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Evidence for Tissue Selectivity of the Synthetic Androgen 7α-Methyl-19-Nortestosterone in Hypogonadal Men

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The potent synthetic androgen 7α-methyl-19-nortestosterone (MENT) is resistant to 5α-reductase but is a substrate for aromatase. It may therefore offer selective sparing of the prostate gland while supporting other androgen-dependent tissues. MENT acetate implants were administered for 24 wk to 16 hypogonadal men, randomly allocated to 1 or 2 implants (groups I and II, respectively; releasing ~400 μg/d·implant). Hemoglobin concentration and hematocrit were maintained during MENT treatment. Prostate volume fell in group I and to a small, but statistically nonsignificant, degree in group II; the level of prostate-specific antigen fell significantly in both. Lumbar spine bone mineral density decreased in both groups. Sexual behavior and erectile function declined in group I, but were maintained in group II. Thus, overall, one MENT implant appeared to provide subphysiological androgen replacement. The 2-implant dose of MENT was able to maintain most androgen-dependent functions, except bone mass, and there was evidence to support selective sparing of the prostate gland. These results demonstrate for the first time in humans the selectivity of MENT in tissues dependent on 5α-reductase. In addition, our data are consistent with the importance of adequate estrogenicity as part of the necessary spectrum of activity of an androgen for replacement therapy in men. (*J Clin Endocrinol Metab* 88: 2784–2793, 2003)

TESTOSTERONE IS REQUIRED to support a wide range of physiological processes in men. These include muscle, bone, and liver metabolism, erythropoiesis, behavioral and sexual function, support of accessory sex organs, particularly the prostate gland, and regulation of gonadotropin secretion. Some of these, notably support of liver, muscle, and bone marrow function, are mediated by testosterone itself (1). Testosterone can also act as a prohormone; conversion by the enzyme 5α-reductase to dihydrotestosterone (DHT) is of particular importance in the prostate (2, 3), whereas conversion by aromatase to estradiol is recognized to be important in maintaining bone mass (4, 5) and regulating serum lipids (6) and gonadotropin secretion (7, 8). Other functions, such as sexual interest, may also be at least partially dependent on aromatization, although the evidence is less clear in humans than in animal species (9–12).

Currently available androgen preparations are limited. Most men on androgen replacement receive injectable testosterone 17α-hydroxyl esters at frequent intervals. Alternative, but less commonly used, preparations include sc pellets, nonscrotal and scrotal transdermal patches, and transdermal gel, all of which are testosterone based. The effects of these preparations therefore largely reflect those of testosterone itself, although scrotal preparations result in relatively higher DHT concentrations. A synthetic androgen might have the advantages of tissue or metabolic selectivity, reflecting its relative androgenicity and metabolism by aromatase and 5α-reductase. 7α-Methyl-19-nortestosterone (MENT) is a potent synthetic androgen that is resistant to 5α-reduction, but can be converted by the enzyme aromatase to an active estrogen (13, 14). Theoretically this will result in relative sparing of the prostate from androgenic stimulation, because this gland is sensitive to potent 5α-reduced androgens while maintaining other physiological androgen-dependent functions, such as sexual behavior, muscle and bone anabolism, erythropoiesis, and hypothalamic-pituitary feedback. MENT may therefore have advantages over testosterone in both hypogonadal men and as a component of hormonal male contraception (15, 16). Data to support the relative sparing of the prostate by MENT have been obtained in nonhuman primates (17), and we have demonstrated the ability of MENT to support androgen-dependent mood and sexual behavior in hypogonadal men (18). Gonadotropin secretion in normal men is also potently suppressed by MENT (19), but there are no human data on the effects of MENT on the prostate or on nonreproductive tissues such as bone.

MENT is not bound by SHBG; thus, it is rapidly cleared from the circulation (20). Administration by sc implant or by transdermal patch or gel is therefore required. MENT acetate (MENTAc) has been formulated in ethylene vinyl acetate implants, thus giving the potential for long-term therapy. MENTAc is rapidly hydrolyzed on release from the implant into MENT, which is the biologically active moiety in the circulation. These implants result in relatively stable serum concentrations of MENT releasing the dose required for an-

Abbreviations: BMD, Bone mineral density; CV, coefficient of variation; DEXA, dual energy x-ray absorptiometry; DHT, dihydrotestosterone; MENT, 7α-methyl-19-nortestosterone; MENTAc, 7α-methyl-19-nortestosterone acetate; NPT, nocturnal penile tumescence; PSA, prostate-specifice antigen; SES, Sexuality Experience Scales.

drogen replacement (15), but have only been used in short-term (4–6 wk) studies (18, 19). We here report the results of longer-term administration in hypogonadal men to investigate the safety of MENT and its effects on androgen-dependent target tissues and functions, including prostate, bone mass, body composition, and sexual function.

Subjects and Methods

Study design

This was an open, randomized, parallel group, single center study investigating MENTAc implants in two doses as hormonal replacement therapy in hypogonadal men. To allow comparison with conventional testosterone treatment, subjects were maintained on testosterone for 24 wk before MENT administration. After study entry, subjects continued with their regular testosterone treatment for 15 wk. This was then standardized for the last 9 wk, with all subjects receiving 250 mg testosterone enanthate i.m. (Testoviron, Schering AG, Berlin, Germany) at wk 15, 18, and 21. Subjects were then randomized in blocks of six by random number allocation to receive one or two MENTAc implants (groups I and II, respectively) for a further 24 wk. Implants were then removed, and subjects returned to their regular testosterone treatment.

