0021-972X/03/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 88(7):3167–3176

doi: 10.1210/jc.2002-021827

Randomized Placebo-Controlled Trial of Androgen Effects on Muscle and Bone in Men Requiring Long-Term Systemic Glucocorticoid Treatment

BRONWYN A. L. CRAWFORD, PETER Y. LIU, MARY T. KEAN, JANE F. BLEASEL, AND DAVID J. HANDELSMAN

Department of Endocrinology (B.A.L.C., M.T.K.,), ANZAC Research Institute, and Department of Andrology (P.Y.L., D.J.H.), Institute of Rheumatology and Orthopaedics (J.F.B.), Royal Prince Alfred (B.A.L.C., M.T.K., J.F.B.), and Concord (P.Y.L., D.J.H.) Hospitals and University of Sydney, Sydney, New South Wales, Australia

Long-term glucocorticoid therapy in men is associated with loss of bone and muscle mass as well as a decrease in serum testosterone. We tested the effect of two androgens, testosterone and its minimally aromatizable analog nandrolone, on muscle mass (dual x-ray absorptiometry), muscle strength (knee flexion and extension by isokinetic dynamometry), bone mineral density (BMD), and quality of life (Qualeffo-41 questionnaire) in 51 men on a mean daily prednisone dose of 12.6 ± 2.2 mg. Men were randomized, double blind, to testosterone (200 mg mixed esters), nandrolone decanoate (200 mg), or placebo given every fortnight by im injection for 12 months. At 12 months, both androgens increased muscle mass (mean change from baseline +3.5%, +5.8%, and −0.9% in testosterone, nandrolone, and placebo groups, respectively, $P < 0.0001$) and muscle strength ($P < 0.05$). Lumbar spine BMD increased significantly only in men treated with testosterone (4.7 ± 1.1%, $P < 0.01$). There was no significant change in hip or total body BMD. Testosterone, but not nandrolone or placebo, improved overall quality of life ($P < 0.001$). These results suggest that androgen therapy may have a role in ameliorating adverse effects of glucocorticoid therapy such as muscle and bone loss and aromatization is necessary for androgen action on bone but not on muscle. (*J Clin Endocrinol Metab* 88: 3167–3176, 2003)

AMONG PATIENTS WITH chronic medical disorders, glucocorticoids are among the most widely used drugs. National estimates from the United Kingdom indicate that 0.5–0.9% of the total adult population are using oral corticosteroids (1, 2), most frequently for respiratory or rheumatological disease or organ transplantation. However, long-term systemic glucocorticoid therapy has significant adverse effects, particularly muscle and bone loss, which may decrease quality of life through frailty, falls, and fractures (3). These glucocorticoid effects are related to the dose and duration of therapy, although prolonged exposure to modest, frequently considered physiological doses of glucocorticoids may also be detrimental and have been shown to increase fracture risk (4, 5).

Glucocorticoid therapy in men also may result in decreased serum testosterone levels (6–8) because of combined effects on reduced GnRH secretion and a direct effect on testosterone production from the testes (9). The resultant relative androgen deficiency may contribute to the development of sarcopenia as well as loss of bone mass. A direct interaction between glucocorticoids and testosterone is supported by molecular studies showing heterodimer formation between androgen and glucocorticoid receptors and mutual inhibition of transcriptional activity (10). We therefore aimed to test the potential of androgen therapy, with associated anabolic effects on protein synthesis, in opposing some of the catabolic glucocorticoid effects on muscle and bone and to determine whether changes in functional status (*i.e.* muscle strength, quality of life) could be achieved.

Androgen replacement therapy in hypogonadal men (11, 12) as well as pharmacological androgen therapy in eugonadal men (13, 14) increases muscle mass and strength. In addition, androgen treatment can restore deficits in bone mineral density (BMD) in androgen-deficient men (12, 15). In contrast, androgen therapy has minimal effects on muscle strength and bone mass in older men with minimal androgen deficiency (16, 17). A key issue in androgen action is the tissue-specific effects of the two bioactive metabolites of testosterone, namely dihydrotestosterone (DHT), produced via 5α reductase especially in the prostate (18), and estradiol, via aromatase activity particularly in bone (19). How these metabolites influence androgen action on muscle and other tissues is not clear (20). By using equivalent doses of testosterone and its minimally aromatizable analog, nandrolone (19-nortestosterone) (21, 22), the study aimed also to determine the importance of aromatization for any potential therapeutic effects of androgen therapy.

Patients and Methods

Study patients

We studied men over 20 yr of age on long-term glucocorticoid therapy, defined as 5 mg or more prednisone daily for at least 6 months or 1000 μg or more of inhaled steroid plus at least one course of oral prednisone within the last 6 months. Men were excluded if they had unstable heart disease; sleep apnea; polycythemia; prostate disease within the last 5 yr; or treatment within the last 12 months with any androgen, antiandrogen, or bisphosphonate drugs. The study was approved by the institutional Human Ethics Committee, and all men provided written informed consent.

Abbreviations: BMD, Bone mineral density; DHT, dihydrotestosterone; DPD, deoxypyridinoline; PSA, prostate-specific antigen; SAE, serious adverse event.

Procedures

Eligible men were randomly assigned to treatment with either testosterone 200 mg (mixed esters, Sustanon; Organon Australia Pty. Ltd.), nandrolone decanoate 200 mg (Deca-Durabolin; Organon Australia Pty. Ltd., Sydney, NSW, Australia), or a matching placebo (arachis oil vehicle) given as 2 ml im injections into the gluteal muscle every 2 wk for 12 months by study staff or the patient's primary care physician. All patients received calcium carbonate 600 mg (Caltrate; Whitehall Consumer Healthcare Pty. Ltd., Australia) daily. Every 3 months fasting blood and urine samples were collected and questionnaires administered; every 6 months BMD, body composition, and muscle strength were measured. At each visit the average daily glucocorticoid dose over the previous 3 months was calculated and changes in other medications noted.

Bone density

Bone density at the lumbar spine (L1–L4), hip and total body was measured by dual x-ray absorptiometry at one of three sites using a DPXIQ, DPX-L, or Prodigy densitometer (Lunar Corp., Madison, WI) with all measurements for an individual conducted on the same machine. Ten serial scans of a spine phantom on the three machines were within 1.6% of each other. *In vitro* and *in vivo* coefficients of variation for lumbar spine, neck of femur, and total body BMD were less than 1.0 and less than 2.5%, respectively. Standardized BMD was determined by comparison of the individual BMD with the appropriate gender-specific North American reference data expressed as a number of SDs different from young normal controls (T-score).

Lean and fat mass

Muscle (lean) mass was calculated by subtraction of fat and bone mass from total body mass. Total body fat and bone mass was measured directly by dual x-ray absorptiometry. In addition, skinfold thickness was measured at four standard sites (biceps, triceps, subscapular, suprailiac) by Harpenden skin calipers (Holtain Ltd. Crymych, Dyfed, UK). Weight (wt) was measured to the nearest 0.1 kg on floor scales (BWB-600, Wedderburn Scales, Summer Hill, Australia) with subjects dressed in a light gown. Height was measured to the nearest 0.1 cm by a wall-mounted stadiometer (Pharmacia & Upjohn, Sydney, NSW, Australia), and waist and hip circumference were measured to the nearest 0.1 cm using a nonstretchable tape.

Muscle strength

Muscle strength (peak torque) was measured at the knee in flexion and extension at rotational speeds of 75, 85, and 95 degrees/sec (in triplicate) by isokinetic dynamometry every 6 months using a Cybex NORM dynamometer (Cybex, Ronkonoma, NY) as described previously (23).

Questionnaires

Quality of life was measured every 3 months by the Qualeffo-41 questionnaire (24). This questionnaire specifically evaluates quality of life in patients with osteoporosis and covers five main domains: pain, physical function (activities of daily living, jobs around the house, general mobility), social function, general health perception, and mental function. Domain scores and the total Qualeffo score were assessed following linear transformation as described (24, 25). Lower urinary tract symptoms were measured every 3 months by the International Prostate Symptom Score (26).

