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Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality ☆

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Abstract

To investigate the role of androgens in increasing bone density and improving low libido in postmenopausal women, we have studied the long-term effects of estradiol and testosterone implants on bone mineral density and sexuality in a prospective, 2 year, single-blind randomised trial. Thirty-four postmenopausal volunteers were randomised to treatment with either estradiol implants 50 mg alone (E) or estradiol 50 mg plus testosterone 50 mg (E&T), administered 3-monthly for 2 years. Cyclical oral progestins were taken by those women with an intact uterus. Thirty-two women completed the study. BMD (DEXA) of total body, lumbar vertebrae (L1–L4) and hip area increased significantly in both treatment groups. BMD increased more rapidly in the testosterone treated group at all sites. A substantially greater increase in BMD occurred in the E&T group for total body ($P < 0.008$), vertebral L1–L4 ($P < 0.001$) and trochanteric ($P < 0.005$) measurements. All sexual parameters (Sabbatsberg sexual self-rating scale) improved significantly in both groups. Addition of testosterone resulted in a significantly greater improvement compared to E for sexual activity ($P < 0.03$), satisfaction ($P < 0.03$), pleasure ($P < 0.01$), orgasm ($P < 0.035$) and relevancy ($P < 0.05$). Total cholesterol and LDL-cholesterol fell in both groups as did total body fat. Total body fat-free mass (DEXA, anthropometry, impedance) increased in the E&T group only. We concluded that in postmenopausal women, treatment with combined estradiol and testosterone implants was more effective in increasing bone mineral density in the hip and lumbar spine than estradiol implants alone. Significantly greater improvement in sexuality was observed with combined therapy, verifying the therapeutic value of testosterone implants for diminished libido in postmenopausal women. The favourable estrogenic effects on lipids were preserved in women treated with T, in association with beneficial changes in body composition.

Keywords: Testosterone; Sexuality; Menopause; Bone density

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1. Introduction

Postmenopausal bone loss has been well documented as the cause of increased numbers of osteoporotic fractures in women compared with men in later life. Estrogen replacement therapy is an established preventive measure and is effective in reducing the likelihood of fracture [1]. Estrogen replacement therapy, however, delays bone loss; once therapy is ceased, bone loss resumes. Androgen therapy, specifically nandrolone decanoate, may increase vertebral bone mineral density in postmenopausal women [2]. Subcutaneous estradiol and testosterone implants have been shown to be "more" effective in preventing osteoporosis in postmenopausal women than oral estrogen, with this effect attributed to the higher concentrations of serum estradiol achieved using estradiol implants as opposed to oral therapy [3]. It may however be that the results of the latter study are due to the implantation of testosterone in addition to estradiol and that the testosterone implants exert an independent anabolic effect on bone in postmenopausal women. Garnett et al. [4] have addressed this issue in a 12-month study, in which moderately high dose estradiol implants were used, and the increase in bone density was related to the high serum estradiol levels achieved. The long-term health consequences of exposure of postmenopausal women to high circulating levels of estradiol are not known.

In clinical practice, testosterone implants are frequently administered to postmenopausal women experiencing reduced libido. However, there is considerable controversy as to the value of such therapy. Many climacteric women experience loss of sexual interest, but there are clearly multiple factors. Controlled studies of the effect of estrogen replacement therapy predominantly show improvement in vasomotor symptoms, vaginal dryness and general well-being, but little change in libido [5,6]. Low estrogen levels, associated with the menopause, may also play a major part in loss of sexual interest, as a result of vaginal dryness and dyspareunia [7]. This hypothesis has been supported by the observation that oral estrogens facilitate normal sexual activity, associated with reduced hot flushes and dyspareunia [8]. Studd [9,10] reported that conjugated equine estrogens alone improved sexual satisfaction in women with atrophic vaginitis causing their dyspareunia; women with low libido without coital discomfort benefited little or not at all. Of the latter group, 80% of patients were reported to experience improved libido when treated with combined estradiol and testosterone implants. Burger et al. [11], reported that postmenopausal low libido improved with combined estradiol and testosterone implants in a study over 6 months and demonstrated greater improvement in women treated with combined therapy as opposed to estradiol alone [12]. This contrasts with the work of Dow et al. [13] who found estradiol implants alone to be as effective as estradiol plus testosterone, though subjects were not selected for low libido persisting after estrogen replacement alone.

