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Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women

Susan R. Davis, MD, PhD,[1] Karen Z. Walker, PhD,[2] and Boyd J. G. Strauss, MD[3]

Abstract

Objective: The cardioprotective effects of postmenopausal estrogen replacement therapy are mediated by several mechanisms, including favorable effects on lipids and lipoproteins. The extent to which the latter reflects modification of body fat distribution by sex steroids is not known. Hence, we investigated the relationships between changes in lipids and measures of body composition in postmenopausal women who were administered estrogen therapy with and without testosterone.

Design: We randomized 33 postmenopausal women to treatment with either estradiol 50 mg (E) alone or estradiol 50 mg plus testosterone 50 mg implants (E&T) administered every 3 months for 2 years in conjunction with cyclic oral progestins for women with an intact uterus.

Results: Both therapies were associated with sustained reductions in total cholesterol and low-density lipoprotein (LDL) cholesterol. In women who received E but not E&T, hip ($p < 0.001$) and abdominal circumferences ($p < 0.05$) and fat mass:fat-free mass (FM:FFM) ratio over the abdomen ($p < 0.05$) declined. E&T but not E resulted in increased FFM ($p < 0.001$) and a reduced FM:FFM ratio ($p < 0.05$). For E but not E&T, the decrease in LDL cholesterol was significantly related to changes in total and compartmental body fat and to change in the FM:FFM ratio ($p < 0.05$).

Conclusion: Estrogen replacement has effects on body fat distribution in postmenopausal women that are associated with improved lipid parameters. Addition of parenteral testosterone does not negate the favorable effects of estrogen on LDL cholesterol levels but may attenuate the reduction in centralized body fat achieved with E implants.

Key Words: Testosterone – Estradiol – Menopause – Body composition – Blood lipids.

Coronary heart disease (CHD), the leading cause of death in women in industrialized countries, generally affects women later in life than men. The loss of ovarian estrogen production at menopause is associated with metabolic changes that adversely influence cardiovascular disease risk. Probably the most studied of these is the effect of estrogen deprivation on lipids and lipoproteins. With increasing age in women and possibly as a consequence of menopause, total cholesterol, triacylglycerol (TAG), and low-density lipoprotein (LDL) cholesterol increase and high-density lipoprotein (HDL) cholesterol and its subfraction HDL-2 decrease.[1] Body composition and fat distribution also change in the postmenopausal years such that women tend to lose lean body mass,[2,3] increase total body fat,[3–5] and develop a more centralized (android) pattern of body fat distribution.[2,5,6] The more android pattern of fat distribution is associated with higher risk of CHD.[7,8] It is likely that these changes in body composition and fat distribution are related to the development of a more adverse lipid profile in the postmenopausal years.

Estrogen replacement therapy (ERT), with and without progestin, improves lipid profiles in both normolipemic[9] and hypercholesterolemic postmenopausal women,[10,11] and these effects do not seem to be ad-

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From the [1]Department of Epidemiology and Preventive Medicine, Monash University, Prahran, Australia; [2]Centre for Population Health and Nutrition, Monash University, Clayton, Australia; and [3]Body Composition Laboratory, Monash Medical Centre, Melbourne, Australia.

Address reprint requests to Dr. Susan R. Davis, Director of Research, The Jean Hailes Foundation, 173 Carinish Road, Clayton, Victoria 3168, Australia.

versely influenced by the use of parenteral testosterone.[9] There are, however, few prospective data pertaining to the effects of ERT on body composition and fat distribution or to the relationships between such changes and the effects of ERT on plasma lipids and lipoproteins and the effects of concomitant testosterone therapy on these relationships.

The administration of androgen replacement therapy, usually in the form of testosterone, is used for the restoration of libido in symptomatic women[9,12] and for the prevention of bone loss after menopause.[9,13] With the increasing availability of testosterone and other androgen supplements for women, the inclusion of androgen therapy in postmenopausal hormone regimens is becoming more widespread. However, the effects of adding testosterone to estrogen therapy on body composition have not been reported. We report the relationships between changes in body composition and fat distribution and lipids and lipoproteins after long-term administration of estradiol alone or estradiol plus testosterone.

MATERIALS AND METHODS

Subjects

As reported previously,[9] 34 postmenopausal women (>12 months of amenorrhea and had serum follicle-stimulating hormone levels > 15 IU/L) who attended the menopause clinic of Monash Medical Centre, Melbourne, Australia, volunteered for this study, which was approved by the Human Research and Ethics Advisory Committee of Monash Medical Centre, Melbourne. All subjects gave their written informed consent. None of these women had previously been treated with androgens or had received hormone implants, although some had received oral ERT.