Laboratory testing

Fasting morning blood samples and second void urine samples were collected every 3 months. For 90% of subjects, blood samples were drawn at the time that the next injection was due (*i.e.* reflecting trough hormone levels); for the remainder, blood samples were at variable times from the last injection. Serum total testosterone, LH, FSH, SHBG, PTH, osteocalcin, and urinary free deoxypyridinoline were measured on the Immulite 2000 autoanalyzer (Diagnostic Products, Los Angeles, CA). Serum-free testosterone was measured by an in-house centrifugal ultrafiltration assay (detection limit 4 pmol/liter) as described previously (27). Estradiol was measured by direct time-resolved fluoroimmunoassay with a detection limit of 12 pmol/liter (Delfia, Perkin-Elmer Pty. Ltd., NSW, Sydney, Australia). Both 25 and 1,25 hydroxyvitamin D were measured by RIA (DiaSorin, Inc. Stillwater, MN) following an initial extraction from serum with acetonitrile and a second solvent column extraction step for 1, 25 hydroxyvitamin D. Serum IGF-I was measured by a double-antibody RIA following acid-ethanol extraction (Bioclone, Sydney, Australia). Hematology (full blood count) and routine biochemistry (electrolytes, urea, creatinine, liver function, cholesterol, triglycerides, high-density lipoprotein) were measured by standard autoanalyzer methodologies. Prostate-specific antigen (PSA) was measured by the Delfia Prostatus kit (Wallac, Inc., Turku, Finland).

Data analysis

Treatment and time effects were estimated by repeated-measures ANOVA using standard and generalized estimating equation approaches (28). Effect modification by key *a priori* baseline variables (testosterone, BMD, prednisone dose) was evaluated by using the baseline value as a covariate in a repeated measures analysis of covariance. Bone density data were analyzed using raw data expressed as gram per square centimeter. Data were analyzed using StatXact (version 4; SPSS, Inc., Chicago, IL), version 10 NCSS 2001 (Number Cruncher Statistical Systems, Kaysville, UT), and ToxTools, version 1.0 (Cytel Software Corp., Cambridge, MA). A value of less than 0.05 (two-tailed) was considered statistically significant. Results are presented as mean ± SEM.

Results

Patients

Fifty-one men (age, 60.3 ± 1.9 yr) were recruited, with 43 men completing 6 months and 37 men completing the full 12 months of the study. The number of men discontinuing from the testosterone, nandrolone, and placebo groups, respectively, were 3, 4, and 1 before 6 months and similarly, 1, 3, and 2 men between 6 and 12 months. In the remainder, attendance at scheduled visits was greater than 95%. Baseline demographic, clinical, and laboratory features of the three groups were well matched (Table 1) apart from an unexpectedly lower lumbar spine BMD in the group destined to receive testosterone ($P < 0.01$). The baseline T scores (SD) for testosterone, nandrolone, and placebo groups, respectively, were -1.9 ± 0.08, -0.7 ± 0.06, and -1.0 ± 0.08 for lumbar spine and -1.6 ± 0.06, -0.9 ± 0.07, and -1.4 ± 0.08 for neck of femur. Prednisone dose both at entry and completion of the study was not significantly different among groups (final prednisone dose: 14.8 ± 5.4 mg, testosterone; 10.5 ± 3.8 mg, nandrolone; 14.0 ± 5.2 mg, placebo). Similarly, inhaled steroids were used by eight men in both the testosterone and placebo groups and nine men in the nandrolone group.

Hormone levels

At entry into the study, 18 men (six in each treatment group) had a testosterone level below the lower limit of the eugonadal reference range (<11 nmol/liter) and another 16 (seven, five, and four men in testosterone, nandrolone, and placebo groups, respectively) had a testosterone level in the low-normal range (11–15 nmol/liter). With nandrolone treatment, plasma total and free testosterone concentrations were markedly suppressed ($P < 0.001$), but there was no change with time in the placebo group (Fig. 1). Mean plasma total testosterone remained within the eugonadal reference range for both the testosterone and placebo treatment groups. Plasma estradiol was also suppressed in the nandrolone

TABLE 1. Baseline characteristics (mean ± SEM) of men randomized to treatment with testosterone, nandrolone, or placebo

Treatment group	Testosterone	Nandrolone	Placebo
Number	18	17	16
Age (yr)	58.7 ± 4.9	62.7 ± 4.2	59.9 ± 4.0
Primary disease			
Respiratory disease	10	11	10
Immune or inflammatory disease	8	6	6
Prednisone dose at entry (mg/d)	13.2 ± 3.9	12.4 ± 3.6	10.7 ± 1.4
Duration of prednisone use (yr)	11.0 ± 3.1	8.6 ± 1.5	8.5 ± 2.3
Bone density (g/cm^2)			
Lumbar spine[a]	0.999 ± 0.04	1.157 ± 0.03	1.125 ± 0.04
Neck of femur	0.866 ± 0.03	0.953 ± 0.04	0.894 ± 0.04
Femoral trochanter	0.784 ± 0.04	0.868 ± 0.04	0.831 ± 0.04
Ward's triangle	0.660 ± 0.05	0.783 ± 0.05	0.706 ± 0.06
Total body	1.150 ± 0.02	1.210 ± 0.02	1.143 ± 0.03
Body composition			
Body weight (kg)	79.1 ± 4.8	76.4 ± 3.4	78.4 ± 3.0
Body mass index (kg/m^2)	26.7 ± 1.6	25.2 ± 1.0	25.5 ± 0.8
Waist circumference (cm)	98.9 ± 3.9	98.4 ± 2.2	97.8 ± 2.3
Waist/hip ratio	1.0 ± 0.02	1.0 ± 0.02	1.0 ± 0.02
Skinfolds sum (mm)	51 ± 5	44 ± 4	47 ± 5
Lean (muscle) mass (kg)	52.2 ± 2.3	50.8 ± 1.8	53.1 ± 2.0
Fat mass (kg)	21.1 ± 3.4	22.1 ± 2.4	20.8 ± 2.5
Total body fat (%)	27.6 ± 2.2	28.5 ± 1.7	27.6 ± 2.4
Hormones and biochemistry[b]			
Total testosterone (nmol/liter)	13.8 ± 0.4	13.2 ± 0.3	15.7 ± 0.5
Free testosterone (pmol/liter)	155 ± 18	160 ± 49	199 ± 53
Estradiol (pmol/liter)	139 ± 7	125 ± 36	142 ± 38
LH (U/liter)	4.9 ± 0.7	5.0 ± 0.9	5.8 ± 1.2
FSH (U/liter)	9.0 ± 2.5	9.1 ± 2.1	9.1 ± 1.5
SHBG (nmol/liter)	37 ± 4	42 ± 5	40 ± 5
25-hydroxyvitamin D (nmol/liter)	77 ± 5	74 ± 8	79 ± 9
1,25-hydroxyvitamin D (pmol/liter)	93 ± 12	75 ± 6	87 ± 10
PTH (pmol/liter)	5.3 ± 0.4	5.5 ± 0.7	5.4 ± 0.3
IGF-I (nmol/liter)	21 ± 1	17 ± 1	20 ± 1
PSA (μg/liter)	1.2 ± 0.2	1.6 ± 0.5	0.9 ± 0.1
Cholesterol (mmol/liter)	5.8 ± 0.3	6.2 ± 0.3	5.9 ± 0.4
High-density lipoprotein (mmol/liter)	1.6 ± 0.1	1.7 ± 0.1	1.5 ± 0.1
Triglycerides (mmol/liter)	1.4 ± 0.1	1.2 ± 0.1	2.0 ± 0.6
Questionnaires			
Quality of Life			
QUALEFFO-41 (total score)	81 ± 4	84 ± 6	76 ± 4
Lower Urinary Tract Symptoms			
IPSS (total score)	6.7 ± 1.0	7.1 ± 1.7	7.1 ± 1.2

[a] The only parameter that was significantly different between groups was lumbar spine BMD ($P < 0.01$).