To further clarify these issues, we have compared the effects of combined estradiol and testosterone implants versus estradiol implants alone on vertebral and hip bone mineral density and sexuality in postmenopausal women. The long-term effects of these treatments on blood lipids and body composition were examined.

2. Methods and materials

The study was approved by the Human Research and Ethics Advisory Committee of Monash Medical Centre, Melbourne, and all subjects gave their written informed consent.

2.1. Subjects

Thirty-four postmenopausal women attending the menopause clinic volunteered for the study. Inclusion criteria required them to have had 12 months of amenorrhea and serum FSH greater than 15 IU/l. Some had had oral estrogen replacement therapy up to the time of commencement. None had hormonal implants previously, nor had any patients been treated with androgens prior to entry into the study. All had indications for implant therapy such as oral estrogen intolerance or inadequate response to oral estrogens. Women specifically seeking therapy for low libido were excluded as it was considered unethical for them to be randomised to the estradiol only group. Bone

mineral density was unknown at the time of entrance into the study.

2.2. Methods

The women were randomised independently by the hospital Pharmacy Department using the Geigy Tables [14], to single blind treatment with either estradiol implants 50 mg alone (E) or estradiol 50 mg plus testosterone 50 mg (E&T) (obtained by bisecting implants of 100 mg of testosterone) administered three-monthly for 2 years (implants donated by Organon Australia Ltd.). Estradiol and testosterone implants were not inserted if serum estradiol was known to be greater than 500 pmol/l or testosterone greater than 4 nmol/l, respectively, from a preceding blood test. Women with an intact uterus were treated with either cyclical medroxyprogesterone acetate (Provera, Upjohn Pty. Ltd. Australia) 5–10 mg, or norethisterone (Primolut N, Schering Pty. Ltd., Australia) 2.5 mg, orally for 12 days per month. All investigations were performed at entry into the study and then 6-monthly for 2 years. The surface density of bone mineral (BMD; g/cm^2) was measured in the supine position by dual energy X-ray absorptiometry (DEXA) [15], (Lunar DPX software version 3.4, Madison, Wisconsin). Total body, L1–L4, neck of femur, Ward's triangle and trochanteric BMD were measured. The precision and accuracy of this methodology has been well documented elsewhere [15,16]. Skin fold thicknesses were measured at the triceps, biceps, subscapular and supra-iliac sites, by a single skilled anthropometrist, using Harpenden calipers (Holtain Ltd., Wales, UK). The sum of the skinfold thicknesses was converted to body fat using the formulae of Durnin and Womersley [17].

Bioelectrical impedance was measured with a tetrapolar electrode arrangement between the right arm and right leg, using an RJL, BIA 101A impedance analyser (RJL Pty. Ltd., Detroit, USA), and converted to body fat using the formula of Lukaski, Bolonchuck et al. [18]. Total body fat was calculated from DEXA measurements of body fat [15], anthropometry [17] and impedance studies [18]. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Sexuality was measured 6-monthly using the Sabbatsberg self-rating scale [19]. Parameters include libido, activity, satisfaction, pleasure, fantasy, orgasm and relevancy. The latter is a score of the importance of sexuality in the woman's life. The maximum possible score for each parameter was 12 points. Serum estradiol was measured by double antibody radioimmunoassay (Diagnostic Product Corp. Estradiol Liquid phase kit, D.P.C., USA) and serum testosterone was measured by an extraction double antibody radioimmunoassay developed at Monash Medical Centre, Melbourne, Australia [20].

Total cholesterol (Total-C) was assayed using the American Monitor Perspective System (Indianapolis, Indiana, USA) by the cholesterol oxidase method using Trace Scientific Cholesterol Reagent (Trace Scientific, Clayton, Victoria, Australia). Triglycerides were measured using the American Monitor Triglyceride Reagent (GPO-PAP method). The HDL-cholesterol (HDL-C) fraction was separated with polyethylene glycol precipitant, the cholesterol was measured on the centrifugal automated spectrophotometer (Roche, Basel, Switzerland), and LDL-cholesterol (LDL-C) was calculated according to Friedwald [21].

