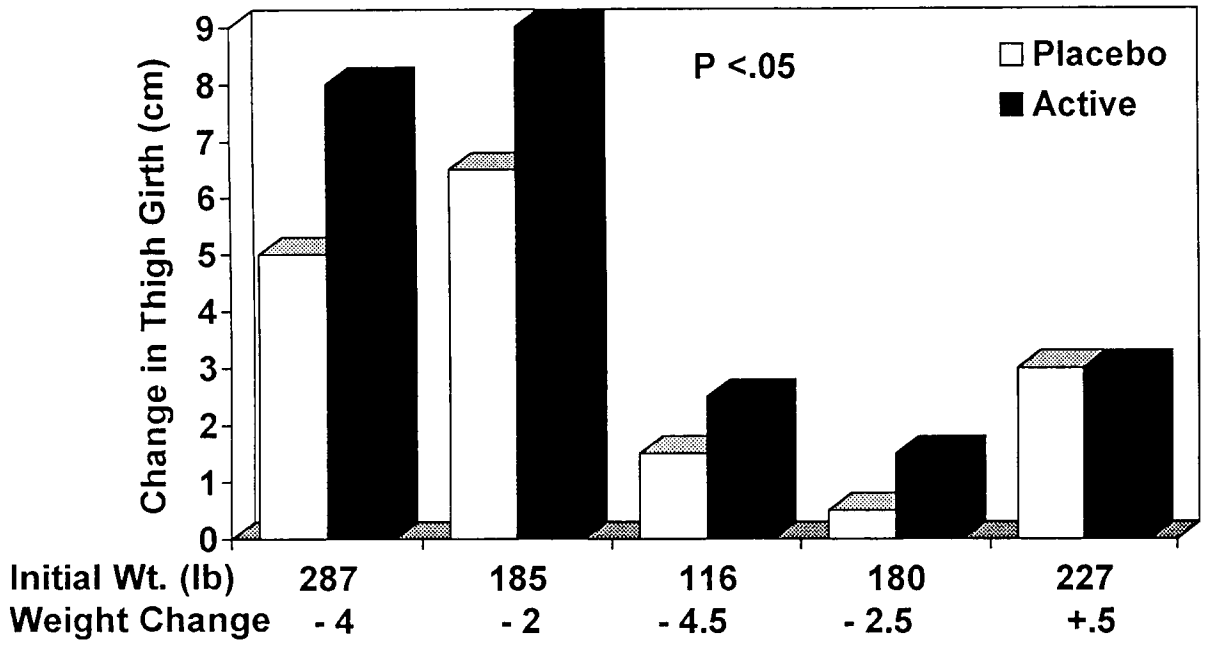


Figure 1: Changes in thigh circumference and total body weight in five subjects after treatment with isoproterenol injection or placebo.

late cyclase can be inhibited or stimulated by the action of inhibitory or stimulatory GTP binding proteins (Gs-proteins) acting on adenylate cyclase. A number of hormones react with cell surface receptors on the adipocyte to influence lipolysis. Stimulation of the β–2 adrenergic receptor stimulates the GTP stimulatory binding protein ($G_s$ protein) which activates adenylate cyclase which, in turn, activates cyclic AMP. The α–2 adrenergic receptor and the adenosine receptor, on the other hand, stimulate GTP inhibitory binding proteins ($G_i$ proteins) which inhibit adenylate cyclase and thus inhibit the lipolytic process. The relative number of β and α–2 adrenergic receptors on the surface of the fat cells determine the lipolytic balance of those cells. Hormones can have long-term effects on the lipolytic processes by influencing the number of α–2 and β receptors on the fat cell. Thus by controlling lipolysis, hormones can determine body fat dis-