Subjects

Sixteen hypogonadal men were recruited (mean age, 32 yr; range, 19–45 yr). Diagnoses were isolated hypogonadotropic hypogonadism (n = 4), adrenal hypoplasia congenita (2), primary gonadal failure or anorchia (4), Klinefelter's syndrome (2), and hypothalamic/pituitary tumor (4). All were receiving androgen replacement therapy at the time of recruitment in the form of testosterone pellets (n = 8), injectable testosterone esters (7), or transdermal testosterone (1). Three men were hypoadrenal and additionally took hydrocortisone (all three) and fludrocortisone (two only), and one had been diagnosed with hypothyroidism and took T_4: the doses of these replacement therapies were constant during the study. No man was receiving GH treatment. The mean off-treatment testosterone concentration was 2.7 nmol/liter, with all men having subnormal concentrations (<8.5 nmol/liter). All men gave written informed consent to take part in this study, which was approved by Lothian Pediatric and Reproductive medicine ethics committee and the institutional review board of The Population Council.

MENTAc implants

MENT implants each contained 135 mg MENTAc and were prepared in the Center for Biomedical Research. Implants were inserted sc under local anesthetic into the medial aspect of the nondominant upper arm and were later removed also under local anesthesia. The amount of drug remaining within each implant after removal was subsequently determined to allow calculation of the average rate of release over the course of the study.

Interventions and outcome measures

Blood samples were taken at all visits. Clinical chemistry and hematology variables were measured at study entry, immediately before MENT implant insertion, and after 8 and 24 wk of MENT treatment. Other investigations were carried out at the same time points. These included a behavioral survey, nocturnal penile tumescence (NPT) measurement, transrectal ultrasound measurement of the prostate gland and dual energy x-ray absorptiometry (DEXA) to measure bone mineral density (BMD) at the lumbar spine (L1–L4) and hip (left femoral neck), and body composition (lean and fat mass, and total body calcium). The behavioral survey consisted of a structured questionnaire/interview and Frenken Sexuality Experience Scales (SES)2 scoring as previously described (18, 21). Sexual activity was scored as the sum of sexual intercourse and masturbation over the preceding 14 d, as not all subjects had sexual partners. NPT was measured using a Rigiscan device on 2 successive nights at the end of the testosterone and MENT treatment phases, with data derived as previously described (18, 22). Prostate ultrasound was performed using a biplanar rectal probe at 8 MHz (Eccoccee, Toshiba, Stirling, UK) with volume calculated according to the volume ($d1 \times d2 \times d3 \times \pi/6$), and DEXA was performed using a QDR-4500A instrument (Hologic, Inc., Bedford, MA). Rectal ultrasound and DEXA were not performed at 8 wk of MENT treatment.

Assays

Serum MENT and leptin concentrations were measured by RIA as previously described (23–25). For MENT, the intraassay coefficient of variations (CV) was 3.8–7.9%, and the interassay CV was 8.0–12.3% for the controls. Because of the cross-reactivity of testosterone (1.1%) and other serum factors in the MENT assay, a value of 0.38 ± 0.04 nmol/liter was obtained pretreatment. For leptin, intra- and interassay CV were less than 8%. Serum testosterone levels were measured by RIA using the Coat-A-Count total testosterone kit (Diagnostic Products, Los Angles, CA). The assay sensitivity was 0.14 nmol/liter. The intraassay CV was 3.4–8.5, and the interassay CV was 1.3–13.9 for the controls used in these assays. Fasting blood was withdrawn for lipid profile via modification of the standard lipid research clinics protocol; the intra- and interassay CV for all lipid measurements were less than 3%. Bone alkaline phosphatase was measured in plasma by ELISA (Alkphase-B, Metra Biosystems, Mountain View, CA); the intra- and interassay CV were less than 8%. Deoxypyridinoline cross-links were measured in urine by ELISA (Pyrilink-D, Metra Biosystems). Intra- and interassay CV were less than 11%. Prostate-specific antigen (PSA) was measured on an Advia Centaur immunoassay analyzer (Bayer Corp., Newbury, UK). Intra- and interassay CV were less than 5%. For MENT and testosterone, data were derived from five assays; for other analytes, two assays were run.

Analysis of data

Results are reported as the mean ± SEM. Hormonal and metabolic data were log-transformed to correct nonequality of variance. The primary analysis used was repeated measures ANOVA on data at the end of the testosterone phase, *i.e.* immediately before MENT administration, and after 8 and 24 wk of MENT treatment. If this analysis suggested a significant treatment effect ($P < 0.05$), Tukey's test was used to investigate the time points at which significant changes were detected. For data obtained only before and after 24 wk of MENT administration, paired *t* tests were used. Behavioral data were analyzed by nonparametric testing, using Wilcoxon's test.

Results

Subjects, discontinuations, and adverse events

There were no serious adverse events during the course of the study. One subject discontinued the study during treatment. He was randomized to receive one MENTAc implant, and over the subsequent weeks he complained of lethargy and tiredness, which he attributed to androgen deficiency. He withdrew from the study after 8 wk of MENT treatment. All other subjects completed the study, and there were no complications arising from either insertion or removal of the MENTAc implants. There were no consistent changes in any of the biochemical or hematological variables indicating any evidence of toxicity. There were no significant changes in blood pressure during the study.