2.3. Statistical analysis

The data comprised repeated measurements on each individual at baseline, and then 6-monthly for 2 years. The baseline data were tested for treatment differences by two sample t-test. For 6, 12, 18 and 24 month data, the sexuality variables and, separately, the bone and body composition variables were analysed by multivariate analysis of covariance (MANCOVA). If a MANCOVA gave a significant result, each of the variables for 6, 12, 18 and 24 month data was analysed by univariate repeated measurements analysis of covariance (ANCOVA); the covariate was the baseline data. Thus treatment means were adjusted for baseline differences. The analysis of covariance increases the power of the test of the treatment effect [13,22]. The least significant difference (LSD) was used to assess pairwise differences when effects were significant in the analysis of covariance. The standard errors of the difference have been shown as error bars in graphs of means, to indicate when means were significantly different.

Table 1
Clinical profiles at baseline after randomisation

	Estradiol ($n = 17$)	Estradiol & testosterone ($n = 16$)	P-value
Mean age (years)	51.3 ± 1.37 (S.E.M.)	57.0 ± 1.26	< 0.01
Hysterectomy	7	6	NS
Oophorectomy	2	0	NS
Smokers	6	2	NS
Alcohol use	3	3	NS

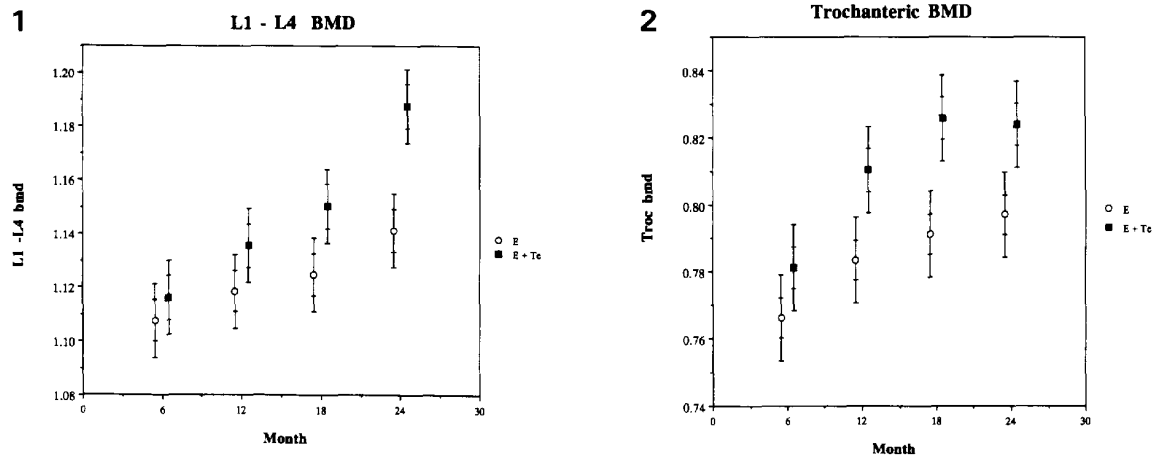
3. Results

The study was completed by 32 patients. One discontinued shortly after commencement for personal reasons and the other discontinued after 12 months due to weight gain. Data from the latter are included in the analysis up to 12 months. The clinical profiles of the two groups showed that they did not differ in smoking or alcohol habits, or hysterectomy or oophorectomy status. However, the mean age of the E group (51.3 ± 1.37 (S.E.M.) years, $n = 17$) was less than that of the E&T group (57.0 ± 1.26 years, $n = 16$, $P < 0.01$, Table 1). The sexuality, bone and body variables were analysed using age as a covariate and no significant effect of age was demonstrated. At baseline there were no significant differences between the two treatment groups for the sexuality, lipid and hormone variables. All the mean BMDs at baseline were significantly lower for the E&T group compared to the E group, which is consistent with the former having a higher mean age. The MANCOVA of bone and body variables gave a significant treatment effect ($\sim \chi^2 = 17.26$, 9 d.f., $P < 0.05$).

