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Effect of percutaneous androgen replacement therapy on body composition and body weight in postmenopausal women

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Abstract

Objectives: This study was carried out to assess the effect of topical androgen replacement therapy on body weight, body composition and fat distribution in postmenopausal women. *Methods:* 39 healthy postmenopausal women (51.4 ± 2.24 years), with increasing body weight, were prospectively studied for 6 months. Body composition (fat mass, kg, %) was measured by means of dual-energy X-ray absorptiometry (DXA). Hormonal and lipid parameters were also measured. Subjects were divided into two groups. An androgen gel (group A) or placebo gel (group P) was topically administered to the abdominal and gluteo-femoral regions. DXA was performed before commencement of topical treatment and after 6 months. *Results:* A highly significant total body weight reduction was found in group A (68.0 ± 13.1 to 65.4 ± 11.8 kg). Abdominal fat (37.3 ± 11.2 to 35.1 ± 9.7%), gluteo-femoral fat (46.3 ± 6.6 to 45.4 ± 7.7%), total body fat (38.2 ± 7.9 to 36.1 ± 8.6%) and BMI (24.8 ± 4.3 to 23.7 ± 3.8) were also found to have decreased significantly in this group. No significant reduction in body weight (kg) and body fat (%) could be measured in the placebo group. No influence on lipid parameters was found although total testosterone increased significantly in group A (0.29 ± 0.24 to 0.72 ± 0.17 ng/ml). *Conclusions:* Topically applied androgen is capable of reducing abdominal fat accumulations as well as total body weight in postmenopausal women with unexplained weight gain. In contrast to systemic androgen application, topical administration has no effect on the lipid profile. Gluteal fat, however, is less effectively influenced by androgens.

Keywords: Body composition; Body weight; Androgen replacement therapy; Topical administration; DXA

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1. Introduction

Obesity and weight gain appear in $\approx 60\%$ of postmenopausal women. Abdominal fat distribution, independent of total adiposity, has been shown to be an important risk factor for metabolic and cardiovascular disease in women [1], as well as men [2]. A number of factors are known to influence abdominal fat distribution, including aging [3], smoking, alcohol consumption and hormones [4,5].

Considerable attention has been focused on the role of androgens and estrogens in modulating abdominal fat distribution. In clinical studies, correlations between testosterone levels and visceral fat accumulation have been shown in both men and women [6]. On the one hand, the increase of visceral and truncal fat is observed in patients with ovarian hyperandrogenism and PCO syndrome [7]. On the other hand, it is well known that hypoandrogenemia in postmenopausal women results in increased subcutaneous abdominal fat [8,9]. Marin et al. [10], demonstrated that administration of testosterone decreased visceral fat without significantly affecting subcutaneous fat or overall body composition. Lovejoy et al. [11], recently demonstrated that the administration of exogenous androgens modulates body composition in obese postmenopausal women and independently reduces visceral and subcutaneous fat.

Data on this field are conflicting. Furthermore, it is known that androgen treatment can decrease abdominal fat as the expression of lipolytic β-adrenergic receptors is positively autoregulated by testosterone [12] and, therefore, enhancement of lipolysis can be expected. To our knowledge there are no data available on the effect of topically administered androgen upon female adipose tissue and body fat distribution. The purpose of this placebo-controlled trial was to determine the effect of topical androgen replacement therapy (Andractim®) on body composition and subcutaneous fat distribution in postmenopausal women.

2. Materials and methods

2.1. Subjects

The data of the present study were collected from 39 healthy postmenopausal women, (mean: 51.4 ± 2.24 years), who were recruited from the Menox® Vienna outpatient menopause clinic between January 1996 and January 1997, to which they had been referred for hormonal check up and body composition measurement because of increasing body weight. None of the women had undergone uni- or bilateral oophorectomy or hysterectomy. All of the patients had already experienced natural menopause 3 months to 2 years previously, as documented by elevated follicle stimulating hormone (FSH > 30 mU/ml) and low estradiol levels (< 25 pg/ml). None of the patients received hormone replacement therapy or any medication known to influence body weight or body composition, such as glucocorticoids, diuretics, insulin, β-blockers or thyroidotherapy. Each patient was interviewed precisely regarding her daily food intake (kcal/d) and activity level (h/week) before entering the study. The intention was to avoid the enrolment of women on a basically hypercaloric diet. To make sure they maintained their diet regime and exercise habits during the course of the study, all women were requested to sign a form pertaining to these facts. At the end of the study, calorie uptake was measured again. The protocol was approved by an institutional ethics commission and written informed consent was obtained from each participant. Patients were assigned randomly—by means of sealed envelopes—to one of our two treatment groups. Group A consisted of 20 women, who received topical androgen replacement therapy and group P consisted of 19 women who received a placebo gel.