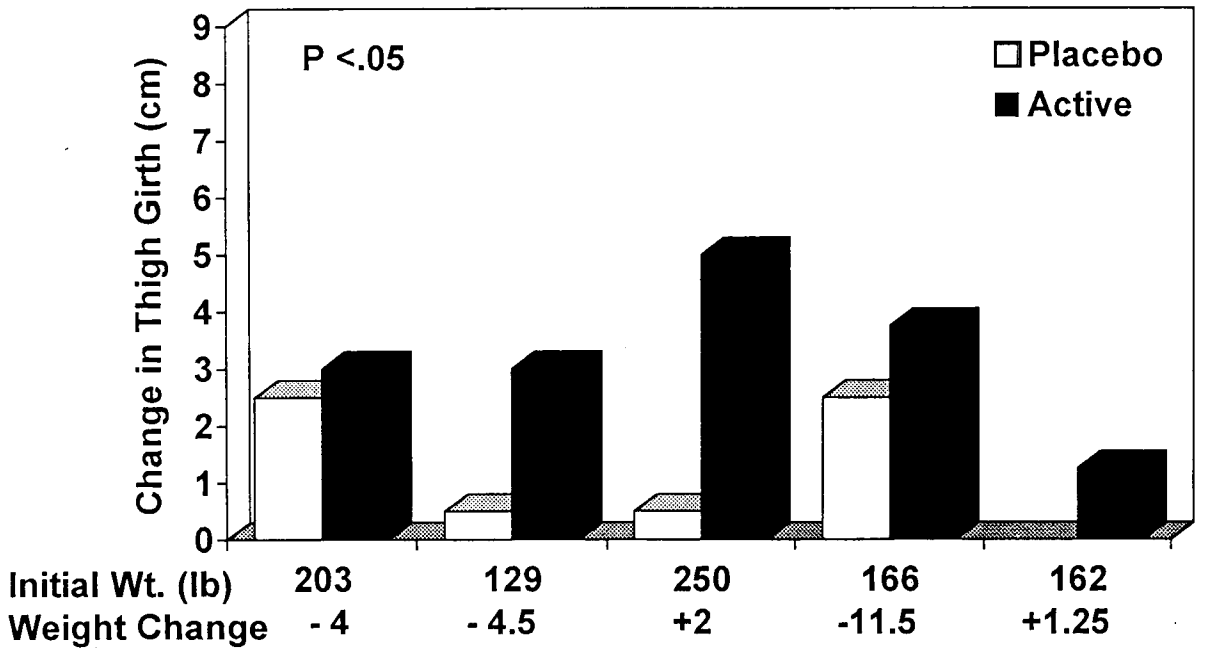


Figure 2: Changes in thigh circumference and total body weight in five subjects after treatment with ointment containing forskolin, aminophylline and yohimbine or placebo.

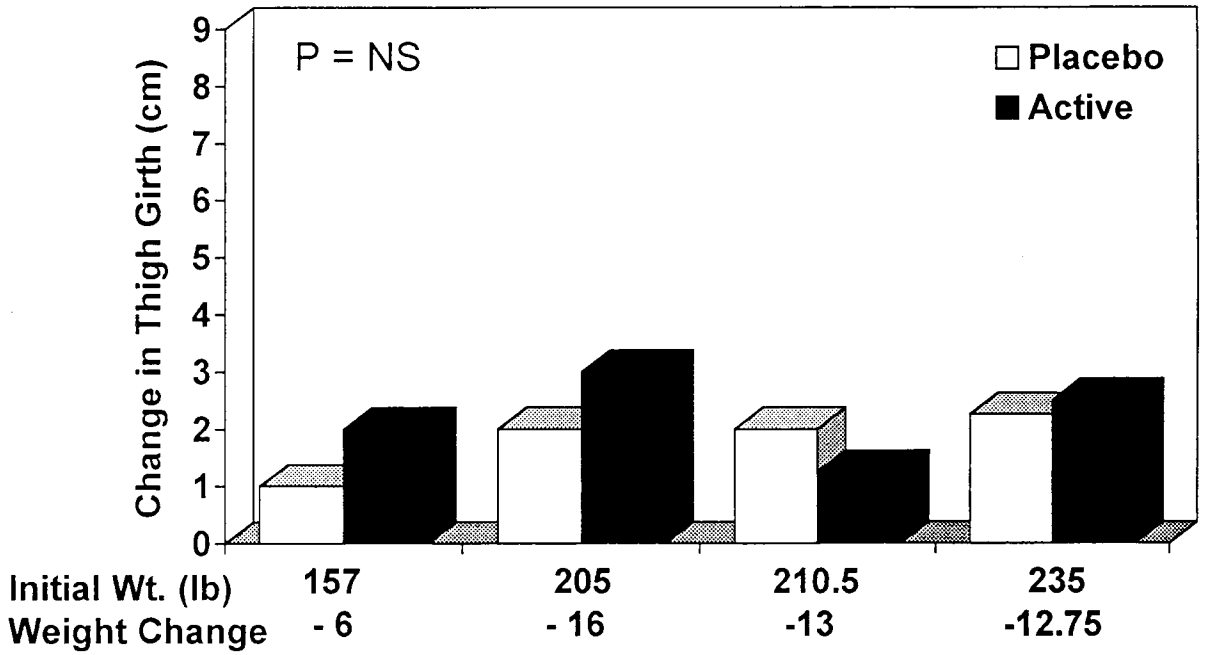


Figure 3: Changes in thigh circumference and total body weight in four subjects after treatment with yohimbine ointment or placebo.

tribution. Women, through the effect of estrogen, have more $\alpha$–2 receptors on the fat cells of their hips and thighs. This gives a higher lipolytic threshold and causes the concentration of fat in that area in women (1,2,9,12).