Raw values for the BMD measurements (Table

Table 2
Unadjusted means (S.D.) for BMD variables (g/cm^2) and P-values for differences from baseline

	Month				
	0	6	12	18	24
Total body BMD					
E	1.15 (0.07)	1.15 (0.07)	1.15 (0.07)	1.15 (0.07)	1.16 (0.07)
E&T	1.05 (0.12)	1.06 (0.12)	1.07 (0.12)	1.08 (0.121)	1.08 (0.12)
P-values vs. baseline					
E		0.85	0.97	0.13	0.00
E&T		0.01	0.00	0.00	0.00
L1–L4 BMD					
E	1.15 (0.12)	1.15 (0.12)	1.16 (0.12)	1.17 (0.12)	1.19 (0.12)
E&T	1.02 (0.13)	1.03 (0.18)	1.05 (0.18)	1.07 (0.18)	1.11 (0.18)
P-values vs. baseline					
E		0.72	0.08	0.01	0.00
E&T		0.08	0.00	0.00	0.00
Trochanteric BMD					
E	0.82 (0.10)	0.82 (0.09)	0.83 (0.09)	0.84 (0.09)	0.84 (0.10)
E&T	0.70 (0.13)	0.72 (0.13)	0.76 (0.13)	0.77 (0.14)	0.77 (0.14)
P-values vs. baseline					
E		0.80	0.05	0.00	0.00
E&T		0.00	0.00	0.00	0.00
Ward's triangle BMD					
E	0.81 (0.11)	0.81 (0.11)	0.82 (0.11)	0.83 (0.12)	0.84 (0.10)
E&T	0.66 (0.14)	0.67 (0.15)	0.72 (0.15)	0.72 (0.16)	0.72 (0.16)
P-values vs. baseline					
E		0.98	0.14	0.05	0.00
E&T		0.27	0.00	0.00	0.00



Figs. 1 and 2. The effects of hormonal implants on BMD (g/cm^2): lumbar spine (L1–L4), and femoral trochanter (TROCH), estradiol (E), estradiol plus testosterone (E&T). Error bars represent S.E.D. Inner error bars are used to compare means between times for the same treatment. The comparison between the treatment groups is made with the outer error bars. If error bars do not overlap, that is differ by more than 2 S.E.D.s, the means are significantly different by a P value of at least 0.05.

2) showed significant increases in BMD at all sites with both treatments. The BMD values for E&T all increased by a statistically significant amount earlier than did the BMD measurements for the E group. The ANCOVAs showed that BMD increased significantly over 24 months in both treatment groups at all sites measured, $P < 0.001$. Figs. 1 and 2 present the results for lumbar spine and femoral trochanter. A significant treatment effect for E&T versus E alone was observed as increases in BMD for total body ($P < 0.008$), vertebral L1–L4 ($P < 0.001$) and trochanteric bone mineral density ($P < 0.05$). The treatment effect approached significance for neck of femur BMD ($P = 0.16$) but was not significant for Ward's triangle BMD. BMD increased more rapidly in the E&T group at all sites with the interaction between treatment and month of measurement being significant for total body ($P < 0.001$) and L1–L4 BMD ($P < 0.001$).

For the MANCOVA of the sexuality variables there was a significant interaction between treatment and month ($\sim \chi^2 = 43.09$, 21 d.f., $P < 0.001$). All measures of sexuality increased in both groups. The E&T group experienced a greater improvement in sexuality compared to E alone. This is measured by the statistically significant treatment effect for activity ($P < 0.03$), satisfaction ($P < 0.03$), pleasure ($P < 0.01$), orgasm ($P < 0.035$) and relevancy ($P < 0.05$). The effect of treatment with E&T versus E approached significance for