2.2. Study design

Subjects were followed up for 6 months. Each subject was examined twice, i.e. before entering the study and on its completion. After 3 months of therapy, however, the subjects were again seen at the clinic for a personal interview to assess their compliance. All examinations were performed by the same team. The baseline and final examinations were identical and included: a structured questionnaire, anthropometric measurements by means of dual-energy X-ray absorptiometry (DXA), physical (including weight and height),

Table 1
Baseline body composition measurement of group A and group P (mean ± S.D.)[a]

	Before therapy	
	Group A	Group P
Total body weight (kg)	68.0 ± 13.1	69.1 ± 9.6
BMI (kg/cm^2)	24.8 ± 4.3	25.1 ± 3.6
Abdominal fat (kg)	12.1 ± 6.5	13.5 ± 4.6
Gluteo-femoral fat (kg)	10.7 ± 4.2	10.1 ± 2.4
Abdominal fat (%)	37.3 ± 11.2	37.8 ± 7.6
Gluteo-femoral fat (%)	46.3 ± 6.6	43.0 ± 6.5
Total body fat (%)	38.2 ± 7.9	39.2 ± 6.5

[a] No significant differences could be found at baseline in any of the items in groups A and P.

gynecological and dermatological examination, hormonal parameters estradiol (E2), FSH, total testosterone (T), sexual hormone binding globulin (SHBG), and lipid profile (total cholesterol, HDL, LDL, triglyceride). The questionnaire contained such items as parity, medical status, smoking behavior and menopausal status. The baseline values of the two groups regarding adiposity and fat distribution parameters are presented in Table 1. The clinical characteristics are presented in Table 2.

Table 2
Clinical characteristics of women entered in the study (mean ± S.D.)[a]

	Androgen replacement therapy (group A, $n = 20$)	Placebo group (group P, $n = 19$)
Age	51.7 ± 1.9	52.2 ± 1.3
Height (cm)	165.3 ± 1.8	166.1 ± 12.4
Months since menopause	11.2 ± 3.3	10.5 ± 4.2
Smoking[b]	7 ± 0.7	8 ± 1.02
Food intake (kcal/d)	1458.75 ± 09.52	1502.12 ± 102.63
Activity level (h/week)	3.5 ± 0.73	3.7 ± 0.58
Parity	2.3 ± 0.28	1.9 ± 0.5

[a] No significant differences have been found between the groups in any of the items.
[b] Values are numbers of cigarettes per day ± S.D.

2.3. Substance and topical administration

Androgen replacement therapy was performed with Andractim® (80 g tube, Besins-Iscovesco, Paris, France) or a placebo gel preparation. Andractim® is a transdermal preparation of dihydrotestosterone, 100 g of which contains 2.5 g androstanolone. Extensive pharmacokinetic studies have been completed for androstanolone [13]. Resorption data and androgen serum concentrations are also available for this substance [14]. The placebo gel was composed of the same ingredients with the exception of the active component and looked, felt and smelled identical to the verum preparation. Both drug and placebo were packed in 100 g tubes of identical appearance. All women were instructed to take 4 cm of gel from a calibrated dispenser and to apply it twice a day to the abdominal and gluteo-femoral region for 6 months. The abdominal region was defined as the area below the umbilicus and above the pubic hair line. The gluteo-femoral region was defined as the area below the pubic hair line, i.e. the area of the big gluteal muscle and the femoral region. A quantity of 4 cm (= 1.54 g) of androstanolone (group A) or a placebo gel (group P) was applied to the skin over a surface area of ≈ 30 cm^2. The weight of 1.54 g for each 4 cm was the mean value determined on the basis of 10 measurements (a quantity of 4 cm of gel was weighed on 10 occasions). A dose of 1.54 g of androstanolone gel contained 0.0375 g of the active substance.

2.4. Laboratory determinations

Hormonal parameters (FSH, E2, total T, SHBG) and blood lipids (CHOL, HDL, LDL, Trigl) were collected in all subjects at the Menox clinic between 08:00 and 11:00 h. Quantitative determination of parameters was performed at the Menox® laboratory using commercially available standard enzymeimmunoassay and radioimmunoassay kits.