Many women are distressed as they lose weight that their hips and thighs remain undesirably fat. To test the hypothesis that local fat reduction could occur by modulating normal fat cell function, we chose women's thighs as the test area for two reasons. First, thighs offer a key advantage in that each woman has a matched set so that one can be used as a control and the other treated. Second, reduced lipolytic receptor activity made this an easy area to test.

## Methods and Experimental Protocols

### *Study 1*

The first study compared injections of a $\beta$ adrenergic agonist against placebo (4,6). Isoproterenol ($10^{-5}$ mM = 2 p moles), a highly selective $\beta$ agonist, was injected in 0.2 mL of physiological saline at 4 cm intervals around the circumference of the thigh two-thirds of the way from the knee to the

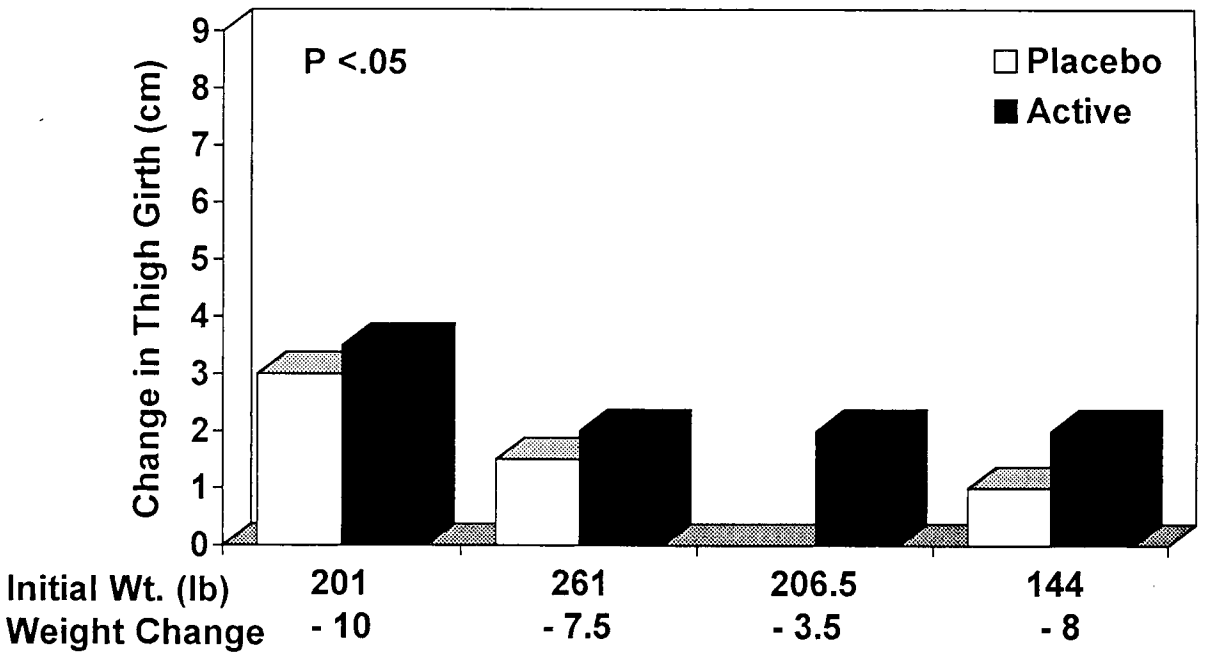


Figure 4: Changes in thigh circumference and total body weight in four subjects after treatment with forskolin ointment or placebo.