MENT and testosterone concentrations

Serum MENT concentrations were determined at 4-wk intervals (Fig. 1). Both groups showed a rise in MENT concentrations, with a peak at 4 wk. MENT concentrations were similar in the two groups at 8 wk, but then declined, and were close to the limit of sensitivity of the assay in group 1 from 12 wk onward. In group II, serum MENT concentrations at the time of removal after 24 wk were approximately 50% of those at 4 wk.

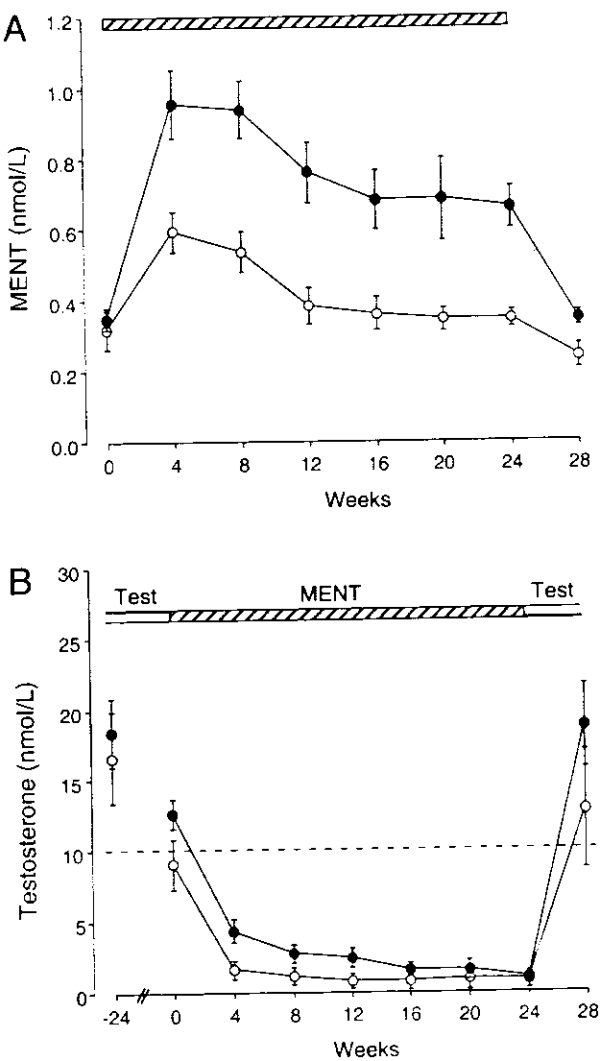

FIG. 1. Serum MENT (A) and testosterone (B) concentrations during the study. The duration of administration of the MENTAc implants is indicated by the *bar*. B, Testosterone administration both before and after MENT administration. *Open symbols*, Group I; *filled symbols*, group II. Values are the mean ± SEM.

Analysis of the amount of MENT remaining in the implants after removal demonstrated that the implants released an average of 48% of the MENTAc they originally contained. The mean MENTAc release rate per implant was 397 ± 7 μg/d in group I and 382 ± 6 μg/d in group II.

Testosterone concentrations were 9.0 ± 1.8 and 12.6 ± 1.0 nmol/liter in groups I and II, respectively, at the time of insertion of the MENTAc implants. These were trough concentrations, 21 d after last administration of TE. Testosterone concentrations fell during MENT administration (Fig. 1) to 0.8 ± 0.5 nmol/liter at 12 wk of MENT treatment in group I with no further change, and progressively to 1.1 ± 0.3 nmol/liter in group II at 24 wk of MENT treatment.

Erythropoiesis

There were significant increases in both hemoglobin concentration and hematocrit during the study (Table 1). These were, however, largely confined to the testosterone phase of the study in group II ($P < 0.05$ in both cases), with no significant change during MENT treatment in either group. There were no significant changes in white blood cell or platelet count during the study.

Lipoproteins

There were no significant changes in total cholesterol; high, low, and very low density lipoprotein cholesterol; triglycerides; or apolipoprotein A during MENT treatment in either group (Table 1). There was, however, a progressive and significant rise in apolipoprotein B in group I during MENT treatment ($P = 0.05$) and a smaller nonsignificant rise in group II (Table 1).

Behavioral data

The frequency of sexual activity showed no significant change over the course of the study (Fig. 2). There was, however, a trend toward a reduction in frequency of sexual activity in group I that was not seen in group II. There were similar findings for self-reported frequency of waking penile erection (Fig. 2). SES2 scores also showed a similar pattern, with a lower score (*i.e.* less negative) after 24 wk of MENT in group I ($P = 0.02$ *vs.* 8 wk MENT; Fig. 2). There were no significant changes in group II.

NPT measurement showed significant declines in group I in both the total number of erectile events ($P = 0.03$) and in those achieving rigidity of greater than 60% and lasting longer than 10 min during MENT administration ($P = 0.04$; Fig. 3), but there was no change in group II. There was no change in average event rigidity in either treatment group.

Prostate volume and serum PSA

There were significant changes in prostate volume during the study in group I but not group II (Fig. 3). There was a small increase in prostate volume during testosterone treatment, which did not reach statistical significance in either group. In group I prostate volume decreased during MENT treatment from 16.4 ± 1.9 to 12.0 ± 2.4 ml ($P = 0.016$) whereas there was no change in group II (13.3 ± 1.7 to 11.7 ± 1.5 ml; P = NS).