2.5. Dual-energy X-ray absorptiometry

DXA allows determination of body composition by measuring the attenuation of the X-ray

Table 3
Body composition before and after therapy in 20 women of group A (mean ± S.D.) and in 19 women of group P (mean ± S.D.)[b]

	Group A (androgen replacement therapy)		Group P (placebo)	
	Before therapy	After therapy	Before therapy	After therapy
Body weight (kg)	68.0 ± 13.1	65.4 ± 11.8[a]	69.1 ± 9.6	69.2 ± 9.8
BMI (kg/cm^2)	24.8 ± 4.3	23.7 ± 3.8[a]	25.1 ± 3.6	25.1 ± 3.8
Abdominal fat (kg)	12.1 ± 6.5	11.1 ± 6.4	13.5 ± 4.6	13.4 ± 4.8
Gluteo-femoral fat (kg)	10.7 ± 4.2	10.5 ± 4.3	10.1 ± 2.4	10.2 ± 2.6
Abdominal fat (%)	37.3 ± 11.2	35.1 ± 9.7[a]	37.8 ± 7.6	37.6 ± 7.7
Gluteo-femoral fat (%)	46.3 ± 6.6	45.4 ± 7.7[a]	43.0 ± 6.5	43.1 ± 6.6
Total body fat (%)	38.2 ± 7.9	36.1 ± 8.6[a]	39.2 ± 6.5	38.9 ± 6.8

[a] $P < 0.05$, baseline measurement before therapy and after 6 months of topical androgen replacement therapy.
[b] No significant differences have been found in any of the items in the placebo group.

beam on a pixel-by-pixel basis over the entire body surface. Measurements were performed using a total body scanner (QDR-2000, Hologic, MA). This scanner uses an X-ray source, an internal wheel to calibrate the bone mineral component and an external lucite and aluminium phantom to determine the percentage of fat of each soft tissue sample scanned. Special software provides lines to divide body measurements into areas corresponding to head, arms, legs and trunk [15]. The proportion of android fat mass was determined by the amount of fat tissue in the trunk region, whereas the proportion of gynoid fat mass was determined by the amount of fat tissue in the femoral region, as previously described by Ley et al. [16].

2.6. Statistical analyses

All statistical analyses were done with an SPSS-X program version. Student's *t*-tests were carried out in order to test group differences with respect to their statistical significance. Values of $P < 0.05$ were regarded as statistically significant. Data are presented as means ± S.D.

3. Results

As all of the women who entered the study completed the trial after 6 months, data of 39 subjects could be evaluated.

In group A, significant changes were observed after 6 months of treatment in respect of the following parameters: total body weight ($P < 0.05$), body mass index ($P < 0.05$), percentage of abdominal fat ($P < 0.05$), percentage of gluteo-femoral fat ($P < 0.05$) and percentage of total body fat ($P < 0.05$). Absolute fat reduction in the abdominal and gluteo-femoral region, measured in kilograms, was markedly but not significantly, reduced. The results are shown in Table 3.

Regarding the placebo group, no significant or remarkable differences between the two investigations both before and after therapy could be observed (Table 3).

The percutaneous administration of androstanolone did not cause any undesirable increase in lipid parameters or estradiol serum levels during the 6 months of application (Table 4). Total testosterone increased significantly in group A but not in group P, still within the physiological range. During the time of treatment, no skin irritation or allergic reaction occurred, nor could any hyperandrogenemic side effects such as hirsutism, acne or effluvium be observed.

4. Discussion

In our placebo-controlled, prospective, clinical study, we investigated the lipolytic effect of androgen replacement therapy on adipose tissue, body weight and body composition by applying a

Table 4
Hormonal and lipid parameters before and after therapy in 20 women of group A (mean ± S.D.) and in 19 women of group P (mean ± S.D.)[b]