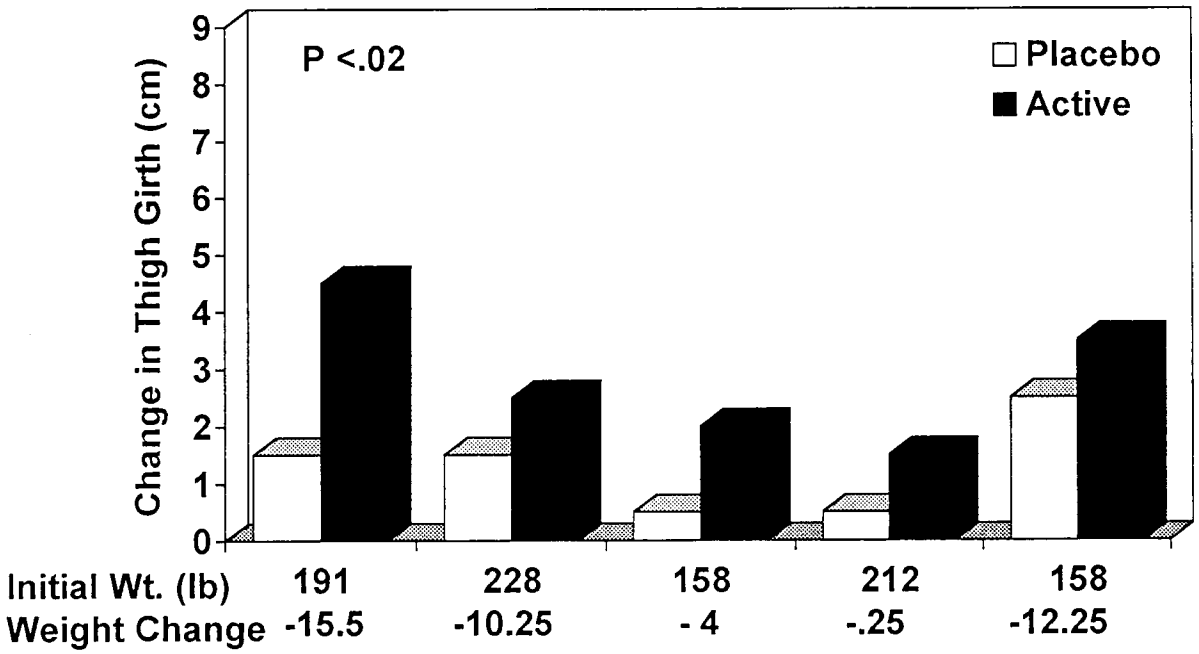


Figure 5: Changes in thigh circumference and total body weight in five subjects after treatment with aminophylline ointment or placebo.

greater trochanter. This dose of isoproterenol was selected since it gives maximal lipolysis in vitro. The spheres of diffusion of the isoproterenol overlapped as judged by the vasodilatation at the skin surface. Five women participated in this single-blind study. The participants were more than 20% above their desirable weights (mean weight 95 kg) and were placed on a 600 kcal/day diet and asked to participate in a walking program. Injections were given three times a week for 4 weeks using one thigh as a saline-injected control. The subjects had their thigh girths measured weekly.

***Study 2***

The second study tested whether fat loss could be produced using a topical preparation (4,6). In this study, women more than 20% above their desirable weights were given a 600 kcal/day diet and encouraged in a walking program. A combination of compounds that could affect the lipolytic process by different mechanisms was compounded.