Serum PSA also showed significant changes during treatment, in both study groups (Fig. 3). In group I there was no change during testosterone treatment, but there was a significant decline during MENT treatment ($P = 0.016$). This decline in PSA was significant by 8 wk of treatment ($P < 0.0001$) with a further slight decline by the end of MENT treatment. Group II also showed no significant change during testosterone treatment, but an overall fall in serum PSA during MENT treatment ($P = 0.011$). However, in this group serum PSA showed a small, but significant, rise at 8 wk of MENT treatment ($P = 0.004$ *vs.* start of MENT treatment), followed by a significant fall by the end of MENT treatment ($P = 0.0004$ *vs.* start of MENT treatment).

BMD

In general, BMD was low compared with that of the general population, although none of the subjects showed osteoporosis at either site examined. Lumbar spine BMD

TABLE 1. Hematological variables and lipoproteins during testosterone and MENT administration

	Group	Study start	24 wk T	8 wk MENT	24 wk MENT
Hemoglobin (g/liter)	I	148 ± 12	151 ± 10	151 ± 8	152 ± 8
	II[a]	149 ± 8	155 ± 8	160 ± 7	159 ± 7
Hematocrit	I	0.43 ± 0.04	0.44 ± 0.02	0.44 ± 0.02	0.45 ± 0.02
	II[a]	0.44 ± 0.03	0.46 ± 0.03	0.48 ± 0.03	0.47 ± 0.03
Cholesterol (mmol/liter)	I	5.0 ± 0.8	4.7 ± 1.1	5.0 ± 1.1	5.2 ± 1.0
	II	4.3 ± 1.7	4.5 ± 1.6	4.4 ± 1.5	4.7 ± 1.9
HDL-C (mmol/liter)	I	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3
	II	1.2 ± 0.4	1.2 ± 0.4	1.1 ± 0.2	1.1 ± 0.3
LDL-C (mmol/liter)	I	3.1 ± 0.9	2.9 ± 0.9	3.2 ± 1.1	3.4 ± 1.1
	II	2.5 ± 1.6	2.4 ± 1.3	2.6 ± 1.5	2.8 ± 1.7
VLDL (mmol/liter)	I	0.7 ± 0.5	0.7 ± 0.5	0.6 ± 0.3	0.8 ± 0.5
	II	0.6 ± 0.4	0.9 ± 0.6	0.7 ± 0.3	0.8 ± 0.5
Triglycerides (mmol/liter)	I	1.5 ± 1.0	1.5 ± 1.1	1.4 ± 0.6	1.7 ± 1.0
	II	1.3 ± 0.9	2.0 ± 1.2	1.5 ± 0.7	1.6 ± 1.0
Apolipoprotein A1 (mg/dl)	I	124 ± 20	119 ± 15	119 ± 15	116 ± 21
	II	119 ± 16	121 ± 20	114 ± 15	115 ± 13
Apolipoprotein B (mg/dl)	I[b]	99 ± 21	95 ± 27	101 ± 29	108 ± 28
	II	77 ± 31	84 ± 32	86 ± 31	90 ± 32

Data are mean ± SD. 24 wk T, Time point at which MENTAc implants were inserted, after 24 wk of testosterone treatment since the start of the study; VLDL, very low density lipoprotein.

[a] There were significant increases in both hemoglobin concentration and hematocrit in group II during testosterone treatment; changes during MENT treatment did not reach statistical significance.

[b] There was a significant rise in apolipoprotein B in the one implant group during MENT treatment ($P < 0.05$).

