

# Regional Fat Loss from the Thigh in Obese Women after Adrenergic Modulation

**Frank L. Greenway, M.D.**

*Department of Medicine, UCLA School of Medicine, Los Angeles, California*

**George A. Bray, M.D.**

*Department of Medicine, University of Southern California School of Medicine, Los Angeles, California*

---

## ABSTRACT

Beta-adrenergic stimulation and alpha 2 adrenergic inhibition increase lipolysis from fat cells. Twenty-eight obese women were placed on a calorie-restricted diet and one of five treatments was applied to one thigh three to five times per week for four weeks: (1) isoproterenol injections; (2) cream containing colforsin (forskolin), aminophylline, and yohimbine; (3) yohimbine cream; (4) colforsin cream; or (5) aminophylline cream. The opposite thigh was treated with a placebo (injection or cream). The treated thighs lost significantly more girth after treatment, both by injection and by cream. No adverse reactions were attributable to either the cream or the injections. It is concluded that local fat reduction from the thigh can be safely accomplished.

## INTRODUCTION

Fat is lost more rapidly from the abdomen than from the thigh after intestinal bypass surgery. Studies of fat cells have shown that beta-adrenergic agonists can directly increase cyclic adenosine monophosphate levels and stimulate lipolysis. There is a regional difference in this responsiveness to beta-agonists.<sup>2</sup> Fat cells from the abdomen are more sensitive to the lipolytic effects of beta-adrenergic stimulation than are those from the thigh. This appears to be because there are more alpha2-receptors on fat cells of the thigh than of the abdomen.<sup>3,4</sup> Raising the norepinephrine concentration in the medium suspending the fat cells from the thigh increases in vitro lipolysis from these cells.<sup>2</sup> The maximal lipolytic rate in fat cells from the two locations is equal, but higher concentrations of norepinephrine are needed to reach that maximum when fat cells from the thigh are used. Blocking the alpha2-receptors on fat cells from the thigh enhances lipolysis in the presence of norepinephrine.<sup>2,4</sup>

We hypothesized that by increasing the local concentration of beta agonists or by inhibiting phosphodiesterase or Alpha<sub>2</sub>- adrenergic receptors to fat cells in the thigh, fatty acids could be released more readily. We report the results of a series of small trials to test this **hypothesis**.

## MATERIALS AND METHODS

### *Study 1*

Five women who were more than 20% above their desirable body weight (mean weight, 209 lb) and wished to lose weight from their thighs were recruited and placed on a diet of 600 kcal daily and encouraged to engage in a walking program. They received injections of 0.2 ml of  $10^{-5}$  mol/L isoproterenol at intervals of 4 cm around the circumference of one thigh, two thirds of the way from the knee to the greater trochanter, three days per week for four weeks. The 4-cm interval was chosen because calculations from the area of vasodilation on the skin suggested that the spheres of diffusion would overlap when this distance was kept. The opposite thigh was treated similarly, but using normal saline in a double-blind design.

### *Study 2*

Five women (mean weight, 182 lb) who were more than 20% above desirable body weight and wished to lose weight from their thighs were recruited and placed on a diet of 600 kcal daily and encouraged to engage in a walking program. They were seen five days a week for four weeks. At each visit, warm wraps of 600 to 900 mosm/L of magnesium sulfate solution were applied to each thigh for 30 minutes, followed by an application of cream and plastic wrap. The cream applied to one thigh contained  $1.2 \times 10^{-5}$  mol/L colforsin (forskolin),  $2.5 \times 10^{-5}$  mol/L yohimbine, and  $1.3 \times 10^{-2}$  mol/L aminophylline in xipamide (aquaphor) base. The other thigh received xipamide base only in a double-blind design.

### *Study 3*

Eighteen women (mean weight, 197 lb) who were more than 20% above desirable body weight and wished to lose weight from the thighs were recruited and placed on a liquid formula diet of 800 kcal daily and encouraged to engage in a walking program. They were seen five days per week for four weeks. At each visit, warm wraps of 600 to 900 mosm/L of magnesium sulfate solution were applied to each thigh for 30 minutes, followed by cream application. One thigh was treated in each patient with one of the three creams in xipamide: colforsin,  $25 \times 10^{-5}$  mol/L (six patients); yohimbine,  $5 \times 10^{-4}$  mol/L (six patients); or aminophylline,  $1.3 \times 10^{-2}$  mol/L (six patients). The other thigh in each subject was treated with xipamide only, in a double-blind design.

In each study, treatment effectiveness was judged by measuring the thigh circumference two thirds of the way from the knee to the greater trochanter, using the saline- or xipamide-treated thigh as the control. Differences were compared with Student's *t* test for paired observations.

## RESULTS

In Study 1, all five women completed the four weeks of treatment and all but one lost weight. The four subjects who lost weight lost more girth from the thigh treated with isoproterenol injections than from the control thigh. In the total group, the thighs treated with isoproterenol lost a mean of  $1.8 \pm 0.89$  cm more than the control thighs ( $P < 0.05$ ). No changes in pulse rate, blood pressure, or other clinical parameters were noted.