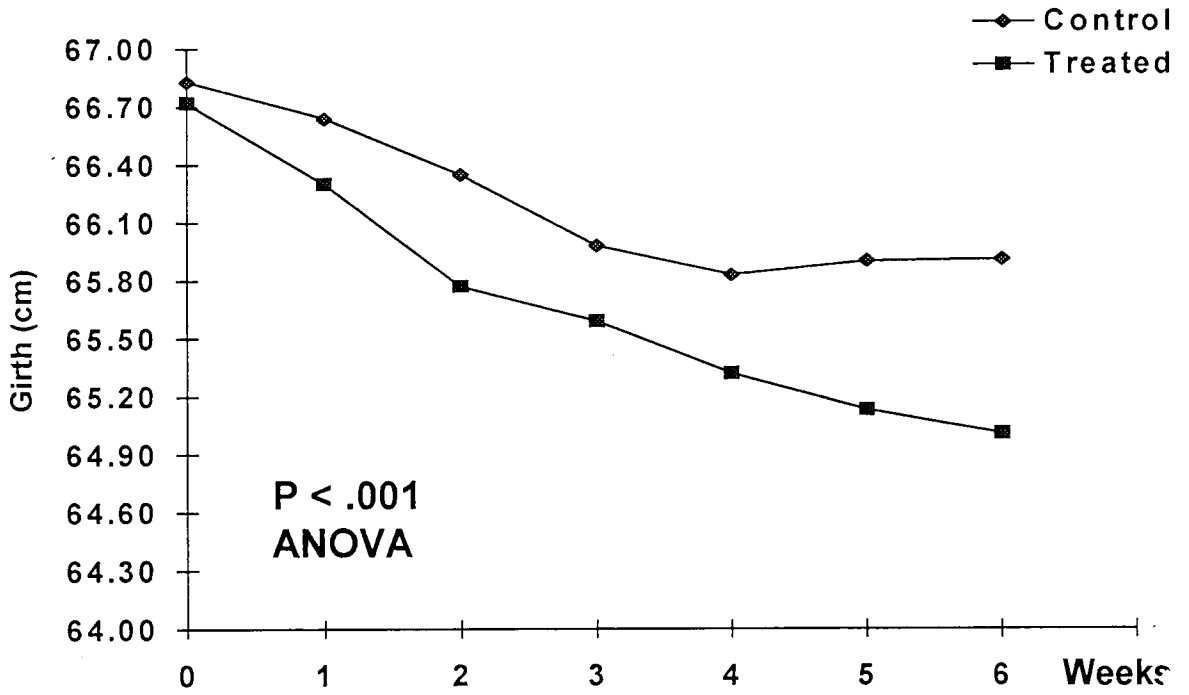


Figure 6: Changes in thigh circumference in 23 subjects after treatment with 10% aminophylline ointment or placebo.

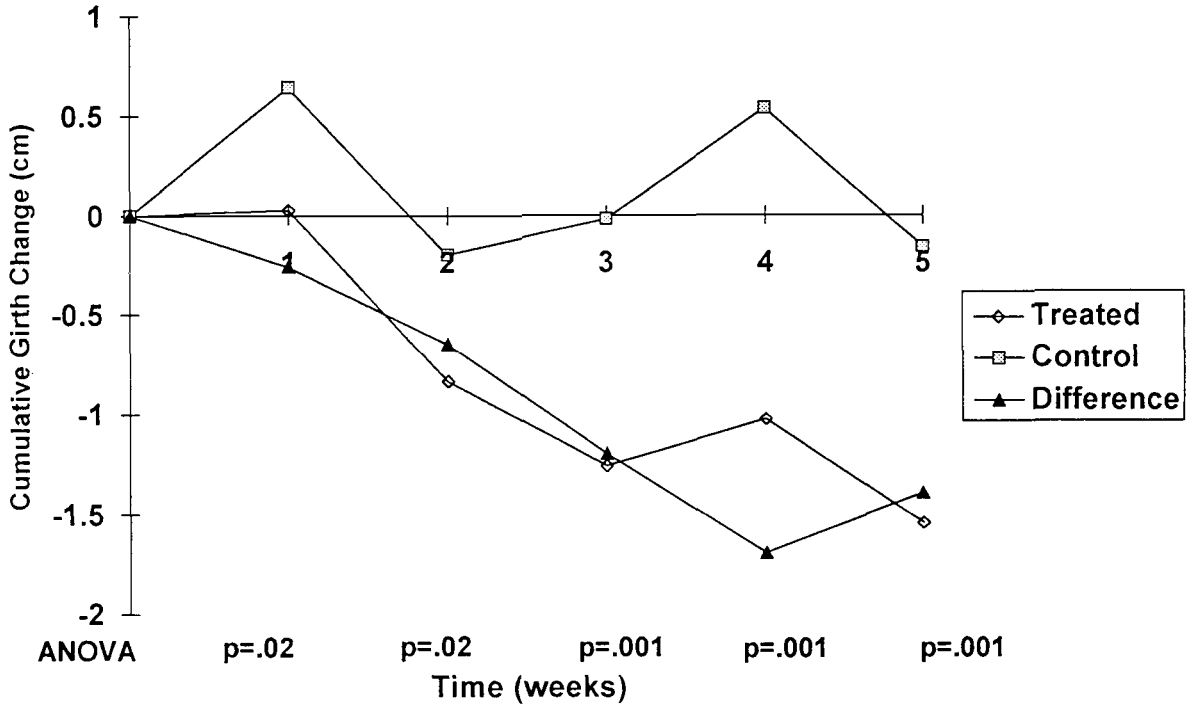


Figure 7: Changes in thigh circumference in 11 subjects after treatment with 2% aminophylline cream or placebo.