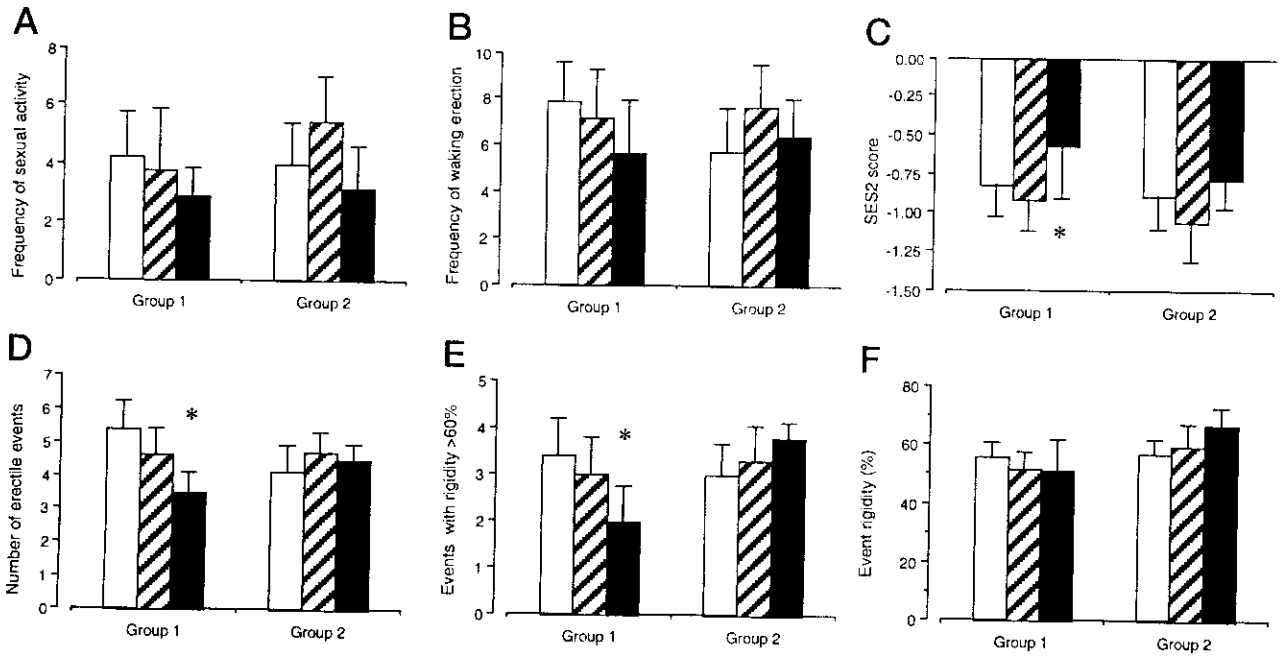

FIG. 2. Behavioral outcomes. The number of events for sexual activity (A) and waking erection (B) in the preceding 2 wk are shown. C, SES2 scores. D–F, Nocturnal penile tumescence data: number of erectile events, number of erectile events where rigidity exceeded 60% for x minutes, and average event rigidity. □, At start of study (*i.e.* during testosterone administration); ▨, after 24 wk of testosterone; ■, after 24 wk of MENT. Values are the mean ± SEM. *, Significant change during MENT administration ($P < 0.05$).

showed a significant decrease during the study in both group I ($P = 0.04$) and group II ($P = 0.03$), whereas BMD at the hip showed no change in either group (Fig. 4). In group I there was no significant change in lumbar spine BMD during testosterone treatment (median change, +1.7%), but there was a significant decrease from 1.09 ± 0.05 to 1.04 ± 0.06 g/m^2 ($P = 0.05$) during MENT treatment (median change, −3.0%). In group II lumbar spine BMD fell from 1.00 ± 0.04 to 0.98 ± 0.04 g/m^2 during MENT treatment ($P = 0.05$; median change, −2.8%).

Biochemical markers of bone turnover

Serum bone-specific alkaline phosphatase was unchanged during testosterone treatment in group I, but showed significant changes during MENT treatment ($P = 0.017$; Fig. 4). There was a significant decline at wk 8 of MENT treatment ($P = 0.004$), but this had returned to pre-MENT treatment concentrations by 24 wk of MENT ($P = 0.04$ *vs.* 8 wk; P = NS *vs.* pre-MENT). Group I also showed a significant rise in urinary deoxypyridinoline cross-link excretion in urine dur-

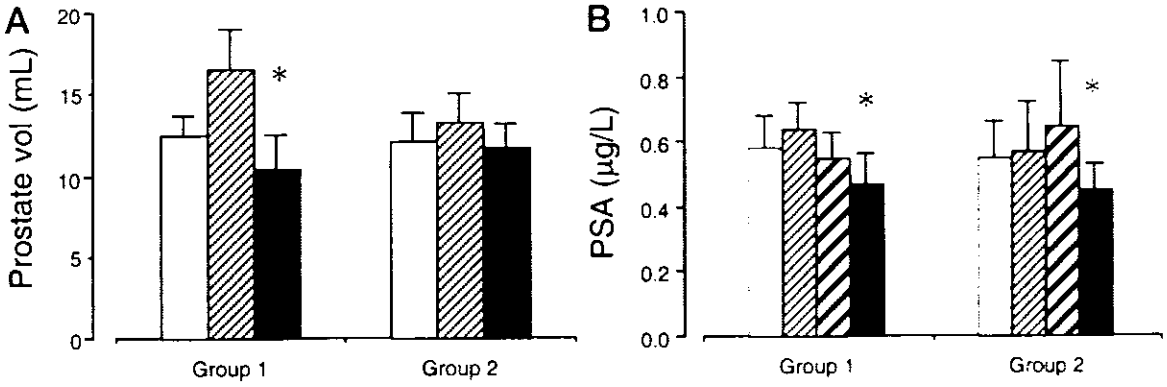

FIG. 3. Prostate volume (A) and serum PSA (B) during testosterone and MENT administration. *Open columns*, At start of study; *lightly shaded columns*, after 24 wk of testosterone; *heavily shaded columns*, after 8 wk of MENT; *filled columns*, after 24 wk of MENT. Values are the mean + SEM. *, Significant change during MENT administration (by ANOVA, $P < 0.05$).