[b] Normal ranges for hormones: total testosterone, 11–35 nmol/liter; free testosterone, 170–510 nmol/liter; SHBG, 9–45 nmol/liter; estradiol, 80–180 pmol/liter; LH, 1–10 U/liter; FSH, 1.0–8.5 U/liter; 25-hydroxyvitamin D, 39–140 nmol/liter; 1,25-hydroxyvitamin D, 36–120 pmol/liter; PTH, 2.3–6.0 pmol/liter; IGF-I, nmol/liter; PSA, 0–4 μg/liter.

group ($P < 0.001$) but was maintained at consistent levels in placebo group, but the testosterone group had higher levels ($P = 0.02$) (Fig. 1). Serum levels of LH and FSH were significantly suppressed with both androgen treatments but were unchanged with placebo (Fig. 1). SHBG (Fig. 1) and IGF-I levels (data not shown) did not significantly change with time or treatment.

Muscle mass and strength

Lean mass was increased at 6 and 12 months by both androgen treatments but did not change with placebo ($P < 0.0001$) (Fig. 2). There was no significant difference between testosterone and nandrolone in the magnitude of increase in lean muscle. At 12 months, the average change in lean mass was +1.8 kg, +2.8 kg, and −0.5 kg in the testosterone, nandrolone, and placebo groups, respectively. Conversely, total body fat was decreased by testosterone and nandrolone at 6 and 12 months, compared with an increase with placebo ($P < 0.0001$) (Fig. 2), representing an average change in fat mass at 12 months of −2.3 kg, −3.0 kg, and +0.7 kg in the testosterone, nandrolone, and placebo groups, respectively. There were no significant changes with time or treatment in body weight, body mass index, waist circumference, waist: hip ratio, or skin fold thickness (data not shown). Muscle strength (Fig. 3) was increased by both nandrolone and testosterone treatment for 11 of 12 movement and speed combinations ($P < 0.0001$ for left knee flexion at 75 degrees/sec; $P < 0.01$ for left knee flexion at 85 and 95 degrees/sec, and right knee extension at 75 degrees/sec; $P < 0.05$ for left knee extension at 75 and 95 degrees/sec, right knee flexion and extension at 85 and 95 degrees/sec, and right knee flexion at 75 degrees/sec).

Bone density and turnover

Lumbar spine BMD increased progressively with testosterone treatment (+2.9% at 6 months; 4.7% at 12 months ($P <$

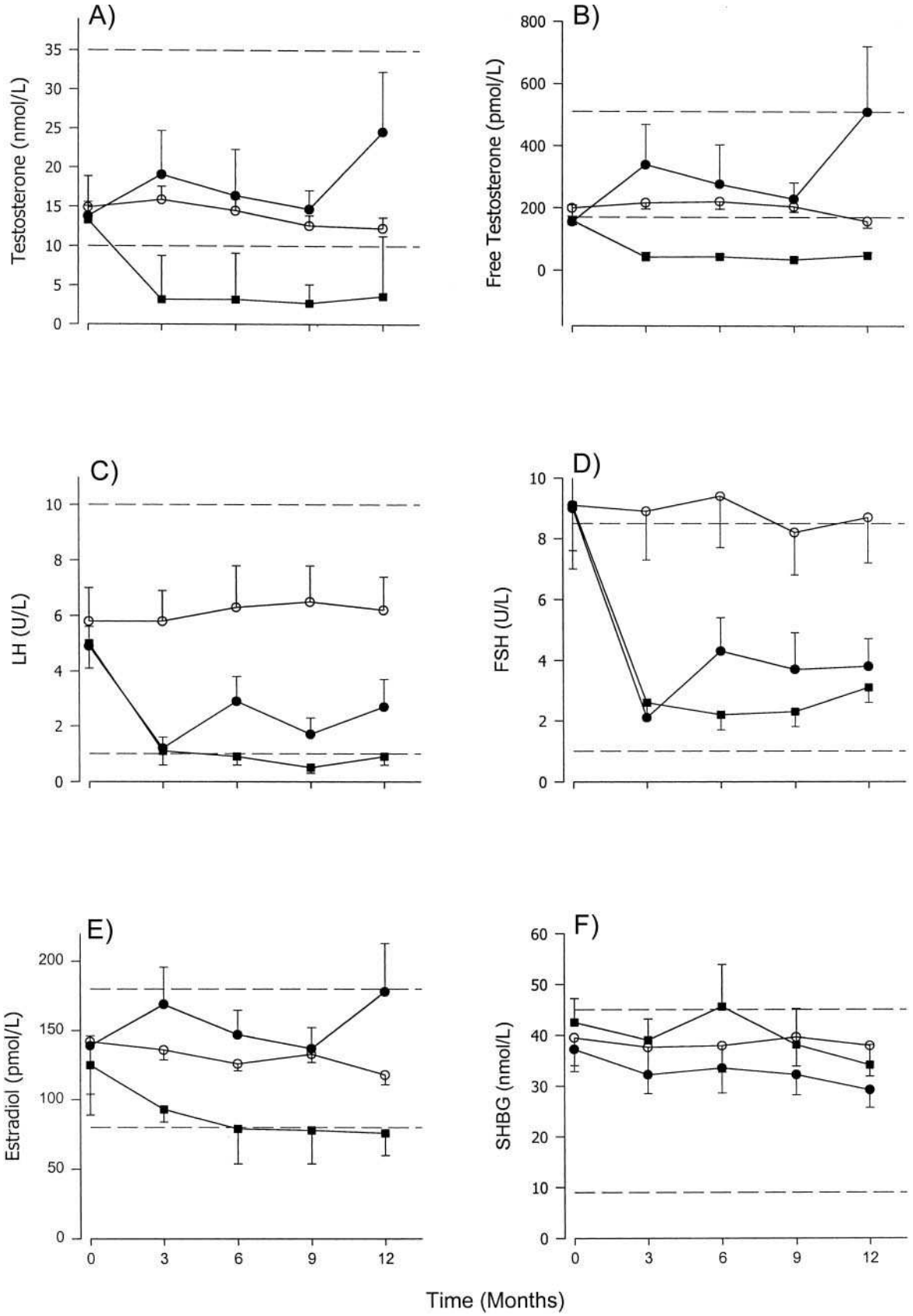

FIG. 1. Serum levels (mean ± SEM) of testosterone (A), free testosterone (B), LH (C), FSH (D), estradiol (E), and SHBG (F) in men treated with testosterone (●), nandrolone (■), or placebo (○). The normal ranges for adult men are represented by *dashed bars*.

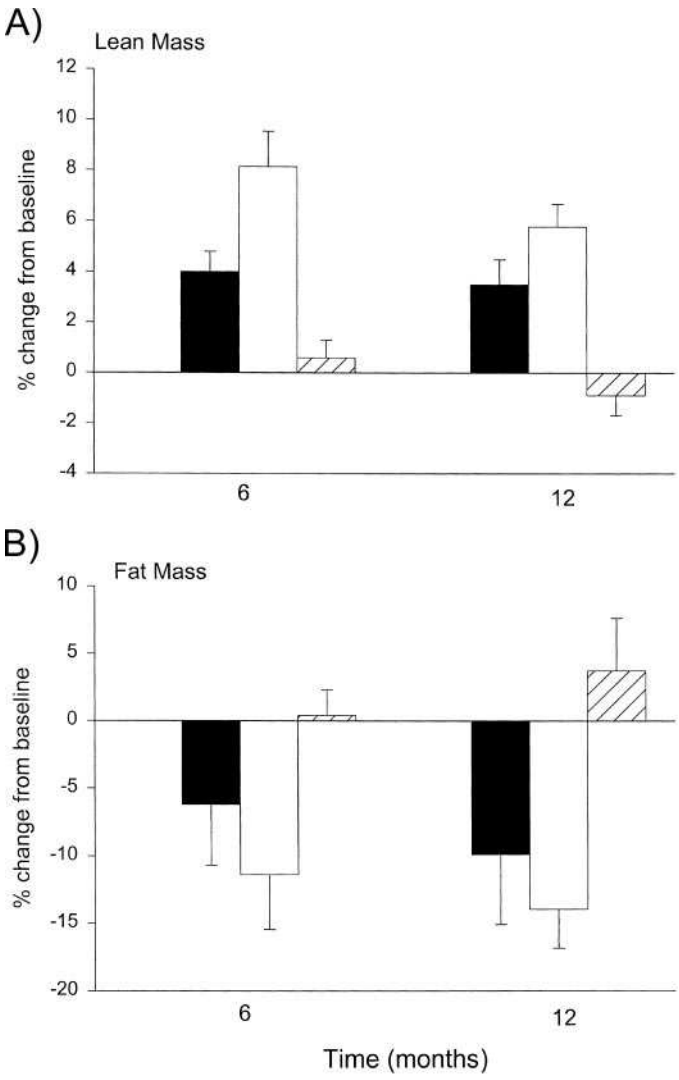

FIG. 2. Change (as percentage from baseline) in total body lean mass (A) and total fat mass (B) in men treated with testosterone (■), nandrolone (□), or placebo (▨). ($P < 0.0001$ between groups).