Methods

Women were randomized independently to single blind treatment with either estradiol 50-mg implants alone (E) or estradiol 50-mg plus testosterone 50-mg implants (E&T), both donated for the study by Organon Australia Ltd.[9] Implants were administered every 3 months for a period of 2 years. E or T implants were not inserted if a preceding blood test indicated that serum estradiol or testosterone levels exceeded 500 pmol/L or 4 nmol/L, respectively. During the study, 13 estradiol implants were withheld from seven women who received E&T treatment, and 7 estradiol implants were withheld from four women who received E alone. Thirteen testosterone implants were similarly withheld.[9] Women with an intact uterus were treated with either cyclical medroxyprogesterone acetate (Provera, Upjohn Pty. Ltd, Rydalmere, NSW, Australia) 5–10 mg or norethisterone (Primolut N, Schering Pty. Ltd., Alexandria, NSW, Australia) 2.5 mg orally for 12 days per month. All investigations were performed at entry into the study and then at six monthly intervals for 2 years. All investigators and research assistants involved in body composition measurements and data analysis were blinded as to each patients therapy.

Women were weighed without shoes and while wearing light clothing or underwear. Weight was measured to the nearest 0.1 kg on a digital scale, and body height was measured using a wall-mounted stadiometer. Body mass index was calculated as weight (kg) divided by height (m) squared. Measurements of body circumferences and skinfold thicknesses were undertaken by a single skilled individual using standard procedures.[14] The World Health Organization abdominal circumference was taken as the greatest circumference between the lowest rib and the top of the pelvis. Skinfold thicknesses were measured at the triceps, biceps, and subscapular and suprailiac sites with Harpenden calipers (Holtain Ltd., Crymych, UK). Body composition was measured by dual-energy X-ray absorptiometry (DXA) after a whole-body scan taken on a DPX-L scanner (DPX-L; Lunar Corporation, Madison, WI), which was standardized daily against a calibration block. Total body fat mass (FM), the sum of fatty elements in all fat tissue,[15] was derived according to computer algorithms supplied by the manufacturer (DPX-L software version 3.4, Lunar Corporation), and free-fat mass (FFM) was taken as total body tissue minus FM. In addition, an abdominal region of interest was defined manually by delineating a superior border at the level of the top of the L2 vertebra, an inferior border at the bottom of the L4 vertebra, and vertical borders drawn through the intersection of the superior border with the left and right costal margins. The ratio of abdominal FM to FFM was then determined after compositional analysis of this region of interest.

Accuracy of total body fat by DXA has been assessed by comparison to underwater hydrodensitometry in 12 healthy adult volunteers. The correlation was $r = 0.895$ ($p < 0.0001$) with a between-method bias of + 4.8% (range = 2–9%). Precision of the DXA was assessed by 10 repeated measures on one healthy volunteer. The coefficient of variability (CV) was 1% for percentage of fat, 0.6% for FFM, and 2.1% for FM. Precision of the sum of the thicknesses of four skinfolds was assessed by eight repeated measures in three healthy volunteers by two trained technicians. The CV varied from 5.9% to 6.3%, depending on the technician.

For accuracy of the sum of the four skinfold thicknesses, the correlation with DXA was $r = 0.921$ ($p < 0.00001$).

Serum estradiol and testosterone were measured by radioimmunoassay.[9] Total cholesterol, TG, and HDL cholesterol were measured by automated standard methods,[9] and LDL cholesterol was calculated according to Friedwald.[16]

Statistical analyses

The data comprised repeated measurements on each individual at baseline and then every 6 months for 2 years. Results are expressed as the mean ± standard deviation (SD). The baseline data were tested for treatment differences by two sample t tests. For 6-, 12-, 18-, and 24-month data, parameters were analyzed by multivariate analysis of covariance (MANCOVA). Data were also compared at baseline and after 2 years in each group by Student's paired t test. Relations between variables were established by Pearson's correlation coefficient. Analyses were performed using Microsoft Excel 5.0 for the Macintosh. The level of significance was taken as 0.05.