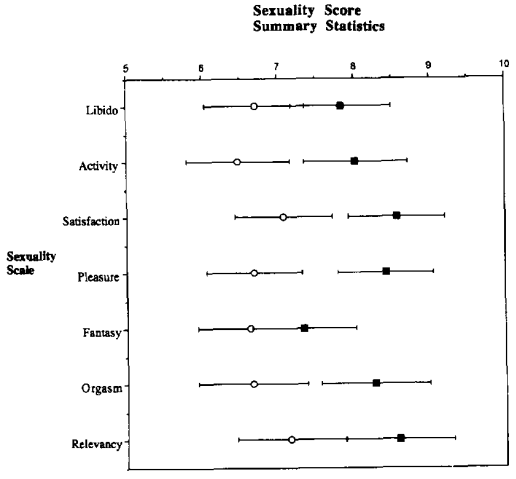
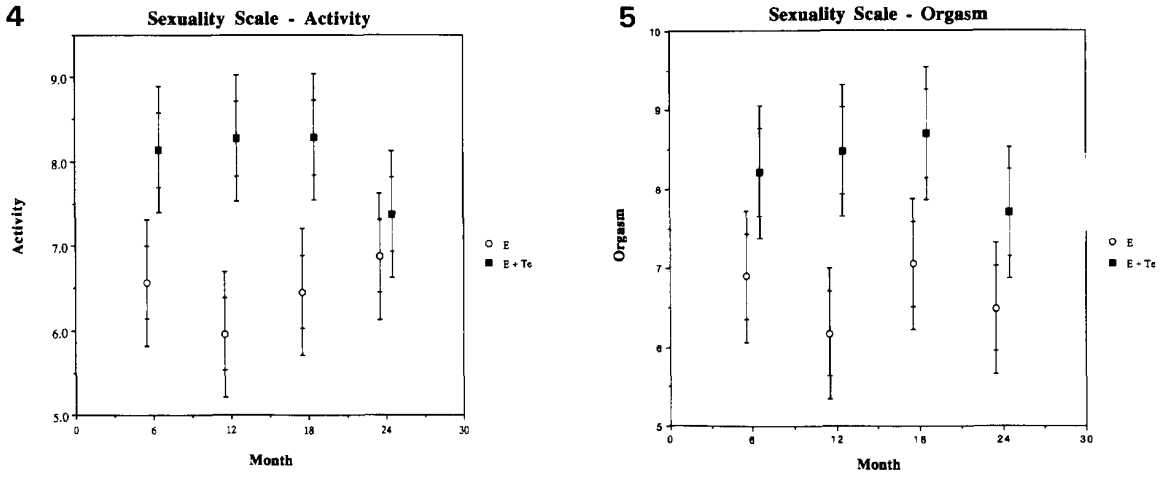


Fig. 3. Summary graph showing the grand mean (i.e. means of 6, 12, 18 and 24 months) for each sexuality parameter adjusted for baseline as a covariate. Error bars represent S.E.D.s for each mean. If the error bars do not overlap for a single parameter the difference is significant with a P value < 0.05.



Figs. 4 and 5. Scores for sexual activity and orgasm (as for Figures 1 and 2).

libido ($P < 0.097$) but was not significant for fantasy (Figs. 3–5). A declining trend in sexuality score was noted in several parameters at 24 months, although the decline was only statistically significant for satisfaction.

The problem of implant accumulation became apparent after the first 12 months of the study in four patients (two from each of the treatment groups), but was more common by 21 months. Two patients from each group had implants withheld at 18 months. E implants were withheld from four patients in the E group and both E and T were withheld from seven patients in the E&T group at 21 months. The total dose of E administered was less in the E&T group than in the E group. (A total of 13 estradiol implants withheld from seven patients in E&T, versus total of seven estradiol implants withheld from four patients in E group). Overall, 13 testosterone implants were withheld, seven of these being in patients at 21

Table 3
Mean values (S.D.) for lipids (mmol/l) at 0, 12 and 24 months for each treatment group

Treatment	Month *P*-values			P-values	
	0	12	24	0 vs. 12	0 vs. 24
Chol					
E	6.2 (0.92)	5.8 (0.76)	5.7 (1.00)	0.01	0.00
E&T	6.5 (0.92)	6.0 (1.05)	5.8 (1.12)	0.00	0.00
Trig					
E	1.8 (0.84)	1.7 (0.04)	1.7 (0.85)	0.60	0.85
E&T	1.9 (1.02)	1.7 (1.05)	1.7 (0.93)	0.29	0.22
HDL					
E	1.5 (0.41)	1.6 (0.40)	1.6 (0.37)	0.49	0.10
E&T	1.6 (0.53)	1.5 (0.44)	1.6 (0.49)	0.14	0.91
LDL					
E	4.0 (0.89)	3.5 (0.67)	3.3 (0.94)	0.00	0.00
E&T	4.1 (0.77)	3.7 (0.97)	3.4 (0.91)	0.01	0.00