0.01), but there was no significant change in BMD in the nandrolone- or placebo-treated groups (+1.4%, −1.1% at 6 months; −0.7%, +0.7% at 12 months, respectively) (Fig. 4). There was no significant change in BMD in the neck of femur in any group (+2.2%, −0.2%, −2.5% at 12 months in testosterone, nandrolone, and placebo groups, respectively) or total body BMD (Fig. 4). Similarly, no significant change was seen in BMD of the trochanter or Ward's triangle (data not shown). To correct for the baseline difference in lumbar BMD, which occurred despite randomization, reanalysis of BMD for each site using the baseline BMD as covariate did not change the significant difference among treatment groups. Inclusion of other key *a priori* potential effect modifiers (baseline testosterone levels, prednisone dose) in the final model also did not alter the findings.

Baseline urinary deoxypyridinoline (DPD)/creatinine (Cr) levels were elevated approximately 2-fold above the ULN in all groups and declined progressively over 12 months to a similar extent. A similar decline was seen for osteocalcin levels (Fig. 5).

Quality-of-life questionnaire

Testosterone, but not nandrolone, improved the total Qualeffo-41 score, compared with placebo ($P < 0.001$) (Fig. 6), but there was no difference for any of the five individual domains. There were no consistent time (learning) effects.

Safety

No men developed polycythemia, sleep apnea, lower urinary tract symptoms, prostate cancer, mood/behavioral disturbance, acne, or edema. Plasma PSA concentrations were not significantly altered and all PSA values remained within the normal range apart from a transient elevation in one man, possibly related to an episode of prostatitis. The total International Prostate Symptom Score score did not significantly change with time or treatment; however, one of eight scores (Q1) decreased significantly with testosterone treatment, indicating more frequent sensation of incomplete bladder emptying.

Mean hemoglobin levels rose in both androgen treatment groups ($P < 0.001$) to a similar extent (~10%) resulting in a mean hemoglobin concentration of 160 ± 3 g/liter (testosterone) and 162 ± 6 g/liter (nandrolone), compared with 151 ± 4 g/liter with placebo. There was no significant change in serum creatinine levels. There were no changes in lipid levels with time or treatment. At entry, 12 men were using lipid-lowering drugs, and during the study four increased and four decreased antilipid agents, Similarly, there were no significant changes in biochemical tests of liver or kidney function. During the study, 15 serious adverse events (SAEs) were reported in 13 men, causing discontinuation of eight participants. The SAEs included myocardial ischemia (four), lung cancer (two), pulmonary embolism (two), ruptured aortic aneurysm (two), carotid artery thrombosis (one), cardiomyopathy (two), spinal stenosis (one), and avascular necrosis of head of femur (one). There was no significant difference among treatment groups in distribution of SAEs or all adverse events or discontinuations. Other discontinuations were due to loss to follow-up (three), ankle fracture (one), and injection discomfort (two).

Discussion

High-dose glucocorticoids are among the most widely used and valuable drugs in the modern therapeutic armamentarium because of their potent antiinflammatory and immunosuppressive effects. The need to ameliorate the substantial iatrogenic complications associated with widespread use of high-dose glucocorticoids raises the possibility of using androgens as an effective adjuvant therapy among men who are using high-dose glucocorticoids. The present study provides support for the feasibility of this approach together with some guidance on the optimal pharmacological features of the most suitable androgens for this application. Testosterone, administered at a standard androgen replacement dose, produced an increase in muscle mass and strength, lumbar BMD, and some improvement in quality of life. By contrast, nandrolone produced similar improvements in muscle mass and strength but not in BMD or quality of life. These beneficial effects, sustained for 12 months' duration,

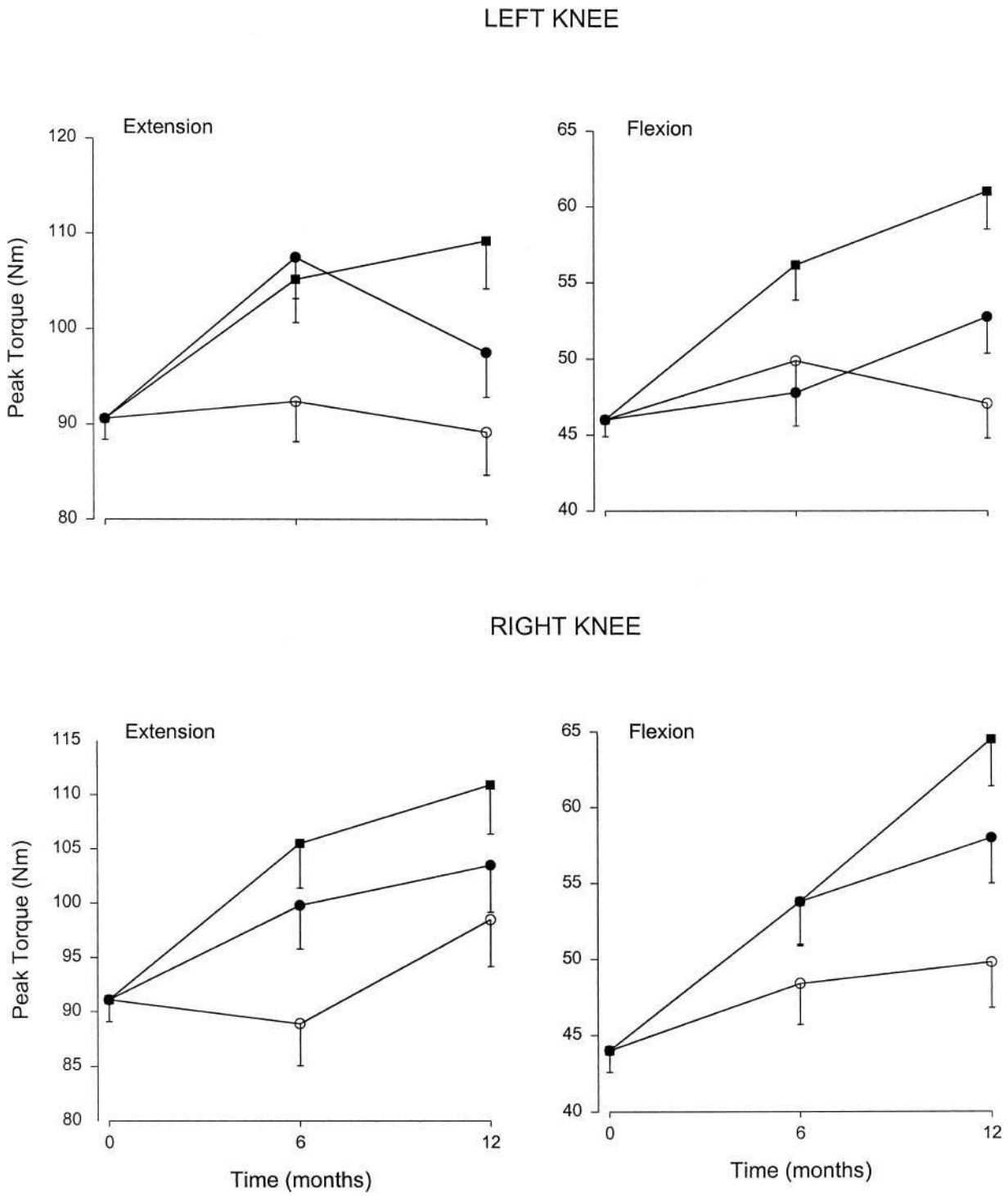

FIG. 3. Muscle strength (peak torque) in flexion ($P < 0.0001$ between groups) and extension ($P < 0.05$ between groups) movements at 75 degrees/sec of the left and right knee in men treated with testosterone (●), nandrolone (■), or placebo (○). A similar pattern of change was seen for knee flexion and extension at 95 degrees/sec and knee flexion at 95 degrees/sec. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.0001$.

were evident among men without overt androgen deficiency or frank osteoporosis. The present findings also provide evidence that the beneficial effects of androgens require aromatization for its effects on bone but not muscle.