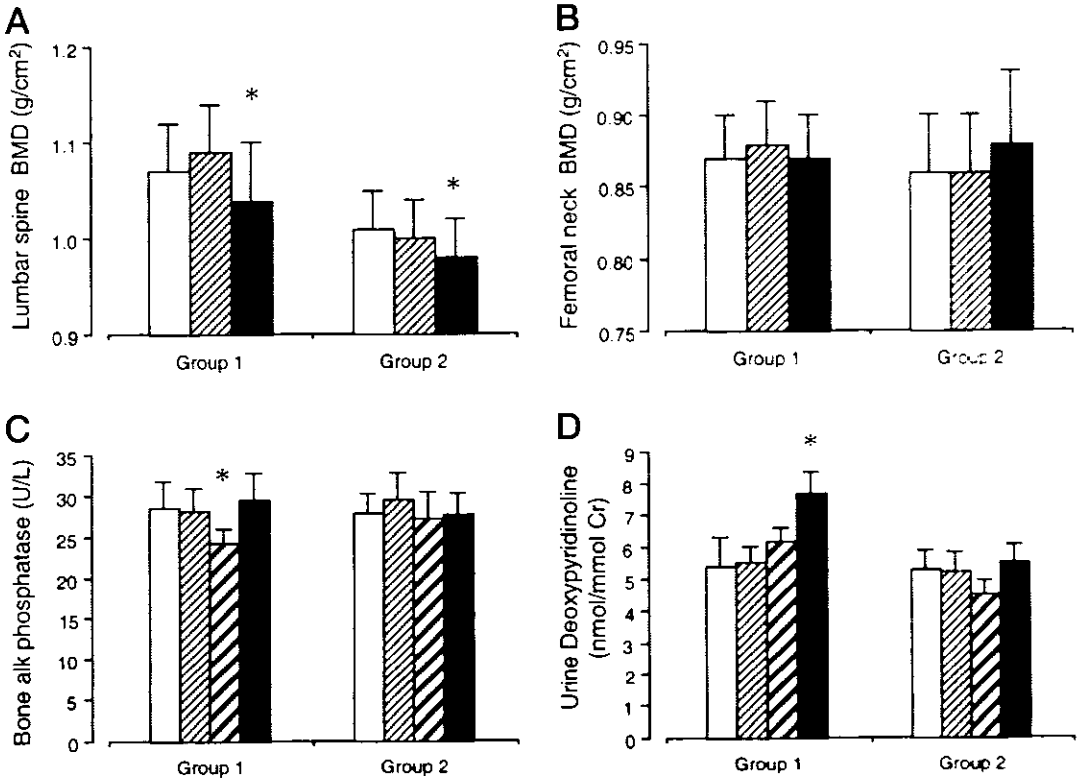

FIG. 4. Bone mass and urinary markers of bone turnover. A, BMD at lumbar spine; B, BMD at femoral neck; C, serum bone-specific alkaline phosphatase; D, urinary deoxypyridinoline. *Open columns*, At start of study; *lightly shaded columns*, after 24 wk of testosterone; *heavily shaded columns*, after 8 wk of MENT; *filled columns*, after 24 wk of MENT. Values are the mean + SEM. *, Significant change during MENT administration (by ANOVA, $P < 0.05$).

ing MENT treatment ($P = 0.01$; Fig. 4). Although this rise was apparent at 8 wk of treatment, it was not statistically significant at that time point. There were no significant changes in either serum bone-specific alkaline phosphatase or urinary deoxypyridinoline cross-link excretion in group II during either testosterone or MENT treatment.

Body weight and composition

There was a small increase in body weight in group I ($P = 0.04$), but not group II, during the study (Fig. 5). The increase in body weight in group I was confined to the MENT treatment phase ($P = 0.03$). Lean mass also showed a significant change in group I ($P = 0.003$), also confined to the MENT phase ($P = 0.006$; Fig. 5). Although lean mass also increased in group II ($P = 0.01$), this was largely during testosterone treatment ($P = 0.02$) with no significant change during MENT treatment. There was no change in fat mass in group I, but there was a decrease in fat mass during MENT treatment in group II (Fig. 5).

Serum leptin concentrations were unchanged during both testosterone and MENT treatment in group I and were unchanged during testosterone treatment in group II (Fig. 5).

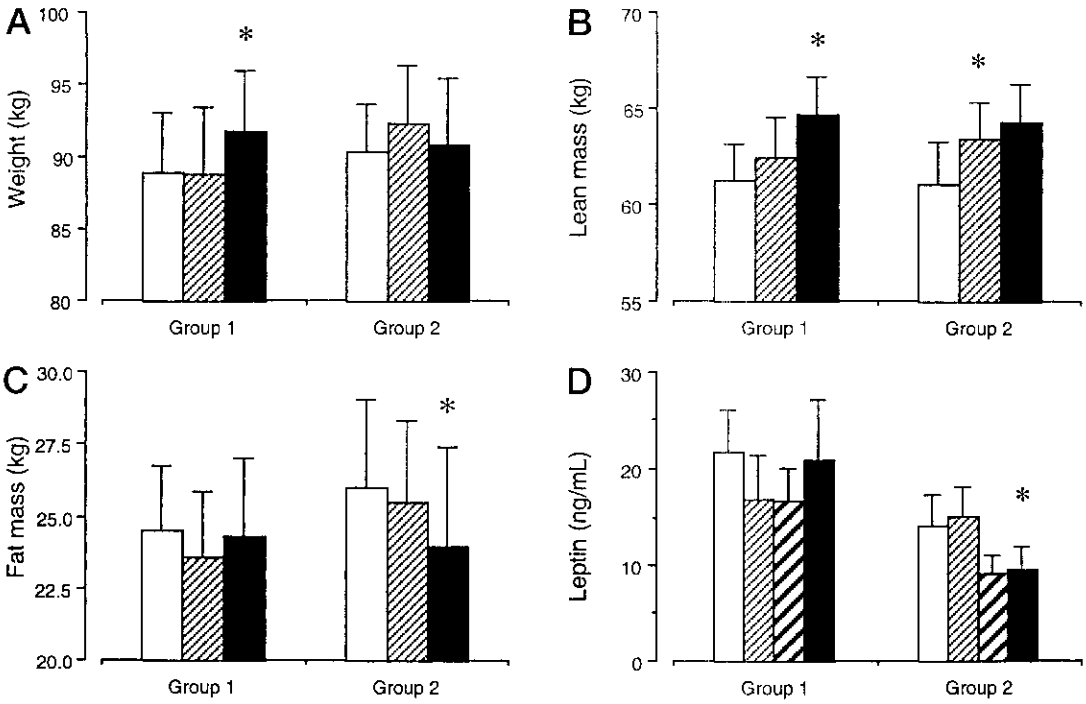

FIG. 5. Body composition. Total body weight (A), lean mass (B), fat mass (C), and serum leptin concentration (D). *Open columns*, At start of study; *lightly shaded columns*, after 24 wk of testosterone; *heavily shaded columns*, after 8 wk of MENT; *filled columns*, after 24 wk of MENT. Values are the mean ± SEM. *, Significant change during MENT administration (by ANOVA, $P < 0.05$).