This necessitated using a carrier that would accept compounds with diverse solubility characteristics. The final concentrations in the aquaphor base were 1.2 x $10^{-5}$ mol/L forskolin (a β stimulator), 2.5 x $10^{-4}$ mol/L yohimbine (an α-2 antagonist), and 1.3 x $10^{-2}$ mol/L aminophylline (an adenosine receptor antagonist and an inhibitor of phosphodiesterase). In this double-blind study, the subjects' thighs were wrapped with warm 600 to 900 mOsm/L magnesium sulfate solutions for 30 minutes prior to each of the five day/week ointment application to maximize transcutaneous absorption. An occlusive plastic wrap was placed over the area to which the ointment was applied throughout the 4-week study period. Measurements of girth two-thirds of the way between the knee and the greater trochanter were used to judge local fat loss of the thigh treated with the aquaphor vehicle and compared to the thigh receiving active treatment. Five women greater than 20% over weight (mean weight 83 kilograms/182 pounds) participated in the study.

*Study 3*

Study 3 was divided into three smaller studies which tested the effect of each component of this combination ointment used in Study 2 to determine whether they were effective individually (4,6). A total of 18 women greater than 20% overweight participated in these three studies (mean weight 90 kilograms). The women were placed on an 800 kcal/day diet and encouraged to engage in a walking program. Warm wraps with 600 to 900 mOsm/L of magnesium sulfate solution were again applied to the thighs for 30 minutes five times per week before application of the ointment. An occlusive plastic wrap was not used. Six women had one thigh treated with an ointment containing 25 x $10^{-5}$ mol/L forskolin, six women had one thigh treated with an ointment containing 5 x $10^{-4}$ mol/L yohimbine, and six women had one thigh treated with ointment containing 1.3 x $10^{-2}$ mol/L aminophylline. The other thigh was treated with aquaphor vehicle as the control in a double-blind fashion. Evidence of local fat loss was again taken to be a significant ($p<0.05$) loss of thigh girth at two-thirds the distance between the knee and the greater trochanter on the treated versus the untreated thigh.

*Study 4*

The fourth study used a 10% aminophylline ointment and was performed at the UCLA Medical Center. Thirty women, who were more than 20% overweight, participated in this 6-week trial. They were placed on a 900 to 1,100 kcal/day diet without any specific recommendations regarding exercise. Warm wraps were omitted in this study. Five grams of the 10% aminophylline in aquaphor was applied to one thigh and an equal amount of aquaphor vehicle was applied to the other thigh as a control. The trial was double-blinded and counterbalanced so that 50% of the subjects had active ointment to the right thigh and 50% to the left. Thigh circumferences were measured weekly with weight supported on the measured thigh. Two measurements were taken, one at half the distance between the fibula head and the greater trochanter, a second 5 cm above the first. Body weight, blood pressure, and pulse were recorded weekly. Patch tests for allergy of the active ointment and the vehicle were done during the last week of the study. A chemistry panel was drawn at the beginning and end of the study. Theophylline levels were measured during the third week of the study. At the end of the study, theophylline levels were drawn at either 30 and 60 minutes or at 60 and 120 minutes after the application of the active ointment to both thighs. Patients were seen 5 days per week during the study at which time ointments were