RESULTS

Thirty-two women completed the study: 17 in the E group and 15 in the E&T group. One woman discontinued for personal reasons early after commencement, and the other discontinued after 12 months because of weight gain. At baseline, after randomization, the E group did not differ from the E&T group in smoking or alcohol habits, hysterectomy or ovariectomy status, estrogen or testosterone levels, or levels of blood lipids. Body mass index also did not differ between the two groups (24.6 ± 3.1 and 24.6 ± 3.3 kg/m^2 for E and E&T therapy, respectively). The mean age of the 17 women in the E group, however, was significantly lower than that of the 15 women in the E&T group (51.3 ± 5.7 years and 57.0 ± 5.2 years, respectively, $p < 0.01$). All body composition variables were analyzed using age as a covariate; no significant effect of age was demonstrated.

Changes in the hormonal status of women before and after the study intervention are shown in Fig. 1. At baseline, the women who were receiving E and the women who were receiving E&T did not differ significantly in their levels of estradiol or testosterone. After 2 years of therapy, serum estradiol levels were significantly higher than at baseline in both treatment groups ($p < 0.001$), whereas, as expected, serum testosterone remained unchanged in the E group but increased with E&T treatment ($p < 0.001$).

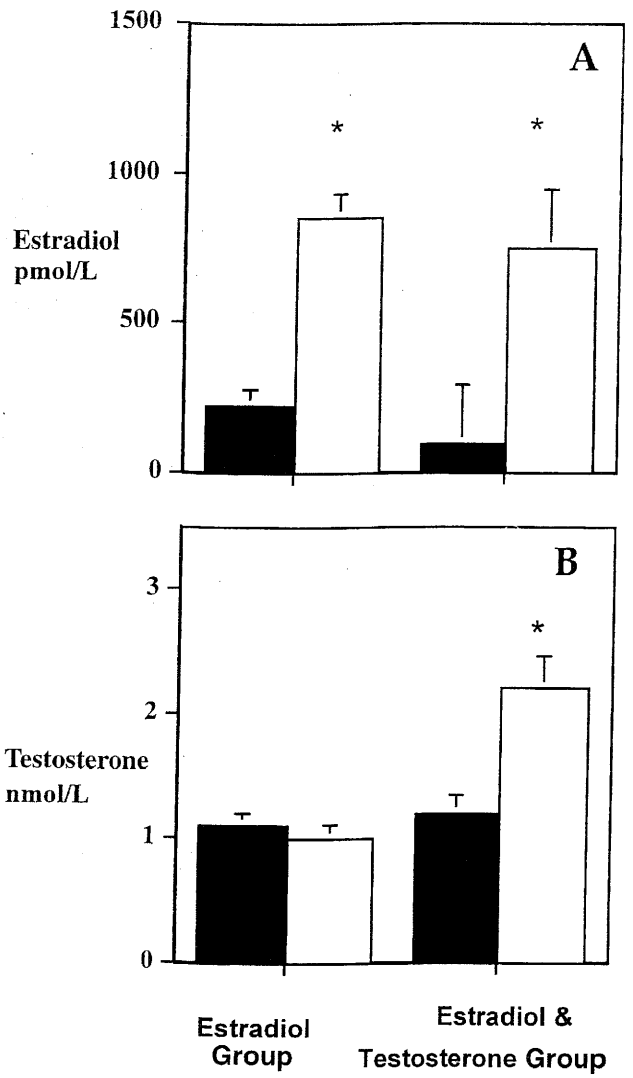

FIG. 1. Serum levels of estradiol (A) and testosterone (B) at baseline (closed histogram) and at 2 years (open histogram) in 32 postmenopausal women who received estradiol implants or estradiol implants plus testosterone. Vertical lines indicate the standard error of the mean. *, significant change from baseline ($p < 0.001$).

The effects of therapy on bone mineral density have been previously reported.[9] Here we report the detailed analysis of change in body composition and fat distribution and the relationships of these changes and change in lipoprotein lipids.