Muscle is highly susceptible to the catabolic effects of pharmacological glucocorticoid therapy (29) as well as the anabolic effects of androgens (14) such as nandrolone and testosterone (30, 31). The striking effects on muscle mass and strength seen with both androgens in this study appear even greater than androgen therapy in hypogonadal (11, 12), eugonadal (13, 14), and male aging (32). This points to specific antiglucocorticoid effects of androgens presumably

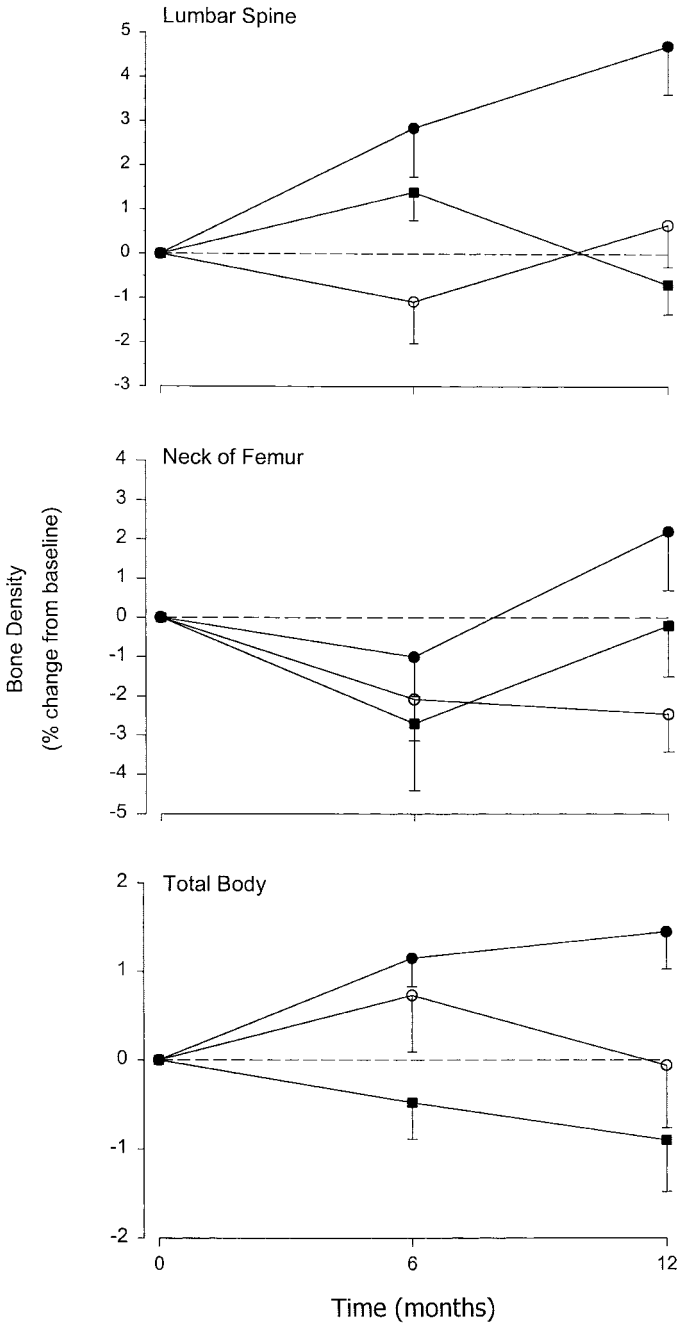

FIG. 4. BMD changes in the lumbar spine, neck of femur, and total body (not significant) in men treated with testosterone (●), nandrolone (■), or placebo (○). The *dashed line through zero* represents no change from baseline. Between-group difference significant only for lumbar spine ($P < 0.01$).

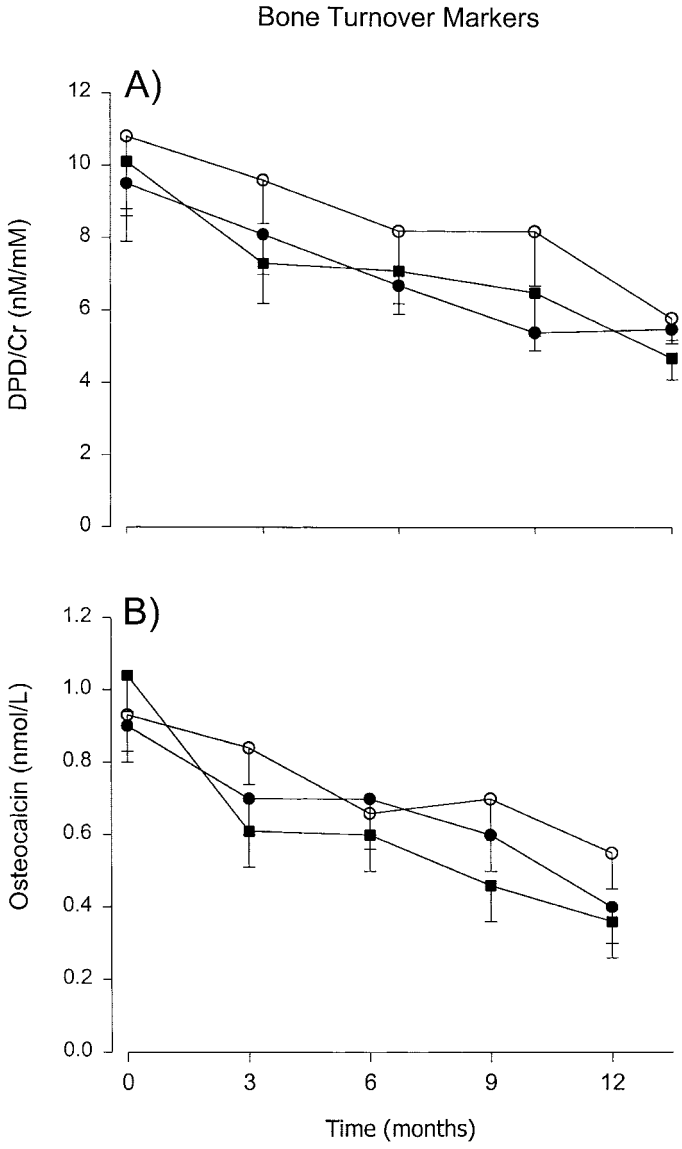

FIG. 5. Bone turnover markers, urinary DPD/Cr (A) and serum osteocalcin (B) in men treated with testosterone (●), nandrolone (■), or placebo (○). The normal ranges for adult men are DPD/Cr 2.3–5.4 nM/mM; osteocalcin 0.7–2.0 nmol/liter.

manifested as steroid receptor interactions rather than just counteraction of general catabolic effects (10). The potential detrimental consequence of such an interaction might be androgen interference with therapeutic glucocorticoid action; however, our data showing no increased requirement for prednisone suggest this is not the case.