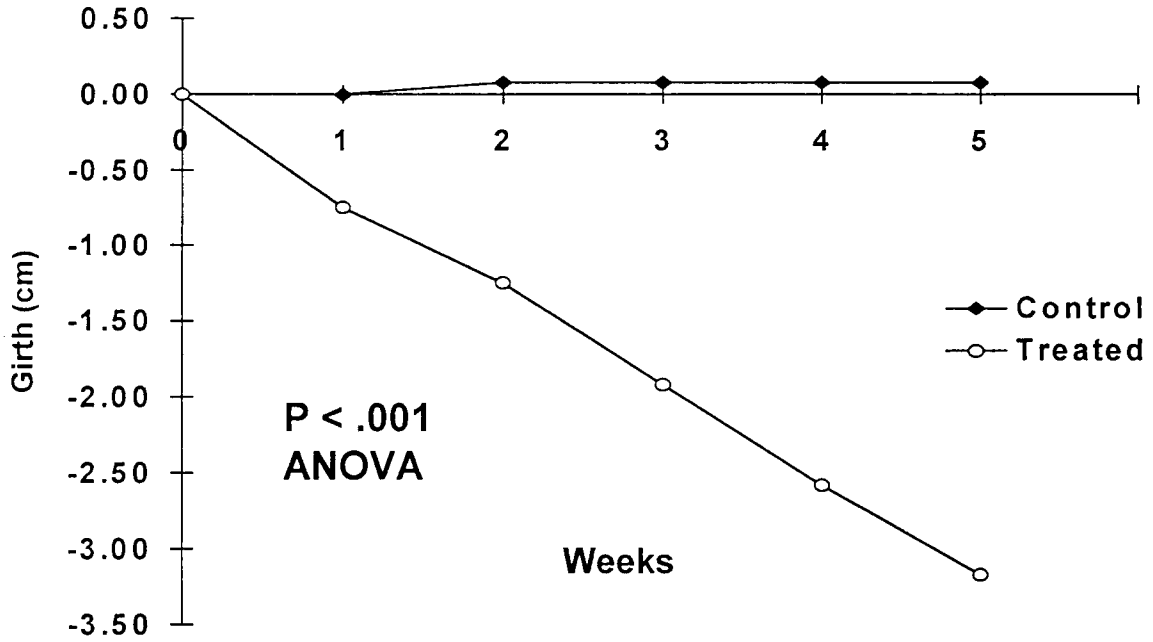


Figure 8: Changes in thigh circumference in 12 subjects after treatment with 0.5% aminophylline cream or placebo.

applied to the thighs by study personnel.

*Study 5*

A 2% concentration of aminophylline in a cream base was used. Twelve women who felt that their thighs were undesirably fat and dimpled were entered into the study. Some women wanted to lose weight while others were satisfied with their present weight. Thus no specific diet was recommended. A chemistry panel was drawn at the beginning and end of the study. Skin patch testing was done during the last week of the study and theophylline levels were drawn on the final day, 90 minutes after the cream containing aminophylline had been applied to both thighs. An aliquot of 5 g of cream was applied by study personnel in a double-blind and counterbalanced fashion so that 50% of the subjects had active cream applied to the right thigh and 50% had active cream applied to the left thigh. Subjects were seen five days a week for six weeks. Thigh circumference was measured at the beginning of each study week with weight supported on the measured thigh. Circumference was measured at one-half the distance from the fibular head to the greater trochanter.

*Study 6*

Twelve women volunteered for a study using 0.5% aminophylline cream. This clinical trial used the same metholodology as Study 5 with only the concentration of the cream being changed.

## Results

*Study 1*

All five women completed this study and four lost weight (Figure 1). The women who lost weight lost more girth from the treated than the control thigh. For the group as a whole, there was a 1.8± 0.89 cm greater girth loss on the isoproterenol-treated thigh than on the control thigh ($p<0.05$ by paired *t*-test). This result was encouraging, although not many women wanted to have multiple injections three times a week around the entire circumference of their thighs.

*Study 2*

All five participants lost more girth on the treated thigh than the control thigh with a mean ± SEM difference of 2.03 ± 1.36 cm ($p<0.05$ by paired *t*-test) (Figure 2). This study showed that local fat reduction could be produced without weight loss. During this study, which was conducted during the summer, one of the women developed a heat rash under the occlusive plastic wrap on both legs that disappeared with discontinuation of the plastic wrap.

*Study 3*

Four of the five subjects completed the yohimbine trial. All lost weight and all but one lost more girth on the treated than on the control thigh (Figure 3). The woman who lost more girth on the placebo thigh was the first entrant into the study. After her first visit, it was found that girth measurements were more reproducible if the subject supported her weight on the thigh being measured so as to give a reproducible muscle tension. Since this was not done in this one patient, the omission may account for her unexpected result. The yohimbine group lost more on the treated thigh than the control thigh, 0.75 ± 0.35 cm, although this did not reach statistical significance due to the small numbers. The four subjects who completed the forskolin trial all lost weight and lost more girth on the treated than the control thigh, 1.0 ± 0.61 cm ($p<0.05$ by paired *t*-test) (Figure 4). The five subjects who completed the aminophylline trial all lost weight and lost 1.5 ± 0.77 cm more girth on the treated thigh than the control thigh ($p<0.02$ by paired *t*-test) (Figure 5). There were no rashes or

other adverse events. There were no changes in blood pressure or pulse. The five patients who dropped out of the study did so after 3, 6, 7, 8 and 10 days. Four of the five patients had lost more girth from the treated than the placebo thigh at the time that they left the study. The fifth patient dropped out on the third day of the study and there had been no change in her thigh girth. On the basis of these studies, it was concluded that each agent could produce a change in thigh girth. Aminophylline was selected for further studies for two reasons. First, it is more soluble than other xanthines. Second, there has been a long-term experience with aminophylline as a drug for treating asthma in which its low toxicity has been well defined.