In Study 2, all five women completed the four weeks of treatment and all but one lost weight. The five subjects lost a mean of  $2.03 \pm 1.36$  cm more from the thighs treated with cream containing colforsin, yohimbine, and aminophylline than from the control thighs ( $P < 0.05$ ). The only adverse effect was a pruritic rash that occurred on both thighs in one subject, which was judged to be related to the occlusive plastic-wrap dressing.

In Study 3, 13 of the 18 women completed the trial. In the four subjects who received yohimbine, all lost weight and all but one lost more girth from the thigh treated with yohimbine cream than from the control thigh. The woman who lost more girth from the thigh treated with placebo was the first subject to enter the trial. After her first visit, it was found that having subjects support their body weight on the thigh being measured increased reproducibility. Unfortunately, this was not done in the first patient, and this may have been responsible for the aberrant results in her case. The group as a whole lost a mean of  $0.75 \pm 0.35$  cm more from the yohimbinetreated thighs than from the control thighs, but the difference was not statistically significant.

All four subjects who completed the four weeks of treatment with colforsin lost weight. They lost a mean of  $1.0 \pm 0.61$  cm more girth from the thighs treated with colforsin cream than from the control thighs ( $P < 0.05$ ).

All five subjects who completed the four weeks of treatment with aminophylline lost weight. They lost a mean of  $1.5 \pm 0.77$  cm more girth from the thighs treated with aminophylline cream than from the control thighs ( $P < 0.02$ ).

No adverse reactions were noted in the three parts of Study 3. There were no changes in blood pressure or pulse, nor any evidence of skin rash. The five patients who dropped out did so after seven, eight, ten, six, and three days of treatment, respectively. Four of the five dropouts had lost more girth from the treated thigh than from the control thigh by the time of departure from the study. The fifth dropped out on the third day of treatment, at which time there was no change in thigh circumference. All five dropouts had lost weight at the time of their departure.

When girth loss from the treated thighs is compared with loss from the untreated thighs in all three studies combined, the treated thighs lost an average of  $1.33 \pm 1.12$  cm more than did the control thighs ( $P < 0.001$ ).

## DISCUSSION

It has been generally believed for some time that thigh fat in women is hard to mobilize.<sup>5</sup> Others, however, have been reluctant to accept this concept, believing that all fat cells are metabolically the same. In vitro work, however, has suggested that the adrenergic thresholds to lipolysis are indeed different in different sites, and that thigh fat is more difficult to mobilize than abdomen fat.<sup>24</sup>

Many attempts have been made to achieve local or spot fat reduction through nonsurgical means but none have succeeded.<sup>6</sup> The use of injections in Study 1, although clinically impractical, did support the concept of local adrenergic

modulation of lipolysis in vivo and encouraged us to try the topical application of adrenergic modulators. The results of the first study demonstrated that local fat reduction can be accomplished safely and effectively.

Studies 2 and 3 support the concept that topical application of adrenergic modulators can enhance lipolysis. It might have been postulated that yohimbine, the alpha<sub>2</sub>-inhibitor, would have been the most effective agent, since the higher threshold for lipolysis in thigh fat cells appears to be a result of a higher concentration of inhibitory alpha<sub>2</sub>-receptors. No naturally occurring alpha<sub>2</sub>-inhibitors circulate in human systems, but there are always beta-stimulating catechols present. In these two studies, data on the average loss of thigh circumference suggest that the cream containing a beta stimulator with a phosphodiesterase inhibitor and an alpha 2- inhibitor is the most effective. Of these three components, the phosphodiesterase inhibitor was most effective, followed by the betastimulator, and then the alpha 2- inhibitor. The number of patients in each trial, however, was small, and thus conclusions about the relative potency of the three components of the combined cream are tenuous. The only side effect seen in any of the trials was a skin rash on both thighs in one woman during Study 2 when plastic wrap was used as an occlusive dressing. This complication was not seen in Study 3 when no plastic wrap was used. Clearly, the plastic wrap was not essential to the effectiveness of the treatment. The safety of this treatment was not unexpected since very small amounts of adrenergic modulators could be absorbed into the bloodstream.

## CONCLUSIONS

It is concluded that results of the three studies demonstrate that local fat can be reduced with a cream both safely and effectively.

## REFERENCES

1. Kral JG, Bjornorp P, Schersten T, Sjostrom L. Body composition and adipose tissue cellularity before and after jejunoileostomy in severely obese subjects. *Eur J Clin Invest* 1977; 7:413-419.
2. Smith U, Hammersten J, Bjornorp P, Kral JG. Regional differences and effect of weight reduction on human fat cell metabolism. *Eur J Clin Invest* 1979; 9:327-332.
3. Motulsky HJ, Insel PA. Adrenergic receptors in man. Direct identification, physiologic regulation and clinical alterations. *New Engl J Med* 1982; 308:18-29.
4. Lafontan M, Dang L, Berlan M. Alpha adrenergic anti-lipolytic effect of adrenaline in human fat cells of the thigh. Comparison with adrenaline responsiveness of different fat deposits. *Eur J Clin Invest* 1979; 9:261-266.
5. Ronsard N. *Cellulite. Those lumps, bumps and bulges, you couldn't lose before*. New York: Beauty and Health Publishing Corp, 1973.
6. Kalb SW. The fallacy of massage in the treatment of obesity. *J Med Soc New, Jersey* 1944; 41:406-407.