Benefits in terms of body composition have also been seen with pharmacological androgen therapy in patients with other chronic, catabolic states such as pulmonary disease (33, 34), burns (35), renal disease (36, 37), and HIV (14); however, there has been a variable effect on functional capacity. In contrast to testosterone administration in older men (16) and androgens in HIV infection (14), a low pretreatment testosterone level in the current study was not a predictor of any efficacy outcomes. The majority of men in this study, however, had testosterone levels in the low or low-normal range, and the positive response to androgen therapy may reflect their state of partial or subclinical androgen deficiency, precipitated by the effects of glucocorticoid therapy and chronic illness superimposed on normal aging. These findings suggest that in men on long-term glucocorticoid treatment, adjuvant testosterone therapy may be useful, regardless of prior androgen status.

The positive effect of testosterone on lumbar spine but not hip BMD is consistent with a previous randomized, cross-

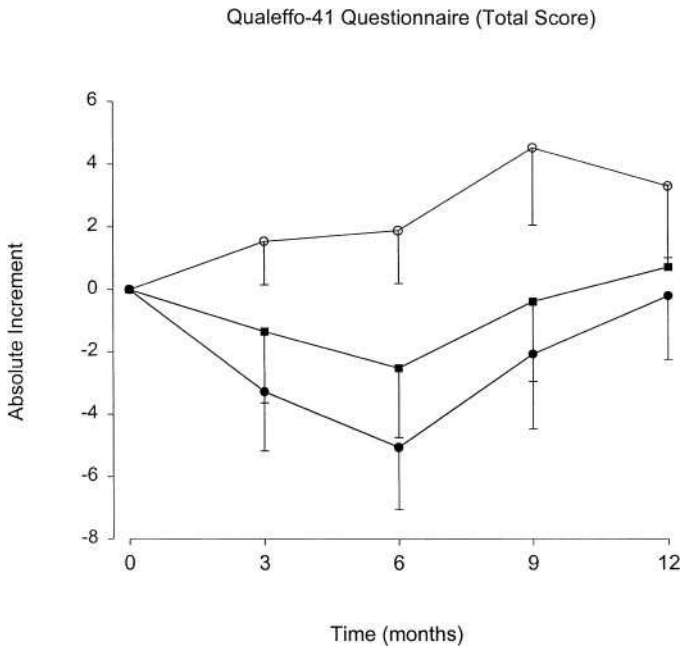

FIG. 6. Change in the total score (absolute increment from baseline) for the Qualeffo-41 in men treated with testosterone (●), nandrolone (■), or placebo (○).

over study using a small, subreplacement dose of testosterone in 15 men taking glucocorticoid medication for chronic asthma (38). The similar findings in these studies despite a 2-fold difference in androgen dosage suggests that the differences according to bone site may be more related to predominant bone type (trabecular in spine, cortical in femoral neck) rather than testosterone dose. Changes in BMD in the lumbar spine usually herald similar but later effects at other bone sites, and the 12-month duration of both these studies may not have been sufficient for demonstration of improved bone mass in cortical bone with a slower metabolic rate, compared with cancellous bone. Because of an imbalance in lumbar spine BMD at baseline among groups, covariate analysis was used; however, the strength of the effect of testosterone treatment on lumbar spine BMD was not altered. An unusual finding in our study was the decrease in bone turnover markers in both androgen-treated groups as well as placebo. We attribute this to the addition of calcium supplementation (600 mg daily) to a population of men with probable low dietary calcium intake, which has been shown previously (39, 40). Alternative treatments in glucocorticoid-induced osteoporosis include bisphosphonates (41–43), but they are expensive and cannot offer concurrent benefits for muscle or quality of life.

Recent studies have highlighted the importance of enzymatic activation of androgens for tissue-specific effects. The present study compared two androgens at equivalent milligram doses that differed in their susceptibility to aromatization and their conversion to DHT. Although testosterone is aromatized to a quantitatively small extent (~0.5%), the high (~100-fold) molar potency of estradiol means that aromatization is an important facet of testosterone action in some tissues, notably in which aromatase is highly expressed. By contrast, nandrolone has higher molar potency at the androgen receptor but is inactivated by 5α reduction and is minimally aromatizable (44–47), making it a prototype pure androgen (*i.e.* nonamplifiable, nonaromatizable). The minimal effect of nandrolone on the prostate, which contains high levels of 5α reductase, confirms a previous study of nandrolone in dialysis patients (48) and resembles that of its 7α methyl derivative 7α-methyl-19-nortestosterone, which has been shown to have striking prostate-sparing effects in rodents and humans (49, 50). By contrast, muscle and bone have minimal expression of 5α reductase and there is little DHT present in muscle tissue (51). The striking similarity of the effects of nandrolone and testosterone on muscle mass and strength are most consistent with direct androgen effects on muscle via the androgen receptor and not via the active enzymatic metabolites of testosterone.

Similarly, 5α reduction probably plays little part in androgen action in bone, although direct androgen effects on bone cells are likely (52). Recent studies of genetic models of congenital complete estrogen blockade by inactivation of the aromatase enzyme or estrogen receptor in man (53–55) and mouse (56–58) have shown consistently that bone development and morphology is markedly impaired, suggesting that aromatization and local estrogen action may be important components of testosterone effects on bone. Nevertheless, the gender differences in bone structure that also persist in genetic models of complete androgen receptor inactivation (59), the presence of androgen receptors on bone cells (52), the low circulating estradiol levels in men, and the known bone anabolic effects of minimally aromatizable androgens (60–62) suggest that local aromatization may be responsible for only part of testosterone's effect on bone. The differences between testosterone and nandrolone in effects on lumbar spine BMD are most consistent with the concept that aromatization is important for maintenance of BMD, at least for trabecular bone. Differences in molar potency between nandrolone and testosterone cannot explain this difference in efficacy on spine BMD because nandrolone is more potent than testosterone; however, the dose or kinetics of nandrolone decanoate may not have been ideal in men on glucocorticoid treatment. The present study cannot further differentiate between these possibilities. The effect of nandrolone therapy on BMD in men previously has been studied only at a lower dose in which positive effects were transient (63); however, in postmenopausal women nandrolone consistently increases BMD (60–62), although these small studies were not rigorously controlled and efficacy was limited because of virilization. The lack of requirement for aromatization in androgen action on muscle, in contrast to bone (19), highlights the need to understand the variation in tissue-specific effects of androgens, particularly for the development of more metabolically and organ selective designer androgens (20).

The marked decrease in body fat seen in the androgen-treated men may help reverse some of the adverse effects of glucocorticoids on body composition and insulin resistance and the concomitant implications for cardiovascular disease. Measurement of insulin resistance was not an end point in this study; however, previous studies have shown testosterone to be an important determinant of regional fat distribution and metabolism in men (64). Percent body fat is increased in hypogonadal men, and epidemiological studies

have reported an inverse correlation of endogenous testosterone levels with abdominal obesity in middle-aged men (11). Testosterone replacement in these men improved insulin sensitivity and decreased blood glucose and blood pressure (64, 65).

The improvement in testosterone-treated men in the total score for the Qualeffo-41 questionnaire is consistent with an improved general sense of well-being that is commonly associated with androgen replacement in hypogonadal men and has also been reported in HIV-treated patients (66). The positive effects of testosterone treatment on quality of life, combined with improvements in muscle strength and mass, has important implications for the function of glucocorticoid-dependent men with chronic illness in whom comorbidity and restrictions in activity levels are common. Other potential benefits of androgen treatment not studied here include improvements in skin fragility, libido, and cognition. In addition, androgen treatment may have effects on the natural history of underlying diseases because of potential modulation of immune function (67, 68) or as a direct result of improved muscle strength.