Over 2 years, mean body weight decreased slightly in the E group (from 65.1 ± 9.2 kg to 64.1 ± 8.9 kg) and increased slightly in the E&T group (from 63.4 ± 7.8 kg to 64.6 ± 9.7 kg), but these changes were not statistically significant. Similarly, total body FM as determined by DXA did not change significantly throughout the study (Fig. 2). Although there was a modest decline in FM with E&T therapy over 2 years (37.4 ± 7.1 kg to 35.9 ± 7.7 kg), this change did not achieve statistical

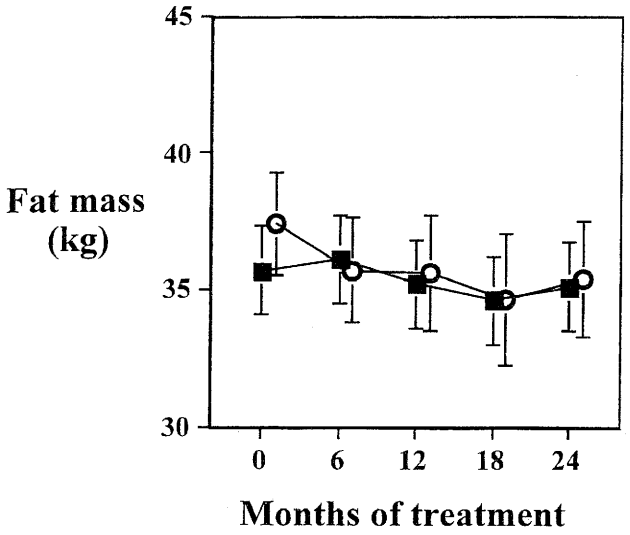

FIG. 2. Total body fat determined by DXA in 32 postmenopausal women who received estradiol implants (■) or estradiol implants plus testosterone (○) over a 2-year period. Vertical lines indicate the standard error of the mean.

significance (Table 1). In the E&T group but not in the E group, levels of FFM increased significantly over the 2-year period (24.8 ± 5.9 kg to 27.9 ± 5.9 kg, $p < 0.01$), whereas the FM:FFM ratio declined ($p < 0.05$). The MANCOVA of body variables gave a significant treatment effect ($\chi^2 \approx 17.26$, 9 df, $p < 0.05$).

Change in the deposition of abdominal fat was also examined. In the group that was given estradiol implants alone, there was a significant decline in the FM:FFM ratio measured in a region drawn directly over the abdomen ($p < 0.05$). This reflected both a decrease in fat over the abdomen from 1.51 ± 0.57 to 1.43 ± 0.59 kg and a concurrent increase in FFM in this area, from 3.12 ± 0.55 to 3.30 ± 0.52 kg, although these changes in themselves did not reach statistical significance.

Changes in anthropometric measures of girth over the 2 years of the study are given in Table 2. Women who received E implants alone showed significant decreases in hip and abdominal circumferences ($p < 0.01$ and $p < 0.05$, respectively). There was also a trend toward a decrease in the umbilical circumference ($p < 0.08$). These changes were not observed in women who were given E&T.

Over 2 years, both total cholesterol and LDL cholesterol declined in both treatment groups (Fig. 3). LDL cholesterol fell from 4.0 ± 0.89 mmol/L to 3.3 ± 0.94 mmol/L ($p < 0.01$) in women who were given E implants and from 4.1 ± 0.77 mmol/L to 3.4 ± 0.91 mmol/L ($p < 0.01$) in women who were given E&T. The decline in the ratio of LDL cholesterol to HDL cholesterol, however, was only significant in women who were given E alone ($p < 0.01$).

Relationships between changes in LDL cholesterol and change in body fat were also examined. With E alone, there was a positive and significant relationship between the change in LDL cholesterol over 2 years and the change in total body fat ($r = 0.494$, $p < 0.05$) (Table 3). Change in LDL cholesterol was also significantly related to change in the FM:FFM ratio over the abdomen ($r = 0.642$, $p < 0.01$), to change in the total body FM:FFM ratio ($r = 0.519$, $p < 0.05$), and to the change in hip circumference ($r = 0.670$, $p < 0.01$). Similarly, the change in the ratio of LDL cholesterol to HDL cholesterol over 2 years was significantly related to change in total body FM, to change in the total body FM:FFM ratio, to change in the FM:FFM ratio over the abdomen, and to the change in hip circumference (all $p < 0.05$) (Table 3). Analysis of comparable data in women who received treatment with E&T indicated that none of the relationships was of statistical significance.

DISCUSSION

Women who are commencing ERT are often anxious that their treatment will exacerbate weight gain. This study confirms that estradiol implants, which result in relatively high circulating levels of estradiol, do not significantly increase body weight or total body fat in postmenopausal women over a 2-year period. Moreover, the addition of testosterone did not adversely affect body weight or total body fat.