Table 4
Unadjusted means (S.D.) for serum estradiol (pm/l) and testosterone (nm/l) and *P*-values for difference from baseline

	Month				
	0	6	12	18	24
Estradiol					
E	225 (202)	348 (147)	510 (216)	683 (328)	853 (319)
P-value	—	0.09	0.000	0.000	0.000
E&T	101 (737)	351 (227)	476 (206)	640 (304)	751 (376)
P-value	—	0.000	0.000	0.000	0.000
Testosterone					
E	1.1 (0.40)	1.7 (0.53)	1.0 (0.59)	1.1 (0.51)	1.0 (0.39)
P-value	—	0.8	0.8	0.9	0.7
E&T	1.2 (0.55)	2.7 (1.39)	2.3 (1.2)	2.6 (1.0)	2.2 (1.0)
P-value	—	0.000	0.000	0.000	0.000

months. Changes in lipids and hormonal values are shown in Tables 3 and 4. Total-C fell in the E and E&T groups by 8% ($P < 0.001$) and 11% ($P < 0.001$), respectively. LDL-C fell 17% in both groups ($P < 0.001$). No significant variation from baseline was observed for either HDL-C or triglycerides (Table 3). Serum estradiol rose over time in both groups, and as expected, serum testosterone was unchanged in the E group but increased with E&T treatment. The mean serum testosterone remained well within the normal female physiological range of 1.0–2.8 nm/l in the E&T group throughout the duration of the study (Table 4). No change in BMI occurred in either group (mean BMI, baseline vs. 24 months: E, 24.6 ± 1.8 vs. 24.2 ± 1.8; E&T, 24.4 ± 1.9 vs. 24.6 ± 1.9 S.E.M. kg/m^2). Total body fat-free mass, measured from bioelectrical impedance, was unchanged in the E patients but increased 3.4% in the E&T group ($P < 0.001$). Total body fat, measured by DEXA and anthropometry did not significantly vary from baseline in either treatment group, however, impedance values decreased over the study period by 6.9% in the E group ($P < 0.01$) and 5.7% in the E&T group ($P < 0.004$). No patients in the E&T group experienced any virilizing side effects of therapy and no other side effects were reported.

4. Discussion

This study confirms that estradiol implants, either alone or with testosterone, increase bone density in postmenopausal women at the clinically important anatomical sites that is, the spine and hip. E&T implant therapy was significantly more effective than E alone with greater gains observed for total body, vertebral (L1–L4), and trochanteric BMD. The increase in bone density at all sites was unrelated to chronological age, which was not a significant covariate.

This observed anabolic effect of parenteral testosterone on bone is consistent with the positive correlation between bone density and androgen levels in young, premenopausal and perimenopausal women [24,25], and the association between declining androgen levels and bone loss in ageing women [26]. That androgens are an important factor in bone cell metabolism is supported by the presence of androgen receptors on human osteoblastic cells [27], and the direct stimulatory effect of androgens on osteoblastic cell proliferation and differentiation [28].

The mean bone density profiles over time were significantly different between the two groups, with the increase in BMD being more rapid in the E&T group for all sites except Ward's triangle. This initially greater impact of E&T on bone density is statistically established by the observed interaction between treatment and month. Garnett et al. [4] found increased BMD correlated with serum estradiol levels over 12 months. We only observed these effects in the E group who did not

achieve significant increases in BMD until toward the end of the study, by which time the mean serum estradiol level was supraphysiological. In contrast, the E&T group had significant increases in all BMD measurements by 6 months, when serum estradiol levels were still within the normal physiological range relative to younger women. This suggests that testosterone independently increases bone mineral density. Therefore, the addition of only 50 mg testosterone may result in an "estrogen-sparing" effect with the potential that lower doses of estradiol can be administered and the positive benefits achieved. We believe that long-term exposure of postmenopausal women to high levels of estradiol is undesirable since the ultimate effects are unknown. Combined low dose E&T appears to be a good clinical alternative.