The power of this study was limited by the number of discontinuations, most of which were due to adverse events occurring in men with concurrent chronic illnesses and significant comorbidity. The safety of androgen administration in older men raises concerns in three main areas: acceleration of cardiovascular or prostate disease and idiosyncratic effects of androgens such as polycythemia, sleep apnea, and mood or behavioral disturbances. There is at present little direct evidence to evaluate these risks. The adverse cardiovascular events observed in the present study did not differ among treatments and reflected the comorbidities of the participants with significant underlying primary diseases. The absence of lipid changes is reassuring, although the significance of lipid changes in a population of men with other life-threatening chronic disease remains unclear. The effects of androgen administration on the prostate and its risk of disease remains unclear. Clearly androgens are contraindicated in men with known or undiagnosed prostate cancer, but the risks of androgen administration in others without prostate cancer remain unclear. Conclusive data of safety of androgen administration to men with chronic nongonadal disease will require larger and more powerful studies with a focus on objective disease end points rather than surrogate variables alone.

Larger studies of longer duration will also be required to determine the effect of androgen therapy on fractures and, in particular, confirm a reduction in vertebral fractures that are the most common fractures associated with long-term glucocorticoid therapy. The importance of this study is the demonstration of benefits of testosterone treatment in glucocorticoid-treated men across a wide range of clinical areas and extending into functional improvement. In men with glucocorticoid-dependent chronic disease treated with androgens, increased strength of muscles and improved exercise tolerance may delay disease progression, and, combined with an improved sense of well-being, would enhance the response to rehabilitation therapy and improve quality of life. The potential for reduction in public health costs may have additional positive implications for the wider community.

Acknowledgments

Received November 21, 2002. Accepted March 17, 2003.

Address all correspondence and requests for reprints to: Dr. Bronwyn Crawford, Endocrinology Department, Royal Prince Alfred Hospital, Camperdown, NSW, 2050, Australia. E-mail: brcrawfo@mail.usyd.edu.au.

This work was supported in part by Organon (Australia) Pty. Ltd.

References

1. **Walsh LJ, Wong CA, Pringle M, Tattersfield AE** 1996 Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. BMJ 313:344–346
2. **Van Staa T, Leufkens H, Abenhaim L, Abenhaim L, Begaud B, Zhang B, Cooper C** 2000 Use of oral corticosteroids in the United Kingdom. Q J Med 99:105–111
3. **Truhan A, Ahmed A** 1989 Corticosteroids: a review with emphasis on complications of prolonged systemic therapy. Ann Allergy 62:375–391
4. **Adinoff A, Hollister J** 1983 Steroid-induced fractures and bone loss in patients with asthma. N Engl J Med 309:265–268
5. **Van Staa T, Leufkens H, Abenhaim L, Zhang B, Cooper C** 2000 Use of corticosteroids and risk of fractures. J Bone Miner Res 15:993–1000
6. **Reid I, Ibberton H, France J, Pybus J** 1985 Plasma testosterone concentrations in asthmatic men treated with glucocorticoids. BMJ 291:574
7. **Kamischke A, Kemper D, Castel M, Luthke M, Rolf C, Behre H, Magnussen H, Nieschlag E** 1998 Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. Eur Resp J 11: 41–45
8. **Hampson G, Bhargava N, Cheung J, Vaja S, Seed P, Fogelman I** 2002 Low circulating estradiol and adrenal androgens concentrations in men on glucocorticoids: a potential contributory factor in steroid-induced osteoporosis. Metabolism 51:1458–1462
9. **Eastell R, Reid D, Compston J, Cooper C, Fogelman I, Francis R, Hosking D, Purdie D, Ralston S, Reeve J, Russell R, Stevenson J, Torgerson D** 1998 A UK Consensus Group on management of glucocorticoid-induced osteoporosis: an update. J Intern Med 224:271–292
10. **Chen S, Wang J, Yu G, Liu W, Pearce D** 1997 Androgen and glucocorticoid receptor heterodimer formation. J Biol Chem 272:14087–14092
11. **Bhasin S, Storer T, Berman N, Yarasheski K, Clevenger B, Phillips J, Lee W, Bunnell T, Casaburi R** 1997 A replacement dose of testosterone increases fat-free mass, and muscle size in hypogonadal men. J Clin Endocrinol Metab 82:407–413
12. **Snyder PJ, Peachey H, Berlin JA, Hannoush P, Haddad G, Dlewati A, Santanna J, Loh L, Lenrow DA, Holmes JH, Kapoor SC, Atkinson LE, Strom BL** 2000 Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 85:2670–2677
13. **Bhasin S, Storer T, Berman N, Callegari C, Clevenger B, Phillips J, Bunnell T, Tricker R, Shirazi A, Casaburi R** 1996 The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 335:1–7
14. **Bhasin S, Woodhouse L, Storer T** 2001 Proof of the effect of testosterone on skeletal muscle. J Endocrinol 170:27–38
15. **Leifke E, Korner HC, Link TM, Behre HM, Peters PE, Nieschlag E** 1998 Effects of testosterone replacement therapy on cortical and trabecular bone mineral density, vertebral body area and paraspinal muscle area in hypogonadal men. Eur J Endocrinol 138:51–58
16. **Snyder P, Peachey H, Hannoush P, Berlin J, Loh L, Lenrow D, Holmes J, Dlewati A, Santanna J, Rosen C, Strom B** 1999 Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 84:2647–2653
17. **Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie M, Haddad Jr J, Strom B** 1999 Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 84:1966–1972
18. **Russell DW, Berman DM, Bryant JT, Cala KM, Davis DL, Landrum CP, Prihoda JS, Silver RI, Thigpen AE, Wigley WC** 1994 The molecular genetics of steroid 5 alpha-reductases. Rec Prog Horm Res 49:275–284
19. **Khosla S, Melton 3rd LJ, Riggs BL** 2002 Clinical review 144: estrogen and the male skeleton. J Clin Endocrinol Metab 87:1443–1450
20. **Negro-Vilar A** 1999 Selective androgen receptor modulators (SARMs): a novel approach to androgen therapy for the new millennium. J Clin Endocrinol Metab 84:3459–3462
21. **Hobbs CJ, Plymate SR, Rosen CJ, Adler RA** 1993 Testosterone administration increases insulin-like growth factor-I levels in normal men. J Clin Endocrinol Metab 77:776–779
22. **Behre HM, Kliesch S, Lemcke B, von Eckardstein S, Nieschlag E** 2001 Suppression of spermatogenesis to azoospermia by combined administration of GnRH antagonist and 19-nortestosterone cannot be maintained by this non-aromatizable androgen alone. Hum Reprod 16:2570–2577