***Study 4***

Twenty-three of the 30 women completed this 6-week trial (Figure 6). No significant changes were seen in the chemistry results except for a reduction in triglycerides from $245 \pm 121$ mg/dL to $139 \pm 57$ mg/dL ($p<0.05$) and an increase in free fatty acids from $0.3 \pm 0.24$ mEq/L to $0.52 \pm 0.35$ mEq/L ($p<0.05$) which could have been due to the effect of the calorie restricted diet and weight loss. No theophylline could be detected at any time point, and patch testing showed no sensitivity. Weight declined by $3.3 \pm 2.2$ kg over the course of the six-week study. There were no significant changes in pulse rate or blood pressure. Thigh girth loss was greater in the treated than in the control thigh at the end of the study (Figure 6), $0.77 \pm 0.66$ cm for the lower girth measurement and $0.78 \pm 0.89$ cm for the upper girth measurement ($p<0.001$ by ANOVA).

***Study 5***

Eleven women completed this study (Figure 7). There was no skin irritation with patch testing. Three weeks after the start of the study, one woman developed a rash on the leg being treated with active cream. The cream was stopped and the rash resolved. This patient was then re-entered into the study using 0.5% aminophylline cream. She did not redevelop the rash and lost 2 cm more in girth on the treated than on the control thigh after five weeks of treatment. Problems with freezing and thawing made chemistry panel analysis unreliable. Theophylline levels were undetectable except for one subject who violated protocol and took theophylline for an asthma attack on the night prior to her theophylline level being drawn. The group of 11 women lost more girth from the treated than from the control thigh, $1.21 \pm 0.31$ cm ($p<0.01$ ANOVA) (Figure 7). Ten of the 11 women lost more girth on the treated than the control thigh at the end of the study. The one woman who, at the end of the study, lost more girth on the placebo thigh had lost more girth on the treated thigh the week before, and the final measurement could have been an error.

Since the 2% aminophylline cream caused a rash in one subject and that subject showed a 2 cm girth differential at the end of five weeks of treatment without a rash on 0.5% aminophylline cream, it seemed prudent to investigate further the lower cream concentration in Study 6.

***Study 6***

All 12 subjects lost more girth on the treated thigh than the control thigh at 5 weeks of treatment, $3.08 \pm 0.27$ cm ($p<0.001$ by ANOVA) (Figure 8). The chemistry panel showed significant decreases in ALT, LDH, globulin and creatinine ($p<0.01$ by paired *t*-test), but these were felt to be clinically insignificant since the changes were within the normal range for the test. There were no rashes, patch testing was negative, and theophylline levels were below the detectable threshold.

## Discussion

These six trials demonstrate that local fat reduction as measured by thigh girth, can be produced by topical application of compounds that stimulate lipolysis. Although we made no direct measurement of fat loss, it seems unlikely that the girth change could be attributable to any other component of the thigh, since the physiology of these compounds is known to affect the lipolytic process, and fat cells are directly under the skin where the active ingredient could modulate normal rates of lipolysis.

Differential thigh girth loss with topical lipolytic treatment does not require weight loss, warm hypertonic saline soaks, occlusive dressings, or an exercise program. Since the fat cells directly under the skin are stimulated first, the thigh skin loses its dimpling as tension is relieved on the subcutaneous tissue that attaches to the undersurface of the dermis. This occurs even before significant girth changes can be measured. Without weight loss, the possibility that under topical treatment fat may be redistributed from the thighs to the intra-abdominal area seems unlikely. Lipolysis and lipogenesis are ongoing processes, and the topical treatment only contacts the cells immediately below or in the dermis. The amount of fat mobilized would presumably redistribute through all other fat depots. Thus, the amount partitioned to any single area is likely to be vanishingly small. Definitive answers to these questions, however, will require CT or MRI scans.

The indication for topical lipolytic treatment is cosmetic. Many women are concerned about the appearance of their thighs whether or not they are obese. The women receiving this cream experienced an improved self-image which can result in tangible improvements in their perceived quality of life. They were offered 2 to 3 months of free active cream after they completed the study and all wanted it. It is easier to measure the benefit to women who are so distressed about the appearance of the fat on their thighs that they resort to a surgical procedure such as liposuction for therapy. Topical lipolysis is almost certainly safer and does not carry with it the attendant risks of a surgical procedure with its scarring and risks of infection as well as the risks of anesthesia.

Attempts have been made over many years to affect local fat reduction by a variety of nonsurgical methods. Of these methods, none have been shown to be effective. Now there is an effective method to achieve local fat reduction topically by manipulating the lipolytic mechanism and obviating the need for more risky surgical interventions.

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