Our results with E alone are in agreement with many previous studies. Although weight gain with ERT has been reported,[17,18] most studies indicate that ERT either decreases or has no influence on body weight.[5,19–22] Similarly, despite one report that ERT increased the percentage of body fat,[17] the present study is consistent with other findings that total body FM by DXA is unaffected by ERT[20,23] and with a recent twin study that indicated that in monozygotic twins discordant for ERT use, the twin that received the hormone therapy had the lower FM.[24]

After menopause, women typically experience a loss of FFM,[2,3] a decline that is not alleviated by ERT.[17,20,23] In this study, FFM remained stable over 2 years of ERT alone, but treatment with E&T significantly increased total FFM ($p < 0.01$) while decreasing the FM:FFM ratio ($p < 0.05$). This change has the potential to influence the lipid profile; a study of 426 women in the Virgilio Menopausal Health Project indicated that levels of both total cholesterol and LDL cholesterol are inversely related to FFM.[25]

mmol/L

FIG. 3. LDL ch who rec one (E& at 2 yea nificant

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TABLE 1. *Change in body composition in postmenopausal women who received hormonal replacement therapy with estradiol (n = 17) or with estradiol plus testosterone (n = 15) implants for a period of 2 years*

	Estradiol		Estradiol plus testosterone	
Parameter	Baseline value	After 2 y	Baseline value	After 2 y
Total body fat mass (kg)	35.7 ± 6.6	35.1 ± 6.6	37.4 ± 7.1	35.9 ± 8.0
Total body FFM (kg)	28.0 ± 6.5	28.2 ± 5.8	24.8 ± 5.9	27.9 ± 5.9[a]
FM:FFM ratio	1.34 ± 0.41	1.31 ± 0.42	1.62 ± 0.58	1.38 ± 0.52[b]
Fat mass over abdomen (kg)	1.51 ± 0.57	1.43 ± 0.59	1.60 ± 0.55	1.64 ± 0.65
FFM over abdomen (kg)	3.12 ± 0.55	3.30 ± 0.52	3.17 ± 0.45	3.31 ± 0.38
FM:FFM over the abdomen	0.48 ± 0.16	0.42 ± 0.14[b]	0.51 ± 0.18	0.51 ± 0.21

Data are the mean ± SD.
[a]Significant change over 2 y, $p < 0.01$.
[b]Significant change over 2 y, $p < 0.05$.

TABLE 2. *Change in anthropometric measures of girth in postmenopausal women who received hormonal replacement therapy with estradiol (n = 17) or with estradiol plus testosterone (n = 15) implants for a period of 2 years*

	Treatment: estrogen		Treatment: estrogen plus testosterone	
Parameter	Baseline value	After 2 y	Baseline value	After 2 y
WHO abdominal circumference (cm)	92.8 ± 10.9	88.4 ± 11.8[a]	93.1 ± 11.5	89.9 ± 9.3
Umbilical circumference (cm)	89.7 ± 11.1	86.7 ± 10.8[b]	89.6 ± 11.1	88.3 ± 9.4
Hip circumference (cm)	100.4 ± 8.3	95.5 ± 9.4[c]	101.2 ± 6.0	97.9 ± 6.2

Data are the mean ± SD.
[a]Significant change over 2 y, $p < 0.05$.
[b]Trend towards a change over 2 y, $p < 0.08$.
[c]Significant change over 2 y, $p < 0.01$.

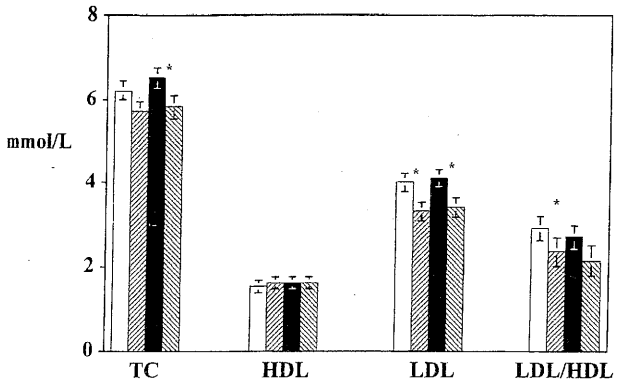

FIG. 3. Changes in the lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, and the ratio of LDL to HDL cholesterol) in 32 women who received estradiol implants (E) or estradiol implants plus testosterone (E&T). □, E at 0 years; ▨, E at 2 years; ■, E&T at 0 years; ▧, E&T at 2 years. Vertical bars indicate the standard error of the mean. *Significant different between 0 and 2 years, $p < 0.05$.