However, there was a significant fall in leptin concentrations in group II during MENT treatment ($P = 0.0004$), which was apparent by 8 wk of MENT treatment ($P = 0.0006$) and sustained at 24 wk MENT treatment.

Discussion

This study provides the first human data on the effects of MENT, a potent synthetic androgen with potential tissue selectivity, on a range of androgen-dependent tissues and functions. The MENT implants investigated here offer the potential for both a long duration of action and theoretically a reduced action on the prostate by virtue of the resistance of MENT to 5α-reduction (13, 26, 27). MENT may also support estrogen-dependent tissues, although the data regarding aromatization are very limited (14). This study reports the investigation of this potential selectivity in hypogonadal men. Effects on the prostate gland and BMD were investigated, using both biophysical and biochemical tests, as androgen-dependent target organs in which 5α-reduction and aromatization, respectively, are of major importance (2, 4, 28, 29). Tissues in which testosterone metabolism is of lesser importance, such as bone marrow, provide an index of the overall adequacy of the androgen dose. It must be recognized, however, that it is unclear how to determine with certainty androgen replacement in the absence of an ability to measure serum testosterone, and indeed this study significantly informs that debate which is central to future studies on androgen derivatives (30).

The MENTAc implants used in the present study contained slightly more steroid than those used in previous studies. In those studies, two implants were demonstrated to support sexual behavior and erectile function in hypogonadal men (18) and to result in dose-dependent suppression of gonadotropin secretion in normal men (19). MENT is approximately 10-fold more potent than testosterone at the androgen receptor (31–33), and the present implants were designed to release approximately 400 μg/d. One and two implants were thus calculated to provide replacement equivalent to the lower and higher regions of the physiological range of testosterone production in normal men (34–36). Analysis of residual steroid in the implants after removal confirmed this average rate of release, although measurement of MENT in serum suggested that there was considerable variation in release over the course of the study, with peaks at 1–2 months, followed by a decline to low concentrations in group I. These changing concentrations complicate interpretation of the data, as it must be borne in mind that it is possible that the effects within one treatment group may vary significantly between those at peak concentrations, *i.e.* at 8 wk compared with those at the end of the study after 24 wk of treatment. Detailed analysis of concentrations, particularly in the second half of the study, is limited however by the sensitivity of the immunoassay.

Hemoglobin concentration and hematocrit were unchanged during MENT treatment. These have been demonstrated to be sensitive markers of androgen treatment in hypogonadal men, showing rapid and marked increases on initiation of testosterone treatment (37). Androgen withdrawal from treated hypogonadal men has been little studied, but induced hypogonadism in normal men with replacement testosterone showed that a dose of 125 mg TE per wk was required to maintain normal hemoglobin concentrations (38). These data therefore suggest that the androgen stimulus

to the bone marrow was adequate in both groups for the duration of MENT treatment.

The prime argument for the potential value of MENT in man has been that it is theoretically prostate-sparing by virtue of its resistance to 5α-reduction (15, 17). Evidence to support this was obtained in this study. Prostate volume was found to fall during the administration of one MENTAc implant and showed a small, but not significant, fall in men administered two implants. These data were supported by measurement of serum PSA, which showed a fall in both groups. Ultrasound measurement of prostate volume and serum PSA concentrations are low in untreated hypogonadal men, rise with androgen replacement, and fall in normal men during induced hypogonadism (39–41), although others have reported increases in prostate volume without change in PSA during testosterone treatment of hypogonadal men (37). Although the fall in PSA was apparent after only 8 wk of MENT administration in group I, PSA concentrations were maintained at that time point in group II, but then fell at 24 wk of treatment. These data are consistent with serum PSA providing a sensitive index of androgen replacement in hypogonadal men and suggest that in group II there might be a reduction in the androgen stimulus to the prostate as serum MENT concentrations declined in the second half of the study period. Serum PSA concentrations show more rapid changes than prostate volume in response to androgen treatment (42). Although MENT is resistant to 5α-reduction, it is still a potent androgen; thus, selectivity at the prostate is only relative compared with its effects on other androgen targets. In the nonhuman primate, MENT was found to be 10-fold more potent that testosterone at suppressing gonadotropin secretion, but only 3 times more potent at the prostate (17). Similar results were obtained in rodents (16). In the present study it is thus likely that ultrasound measurement was insufficiently sensitive to detect any modest reduction in androgen stimulus to the prostate in group II over the time scale involved, and it is also possible that the small prostates of these relatively young hypogonadal men (37, 40, 43) may also have limited our ability to detect a fall in volume. Overall, the present data are consistent with the hypothesis that the doses of MENT administered here do not support prostatic function to the same degree as testosterone.