There is no ideal therapy available to increase bone mass in postmenopausal women with marginally or significantly reduced BMD. Our data indicate that combined estradiol and testosterone implant treatment may be a simple and effective therapeutic option for these situations. However, it is yet to be determined whether any increase in bone density achieved is accompanied by a decrease in the risk of subsequent fracture.

This is the first long-term study of the efficacy of hormonal implants on sexuality in postmenopausal women. Our results indicate that both estradiol alone and combined estradiol and testosterone implants enhance sexuality in postmenopausal women. Furthermore, this effect persisted for the duration of the study. The addition of testosterone resulted in a more rapid improvement in sexuality in all parameters measured and a significantly greater response to treatment in most aspects. This is consistent with an earlier study [12] in which the added testosterone was more effective than estradiol alone in patients selected because of persistent psychosexual problems despite oral estrogen replacement. Our patients were not specifically seeking treatment for low libido yet they all experienced a significant improvement in sexuality. Our data not only confirms the beneficial effects of added testosterone shown in earlier studies [8–10] but establishes this to be a genuine and persistent treatment effect. The apparent late downward trend in response in the E&T group was only significant in the satisfaction score. Several patients had testosterone withheld towards the end of the study and thus may have experienced a diminished response as a result. In normal clinical practice, if the testosterone level remained elevated, one would defer inserting the implant perhaps for a few weeks but not an additional 3 months as was dictated in this instance by the protocol. Thus the lower satisfaction score in the E&T group at 24 months may reflect the withholding of the testosterone implants at 21 months in these individuals.

In both groups, the serum estradiol levels increased steadily throughout the study, consistent with the frequency of implantation used. The 3 month interval was chosen as patients generally require this short interval for their first two or three implants, but subsequently most only require their implants 4 to 6-monthly. This is complicated by the considerable individual variation in the absorption rate of hormonal implants. We attempted to approximate clinical practices as closely as possible by using the 3 month interval with the caveat that implants were withheld should the serum levels of estradiol or testosterone remain elevated (see methods). Importantly, the benefits of testosterone implants were achieved using only 50 mg per dose. This is lower than the amount used in earlier studies [10,11], some of which reported minor virilizing effects. None of our patients experienced any such effects. Furthermore, the total dose of hormonal implants administered was less in the E&T group than in the E group. Overall, the E&T groups received fewer estradiol implants, yet this group ultimately achieved the greater improvement in BMD despite this.

Three-monthly administration of testosterone implants resulted in supraphysiological testosterone levels in several women requiring postponement of implants. Regular monitoring of serum testosterone levels is recommended in women receiving testosterone implants and it should be noted that the long-term effects are as yet unknown. Administration of testosterone implants had no effect on the reduction in total cholesterol and LDL-C induced by estradiol replacement. Burger et al. [12] observed no changes in the concentrations of cholesterol, its subfractions or tri-

glycerides over 6 months in postmenopausal women treated with either estradiol implants alone or with testosterone implants. Farish et al. [29] compared estradiol 50 mg plus testosterone 100 mg implant treatment to estradiol 50 mg implants alone, also over 6 months and reported small reductions in Total-C and LDL-C in both treatment groups. We have observed more significant falls in Total-C and LDL-C, probably attributable to the longer duration of the study and high serum estradiol levels achieved.

In contrast to myths about HRT and weight gain, no alteration in mean BMI occurred over the study period. The reduction in body fat determined by impedance studies may have also contributed to the declines in Total-C and LDL-C over time. The increase in fat-free mass in the E&T group is an interesting observation, as it is well established that people lose fat-free mass with ageing. Any gain in fat-free mass probably reflects increased muscle mass, which would be advantageous in terms of enhancing skeletal stability and thus lessening the likelihood of falls in older women.

In conclusion, this study reaffirms that added testosterone enhances sexuality in postmenopausal women and can be of significant benefit for women experiencing low libido despite adequate estrogen replacement. A potential therapeutic role may exist for parenteral testosterone in the treatment of osteoporosis and fracture prevention, and warrants further investigation.

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