Serum parameter	Group A (androgen replacement therapy)		Group P (placebo)	
	Before therapy	After therapy	Before therapy	After therapy
Estradiol (pg/ml)	15.2 ± 3.7	12.3 ± 2.4	13.7 ± 5.8	15.4 ± 4.9
FSH (mU/ml)	55.7 ± 8.2	57.3 ± 9.3	50.2 ± 7.9	54.8 ± 4.2
LH (mU/ml)	25.7 ± 3.9	24.8 ± 4.2	24.3 ± 4.2	26.3 ± 2.1
Total testosterone (ng/ml)	0.29 ± 0.24	0.72 ± 0.17[a]	0.21 ± 0.12	0.29 ± 1.2
SHBG (nmol/ml)	24.1 ± 1.7	22.4 ± 3.2	25.2 ± 2.1	23.7 ± 1.8
Total CHOL (mg/dl)	182.7 ± 12.4	186.9 ± 9.3	183.3 ± 23.2	187.1 ± 18.9
HDL (mg/dl)	83.1 ± 5.6	80.2 ± 4.4	70.2 ± 15.7	68.3+10.9
LDL (mg/dl)	119.9 ± 11.3	121.4 ± 3.6	120.7 ± 13.9	124.9 ± 11.6
Triglyceride (mg/dl)	124.4 ± 12.0	116.7 ± 14.8	126.6 ± 14.0	118.3 ± 17.9

[a] $P<0.05$.
[b] No significant difference could be found at baseline in any of the items in groups A and P.

steroidal substance in a topical-administration formula to the subcutaneous abdominal and gluteo-femoral region of adipose postmenopausal women. Within 24 weeks of topical treatment with androstanolone, we were able to evaluate a highly significant decrease of adipose tissue in the abdominal region but not in the gluteo-femoral region.

Even though androgens increase insulin resistance and thereby negatively influence body weight, a transdermal application of androgens, nevertheless, appears to have a lipolytic effect. The explanation for this outcome might be found at the receptor level and in differences in receptor expression on adipocytes. As stated by Lapidus et al., the effect of testosterone is modulated via testosterone receptors, which are widely expressed in adipocytes of the subcutaneous abdominal region [1]. Another study has suggested that regional differences in catecholmine-induced lipolysis are regulated at the adrenoceptor level. Higher lipolytic response of abdominal fat cells as compared to gluteal fat cells in men seems to be mainly due to a higher number of β-adrenoceptors in abdominal fat cells than in gluteal fat cells [17]. Xu et al. suggest that the androgen status may at least contribute to these regional differences because of the androgen effects on the regulation of β-adrenoceptor number [18]. In cultured male adipose precursor cells, it was shown that testosterone increased lipolysis. Previous studies of the effect of testosterone on the regulation of lipolysis and adrenoceptors in animal models have shown both species and sex differences [19,20]. Systemic administration of testosterone to men also resulted in elevated catecholamine-induced lipolysis in abdominal adipose tissue [21]. Taken together, these studies have shown that testosterone increases β-adrenoceptor numbers both in vivo and directly in vitro, followed by an increased lipolytic response of β-adrenergic catecholamines. Conclusively, the lower androgen levels found in abdominally obese males [2,22] may cause a reduction of β-adrenoceptor numbers, particularly in the abdominal region. This results in a lower lipolytic response to catecholamines and therefore leads to fat accumulation in this region.

We conclude that the induction of lipolysis due to androgen replacement therapy was why weight reduction could be achieved. Further intensive investigations should reveal whether our findings indicated a local effect on the receptor level of subcutaneous adipocytes or whether the serum testosterone levels, higher than normal in postmenopausal women, caused a systemic effect. Differences in weight reduction and body composition changes might also have been

achieved due to site variations in receptor density in the two body regions. Our findings support the contention made in several studies that adipocytes from the femoral adipose tissue are less responsive to androgen stimulation than adipocytes from the abdominal adipose tissue. This implies that female sex hormones exert regionally specific effects [23]. Obviously, there is an even greater difference in receptor expression in subcutaneous adipocytes and visceral adipocytes than has been expected so far.

Androgen substitution against declining sexual desire at menopause is becoming increasingly important [24,25]. It was also reported recently that corpulent and heavy women suffered far more frequently from a severe decrease in sexual interest after menopause [26]. Although changes of sexual desire were not meant to be evaluated in our study, 15 women of group A nevertheless reported, independently, that their libido had increased during time of therapy. We therefore suggest that not only a decrease in sexual interest, but weight problems and changing body composition in postmenopausal women should be an indication for androgen substitution. As Lovejoy et al. [11] demonstrated in their study, weight loss due to an oral androgen replacement was possible. The paper suggested that other formulations of anabolic steroids, such as sublingual or transdermal delivery systems that do not have adverse effects on blood lipids, might be of interest as an adjunct to obesity treatment. We conclude that topical androgen replacement therapy is capable of reducing subcutaneous abdominal fat apposition more profoundly than gluteo-femoral adipositas in postmenopausal women. Topical androgen replacement therapy appears to independently modulate the subcutaneous fat in women without influencing lipid parameters.

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