23. **Ly L, Handelsman D** 2002 Muscle strength and ageing: methodological aspects of isokinetic dynamometry and androgen administration. Clin Exp Pharm Physiol 29:39–47
24. **Lips P, Cooper C, Agnusdei F, Caulin F, Egger P, Johnell O, Kanis J, Kellingray S, Leplege A, Liberman U, McCloskey E, Minne H, Reeve J, Reginster J-Y, Scholz M, Todd C, de Vernejoul M, Wiklund I** 1999 Quality of life in patients with vertebral fractures: validation of the quality of life questionnaire of the European Foundation for Osteoporosis (QUALEFFO). Osteoporos Int 10:150–160
25. **Oleksik A, Lips P, Dawson A, Minshall M, Shen W, Cooper C, Kanis J** 2000 Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. J Bone Miner Res 15:1384–1392
26. **Barry M, Fowler F, O'Leary M, Bruskewitz R, Holtgrewe H, Mebust W, Cockett A** 1992 The American Urological Association symptom index for benign prostatic hyperplasia. J Urol 148:1549–1557
27. **Hammond G, Nisker J, Jones L, Siiteri P** 1980 Estimation of the percentage of free steroid in undiluted serum by centrifugal ultrafiltration dialysis. J Biol Chem 255:5023–5026
28. **Liang K, Zeger S** 1986 Longitudinal data analysis using generalized linear models. Biometrika 73:13–22
29. **Kanda F, Okuda S, Matsushita T, Takatani K, Kimura KI, Chihara K** 2001 Steroid myopathy: pathogenesis and effects of growth hormone and insulin-like growth factor-I administration. Horm Res 56(Suppl 1):24–28
30. **Friedl KE, Dettori JR, Hannan CJ, Patience TH, Plymate SR** 1991 Comparison of the effects of high dose testosterone and 19-nortestosterone to a replacement dose of testosterone on strength and body composition in normal men. J Steroid Biochem Mol Biol 40:607–612
31. **Hartgens F, Van Marken Lichtenbelt W, Ebbing S, Vollaard N, Rietjens G, Kuipers H** 2001 Body composition and anthropometry in bodybuilders: regional changes due to nandrolone decanoate administration. Int J Sports Med 22:235–241
32. **Bross R, Javanbakht M, Bhasin S** 1999 Anabolic interventions for aging-associated sarcopenia. J Clin Endocrinol Metab 84:3420–3430
33. **Ferreira I, Verreschi I, Nery L, Goldstein R, Zamel N, Brooks D, Jardin J** 1998 The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. Chest 114:19–28
34. **Schols A, Soeters P, Mostert R, Pluymers R, Wouters E** 1995 Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152:1268–1274
35. **Demling R, DeSanti L** 1997 Oxandrolone, an anabolic steroid, significantly increases the rate of weight gain in the recovery phase after major burns. J Trauma 43:47–51
36. **Johansen KL, Mulligan K, Schambelan M** 1999 Anabolic effects of nandrolone decanoate in patients receiving dialysis. JAMA 281:1275–1281
37. **Handelsman D, Liu P** 1998 Androgen therapy in chronic renal failure. Baillieres Clin Endocrinol Metab 12:485–500
38. **Reid I, Wattie D, Evan M, Stapleton J** 1996 Testosterone therapy in glucocorticoid-treated men. Arch Intern Med 156:1173–1177
39. **Horowitz M, Need A, Philcox J, Philcox J, Nordin B** 1984 Effect of calcium supplementation on urinary hydroxyproline in osteoporotic postmenopausal women. Am J Clin Nutr 39:857–859
40. **Ebeling P, Wark J, Yeung S, Poon C, Salehi N, Nicholson G, Kotowicz M** 2001 Effects of calcitriol or calcium on bone mineral density, bone turnover, and fractures in men with primary osteoporosis: a two-year randomized, double blind, double placebo study. J Clin Endocrinol Metab 86:4098–4103
41. **Adachi J, Bensen W, Brown J, Hanley D, Hodsman A, Josse R, Kendler D, Lentle B, Olszynski W, Ste-Marie L, Tenenhouse A, Chines A** 1997 Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 337:382–387
42. **Saag K, Emkey R, Schnitzer T** 1998 Alendronate for the treatment and prevention of glucocorticoid-induced osteoporosis. N Engl J Med 339:292–299
43. **Reid D, Hughes R, Laan R, Sacco-Gibson N, Wenderoth D, Adami S, Eusebio R, Devogelaer J** 2000 Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomised trial. J Bone Miner Res 15:1006–1020
44. **Bergink E, Janssen P, Turpijin E** 1985 Comparison of the receptor binding properties of nandrolone and testosterone under *in vitro* and *in vivo* conditions. J Steroid Biochem 13:259–267
45. **Toth M, Zakar T** 1982 Relative binding affinities of testosterone, 19-nortestosterone and their 5 alpha-reduced derivatives to the androgen receptor and to other androgen binding proteins: a suggested role of 5 alpha-reductive steroid metabolism in the dissociation of 'myotropic' and 'androgenic' activities of 19-nortestosterone. J Steroid Biochem 17:653–660
46. **Lemus A, Enriquez J, Garcia G, Grillasca I, Perez-Palacios G** 1997 5 Alpha-reduction of norethisterone enhances its binding affinity for androgen receptors but diminishes its androgenic potency. J Steroid Biochem Mol Biol 60: 121–129
47. **Van der Vies J** 1985 Implications of basic pharmacology in the therapy with esters of nandrolone. Acta Endocrinol Suppl 271:38–44
48. **Teruel J, Aguilera A, Avila C, Ortuno J** 1996 Effects of androgen therapy on prostatic markers in hemodialyzed patients. Scand J Urol Nephrol 30:129–131
49. **Kumar N, Didolkar A, Monder C, Bardin C, Sundaram K** 1992 The biological activity of 7α-methyl-19-nortestosterone is not amplified in male reproductive tract as is that of testosterone. Endocrinology 130:3677–3683
50. **Cummings D, Kumar N, Bardin C, Sundaram K, Bremner W** 1998 Prostate-sparing effects in primates of the potent androgen 7 alpha-methyl-19-nortestosterone: a potential alternative to testosterone for androgen replacement and male contraception. J Clin Endocrinol Metab 83:4212–4219
51. **Deslypere J, Vermeulen A** 1985 Influence of age on steroid concentration in skin and striated muscle in women and in cardiac muscle and lung tissues in men. J Clin Endocrinol Metab 60:648–653
52. **Colvard D, Eriksen E, Keeting P, Wilson E, Lubahn D, French F, Riggs B, Spelsberg T** 1989 Identification of androgen receptors in normal human osteoblast-like cells. Proc Natl Acad Sci USA 86:854–857
53. **Smith E, Boyd J, Frank G, Takahashi H, Cohen R, Specker B, Williams T, Lubahn D, Korach K** 1994 Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 331:1056–1061
54. **Morishima A, Grumbach M, Simpson E, Fisher C, Qin K** 1995 Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 80:3689–3698
55. **Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J, Korach K, Simpson E** 1997 Effect of testosterone and estradiol in a man with aromatase deficiency. N Engl J Med 337:91–95
56. **Korach K** 1994 Insights from the study of animals lacking functional estrogen receptor. Science 266:1524–1527
57. **Fisher C, Graves K, Parlow A, Simpson E** 1998 Characterisation of mice deficient in aromatase (ArKO) because of targeted disruption of the cyp19 gene. Proc Natl Acad Sci USA 95:6965–6970
58. **Couse J, Korach K** 1999 Estrogen receptor null mice: what have we learned and where will they lead us? Endocr Rev 20:358–417
59. **Vanderschueren D, Van Herck E, Suiker A, Visser W, Schot L, Chung K, Lucas R, Einhorn T, Bouillon R** 1993 Bone and mineral metabolism in the androgen-resistant (testicular feminized) male rat. J Bone Miner Res 8:801–809
60. **Geusens P, Dequeker J** 1986 Long-term effect of nandrolone decanoate, 1a-hydroxyvitamin D_3 or intermittent calcium infusion therapy on bone mineral content, bone remodeling and fracture rate in symptomatic osteoporosis: a double-blind controlled study. Bone Miner 1:347–357
61. **Need A, Nordin B, Chatterton B** 1993 Double-blind placebo-controlled trial of treatment of osteoporosis with the anabolic nandrolone decanoate. Osteoporos Int Suppl 1:S218–S222
62. **Passeri M, Pedrazzoni M, Pioli G, Butturini L, Ruys A, Cortenraad M** 1993 Effects of nandrolone decanoate on bone mass in established osteoporosis. Maturitas 17:211–219
63. **Hamdy R, Moore W, Whalen K, Landy C** 1998 Nandrolone decanoate for men with osteoporosis. Am J Ther 5:89–95
64. **Marin P, Oden B, Bjorntorp P** 1995 Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue *in vivo* in men: effects of androgens. J Clin Endocrinol Metab 80:239–243
65. **Marin P, Krotkiewski M, Bjorntorp P** 1992 Androgen treatment of middle-aged obese men: effects on metabolism, muscle and adipose tissue. Eur J Intern Med 1:329–336
66. **Gold J, High H, Li Y, Michelmore H, Bodsworth N, Finlayson R, Furner V, Allen B, Oliver C** 1996 Safety and efficacy of nandrolone decanoate for treatment of wasting in patients with HIV infection. AIDS 10:745–752
67. **Bizzarro A, Valentini G, Martino G, DaPonte A, De Bellis A, Iacono G** 1987 Influence of testosterone therapy in clinical and immunological features of autoimmune diseases associated with Klinefelter's syndrome. J Clin Endocrinol Metab 64:32–36
68. **Cutolo M, Balleari E, Giusti M, Intra E, Accardo S** 1991 Androgen replacement therapy in male patients with rheumatoid arthritis. Arthritis Rheum 34:1–5