TABLE 3. *Relationships between change in LDL-cholesterol or in change in the ratio of LDL-cholesterol to HDL-cholesterol with change in body fat or hip circumference in postmenopausal women treated with estradiol (n = 17) or with estradiol plus testosterone (n = 15) implants for a period of 2 y*

	Change in LDL-cholesterol		Change in ratio of LDL: HDL-cholesterol	
	E	E & T	E	E & T *r* value
Change in total body fat	0.49[a]	0.34	0.49[a]	
Change in the total body FM:FFM ratio	0.52[a]	0.33	0.49[a]	
Change in FM:FFM over the abdomen	0.64[b]	0.41	0.52[a]	0.31
Change in hip circumference	0.67[b]	−0.04	0.56[a]	0.13

Data given are *r* values.
[a]Significant relationship, $p < 0.05$.
[b]Significant relationship, $p < 0.01$.

Although E and E&T treatment seem similar in their effects on body weight and total body fat, they differed in their effect on tissue composition in the abdomen. Although the women who were treated with E implants alone exhibited a mean decrease in the FM:FFM ratio in a region drawn over the abdomen ($p < 0.05$), the FM:FFM ratio in this region remained unchanged in women who received E&T. There were, however, only 15 women in the E&T group; this caused a lack of statistical power. Nevertheless, our sample size calculations indicate that when observed differences in body composition failed to reach significance in the E&T

group, this was due to a lack of biologically relevant difference because the sample size that was required to show significance was unrealistically high.

Anthropometric measures corroborate our DXA findings. E therapy alone was associated with significant decreases in both hip and abdominal circumferences ($p < 0.01$, $p < 0.05$, respectively). This was not seen for women who were treated with E&T. The anthropometric and DXA data from women who were given E implants are consistent with previous studies that showed by DXA[4,5,23,26] or anthropometry[6,18,21,22,26,27] that ERT either prevents the increase of central body fat after menopause or has a neutral effect, but the difference in the response of the women who were given E&T suggests that the addition of T may attenuate the favorable effect of reducing postmenopausal centralized fat accumulation with E alone. The clinical implication of this observation is that the positive relationships between changes in body fat distribution and LDL cholesterol and the LDL cholesterol:HDL cholesterol ratio seen with E alone were not seen with E&T. Differences in circulating lipoprotein-lipid concentrations have previously been reported to be associated with variations in the regional distribution of body fat.[28] Over the 2-year period of our study, beneficial lipid changes were observed in women who were treated with E. This outcome is consistent with other studies[10,11,29] and supports the hypothesis that the beneficial effects on lipid parameters observed with postmenopausal estrogen replacement are the result of direct effects of estrogen on lipid metabolism combined with favorable effects on central fat deposition. It is of interest that although the addition of testosterone to the estrogen therapy resulted in less pronounced change in central body fat, it was nevertheless associated with an improved lipid profile (Fig. 3). Whether the increase in FFM with testosterone acted as a metabolic counterbalance is not known.

Testosterone levels decline with age,[30] and bioavailable testosterone may decrease further in postmenopausal women who take oral estrogen.[31] A case therefore can be argued for concurrent androgen and estrogen replacement after menopause.[31] In particular, the addition of testosterone can significantly increase bone mineral density,[9,13] and it also markedly improves measures of sexuality.[9] In addition, as we showed here, the addition of testosterone to ERT reverses the decline of FFM seen after menopause,[2,3] but in considering the use of testosterone therapy, these advantages need to be balanced against possible long-term adverse effects on deposition of centralized body fat.

Endogenous androgen excess in postmenopausal women is clearly associated with increased cardiovascular risk, because of perturbations in lipid and carbohydrate metabolism, and a more android weight distribution.[26,28] In this study, undertaken with women of normal body weight, it was found that although testosterone therapy offset the reduction of centralized body fat evident after estrogen alone, it nevertheless still preserved the favorable effects of estrogen on the lipid profile. Therefore, undesirable effects are extremely unlikely and uncommon with testosterone replacement therapy, with the caveat that circulating androgen levels are maintained close to or within the normal female reproductive range and that patients are closely clinically monitored.[9] Additional studies are needed to establish whether testosterone therapy is inappropriate for more obese postmenopausal women, in whom an adverse effect on blood lipids might become apparent.

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