The maintenance of BMD in men is testosterone dependent; it is lower in hypogonadal men and increased by exogenous testosterone administration (44–46). Part of the effect of testosterone is mediated by conversion to estradiol, demonstrated most dramatically by individuals with mutations in the genes encoding the estrogen receptor and the enzyme aromatase (4, 47), although both direct effects and 5α-reductase may have a role (48, 49). Both cross-sectional and prospective studies have demonstrated a closer relationship between BMD and circulating estradiol than testosterone concentrations (50–52), and there is emerging evidence for a threshold estrogen concentration for maintenance of the skeleton in men (29). MENT is a substrate for aromatase (14), although this has not been directly demonstrated in men; it might therefore be supposed that MENT would support BMD. The present data demonstrate a fall in BMD at the lumbar spine in both groups. The magnitude of the fall is similar to that recently reported after treatment of men with a GnRH analog (53). Other studies have shown greater testosterone-dependent changes at the lumbar spine than hip (37, 54), consistent with the present data. Biochemical markers suggested a small fall in bone formation and an increase in bone resorption in group I, consistent with there being a subphysiological androgen stimulus to bone at least in group I. BMD determined by DEXA gives a more important integrative measure of changes over time; thus, these data suggest that both one and two MENT implants, as formulated here, do not provide adequate support to the skeleton. It is possible that tissues in which aromatization of testosterone is important in mediating the effects of androgen may require higher doses of MENT than those tissues that do not. During MENT administration, the circulating androgen concentration is much lower than with testosterone replacement; thus, there is a much lower mass of substrate for conversion by aromatase, both locally in bone and in other tissues, such as fat, that contribute to circulating estrogens. The high potency of MENT as an androgen, by reducing the dosage requirement, thus becomes disadvantageous when metabolism by aromatase is required. However, this interpretation must be regarded as speculative on the basis of the present data.

Measures of sexual behavior and erectile function showed decreases in group I, but were sustained in group II. One subject in group I also withdrew from the study because of symptoms of hypogonadism. The findings in group I may be analogous to those discussed above for BMD, although the relative importance of testosterone metabolism in sexual behavior is very uncertain. Male sexual behavior and erectile function are dependent on testosterone (22, 55–57), although testosterone replacement at the lower end of the physiological range is sufficient for normal sexual activity and erectile function (56, 58, 59). In many animal species it is clear that the effect of testosterone on male sexual behavior is mediated by estrogen (60, 61). In humans, studies using the estrogen antagonist tamoxifen or the aromatase inhibitor testolactone did not provide evidence for an important role for estrogen (10, 11). DHT, which is not a substrate for aromatase, is able to support male sexual behavior (11), although the nonaromatizable androgen mesterolone did not support sexual activity in hypogonadal men as effectively as testosterone (9). Recently, the investigation of an individual with an inactivating mutation of aromatase demonstrated an increase in sexual behavior with estrogen, but not testosterone, treatment (12). It therefore appears that aromatization mediates at least some of the effects of testosterone on sexual behavior. The importance of 5α-reductase in mediating the behavioral effects of testosterone is unclear, as inactivation of the type 2 isoenzyme by genetic mutation or by currently available pharmaceutical agents results in only partial depletion of DHT, and the type I isoenzyme predominates in the brain (3, 62). The decreases in sexual activity, SES2 scores, and erectile function in group I suggest that one MENTAc implant does not provide adequate replacement for these functions. It appears that an increased dose of MENT is able to provide adequate support to sexual behavior and erectile function as previously demonstrated (18), consistent with the relatively low threshold for testosterone-mediated support of these functions (56, 58) and the aromatization of MENT (14).

Concentrations of high density lipoprotein cholesterol are influenced by testosterone concentrations in normal men (38, 63–65). These effects may also be mediated by estrogen (6, 38, 66, 67). In castrate monkeys, MENT had the same relative potency to testosterone in its effects on lipids as on gonadotropin suppression and body weight, consistent with 5α-reductase not being involved (17). No significant changes in serum lipoproteins were detected in the present study, with the exception of a rise in apolipoprotein B in group I during MENT treatment. This is suggestive of androgen under replacement in group I, as elevated apolipoprotein B, which, in turn, relates to greater insulin resistance, correlates better to an increased risk for cardiovascular disease than low density lipoprotein cholesterol (68).

Lean body mass is dose-dependently maintained by testosterone in normal and hypogonadal men (37, 38, 45). Conversely, fat mass is also increased in hypogonadal men, reduced by testosterone treatment in most studies (37, 69, 70), and inversely related to testosterone concentrations in men with induced hypogonadism (38). Changes in lean and fat mass in the present study were complex, reflecting the limited cohort size and the potentially confounding impact of external influences such as changes in diet and the amount of exercise taken, which were not controlled. There was an increase in lean mass in group I during MENT treatment and a fall in fat mass and serum leptin concentration in group II. Leptin is produced by adipose tissue, and serum concentrations are excellent surrogate indicators of fat mass (71). Leptin concentrations are inversely related to testosterone, are suppressed by testosterone administration in normal men, and are increased during induced hypogonadism (72–74). The fall in leptin in this group may therefore reflect the fall in fat mass during MENT administration. The relevance of these observations is that circulating leptin, possibly as an indicator of elevated fat mass, has been independently linked to risk for coronary heart disease events (75). The potential use of MENT in restoring androgen status and reducing fat mass in elderly men therefore merits more detailed investigation with respect to cardiovascular risk.

In conclusion, these data show no evidence of toxicity of MENT at either dose during 24 wk of administration. The differential effects of MENT on the prostate, BMD, sexual behavior, and erectile function and on body composition and erythropoiesis are consistent with relative prostate-sparing by this potent androgen while maintaining functions that are mediated by testosterone directly. However, at the dose of one implant, there was inadequate replacement in tissues and functions in which aromatization is important in mediating the effects of testosterone. The higher dose of MENT investigated appeared to be able to compensate for this in supporting erectile function, but BMD at the lumbar spine still decreased. The apparent benefit at the prostate gland is thus balanced by the effects on bone metabolism. These data are important for the future development of androgens with restricted metabolism compared with testosterone.

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