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Despite partial androgen deficiency, the safety and efficacy of androgen therapy in older men remains controversial because controlled studies of testosterone have given equivocal results. Human chorionic gonadotropin (hCG) can be conveniently and infrequently self-administered, and it increases not only circulating testosterone but also estradiol and other testicular steroids. We evaluated the efficacy and safety of 3 months of treatment with se recombinant hCG (r-hCG, Ovidrel) on muscle mass, strength, mobility, and physical activity in ambulant, community-dwelling men more than 60 yr old having partial androgen deficiency (testosterone < 15 nmol/liter, twice). Forty eligible men (mean age, 67 yr; range, 60–85 yr) were randomized to receive r-hCG (5000 IU, 250 μg) or placebo by twice weekly sc self-injection and were studied before treatment, monthly during treatment, and 1 month after treatment. All completed the study, and treatment groups were well matched. r-hCG significantly increased body weight (−1 kg; P < 0.05) and lean body mass (−2 kg; P < 0.001) and reduced fat mass (−1 kg, P < 0.05). However, anthropometric measures of skinfold thickness (biceps, triceps, subscapular, suprailiac) and circumferences (midarm, waist, hip, and mid thigh), including the waist-hip ratio, did not change significantly. Shoulder and knee strength (peak torque), as measured by isokinetic and isometric dynamometry, was not significantly increased, nor was physical activity (accelerometry and Physical Activity Scale for Elderly self-report) or gait and balance (modified Guralnik and Frailty and Injuries Cooperative Studies of Intervention Techniques performance batteries) altered. Total and free testosterone and estradiol were markedly (150%; P < 0.001) and stably increased, whereas LH, FSH, and urea were significantly decreased. Testis volume was significantly decreased (−5 ml; P < 0.05). There were no significant changes in hemoglobin, osteocalcin, or prostate-specific antigen, and the International Prostate Symptom Score did not change. Three men developed nipple tenderness that did not progress to gynecomastia. We conclude that 3 months of treatment with twice weekly r-hCG demonstrates sustained androgenic effects on hormones and muscle mass but has no effect on muscle strength or physical functioning. (J Clin Endocrinol Metab 87: 3125–3135, 2002)

AFTER DECADES OF controversy arising from contradictory cross-sectional data, longitudinal population-based studies now clearly show that in the general male population total testosterone concentrations decline by up to 1% per annum (1, 2). The rate of this decline is modulated by lifetime exposure to concomitant disease (3), and its magnitude depends upon which derived measure of testosterone is used. Furthermore, many features of aging (a reduction in muscle, bone, and brain function resulting in decreased mood and quality of life) occur in tissues that are androgen responsive in younger men (4–6). Whether androgen supplementation is beneficial in older men requires objective testing because aging tissues may not remain androgen responsive, and even the safety of intended physiological replacement needs to be established in a population with a higher background prevalence of potentially androgen-sensitive disease (particularly prostate disease).

Several randomized controlled clinical trials of androgen supplementation in older men have so far reported only marginal benefits (7–14). None thus far have examined recombinant human chorionic gonadotropin (r-hCG). This is particularly interesting, because in some aging men the reduction in serum testosterone is sometimes associated with near normal gonadotropin levels, suggesting that aging is associated with partial hypothalamic-pituitary dysregulation (15–17). In the most important study thus far, testosterone supplementation aiming to replicate androgen exposure in young normal men did not improve either muscular strength or bone density (7, 8). But crucially, benefits were most likely to occur in those with the lowest pretreatment serum total testosterone, regardless of whether this fell within the lower young eugonadal range, thus confirming that baseline serum testosterone can be used to target a group that might be particularly androgen responsive. This crucial observation has been confirmed in studies that have not attempted to replicate androgen exposure in young normal men (18). Whether physiological or supraphysiological administration is used in this target group is not important if there is a proper evaluation of the efficacy and safety of androgen supplementation, as would be done for any xe-
nobiots and therapy. Other studies of fewer men and of shorter duration have shown that testosterone treatment in older men produces only modest and inconsistent benefits for muscle, bone, and mental functioning or quality of life (9, 11–14, 19). Whether any supplementation in an older population can be considered physiological is debatable, given that the reference group is usually a young population.

Systematic reports of the use of hCG in men have been limited to the use of urinary hCG in young men with gonadotropin deficiency (20) or idiopathic infertility (21), middle-aged obese men (22, 23), and men of various ages with Kaposi sarcoma (24). These reports have respectively concluded that urinary hCG can induce spermatogenesis or puberty in gonadotropin-deficient men, but it is not otherwise useful for idiopathic infertility, is not effective in reducing weight using the Simeons protocol, and can cause local regression of Kaposi sarcoma. Although urinary hCG is sporadically used clinically for androgen supplementation in older men (Nieschlag, E., personal communication), we report the first systematic investigation of r-hCG as androgenic supplementation in older men with partial androgen deficiency defined on the basis of two morning serum testosterone concentrations being less than 15 nmol/liter. Such a definition is consistent with previous studies (9, 11–14, 19).

**Subjects and Methods**

**Study design**

The study had a double-blind, placebo-controlled randomized parallel-group study design. Based on our reproducibility studies (25), a sample size of 40 men would have over 90% power to detect a 20% increase in muscle strength. A dose of 250 μg (5000 IU) r-hCG administered twice each week was chosen on the basis of the combined literature that suggests an increase in testosterone from 50% (26–28) to 150% (29–31). All study procedures were approved by the Central Sydney Area Health Service Ethics Committee within the National Health and Medical Research Council Guidelines for Human Experimentation and Good Clinical Practice (32, 33). The primary end-point was muscular strength measured as peak torque (PT) by isokinetic dynamometry in the knee and shoulder joints and by isometric dynamometry in the dominant knee. The primary hypothesis was that r-hCG treatment would increase strength and that this increase in strength would be associated with an improvement in muscular function (gait, balance, mobility, and physical activity). The secondary end-points include evaluation of efficacy and safety effects of r-hCG treatment on body composition, reproductive hormones, hematopoiesis, prostate-specific antigen (PSA), and lower urinary tract symptoms.

**Subjects and treatment**

Generally healthy, ambulatory, and community-dwelling men older than 60 yr of age were recruited if they had a plasma testosterone level no greater than 15 nmol/liter on two separate occasions. Men were excluded due to 1) prostate cancer or disease requiring further treatment; 2) unstable, uncontrolled or severe chronic disease; 3) medical conditions that might interfere with muscle testing; or 4) medication use known to interact with sex steroid action.

**Study procedures**

Volunteers were recruited through public advertisement or referred from primary care physicians. Respondents were provided with an explanation of the study and a written information sheet, and they signed a consent form before screening that was drafted in accordance with the *Declaration of Helsinki*. Standardized medical history, physical examination, and blood samples were obtained at entry (and then monthly while on study). Eligible subjects who satisfied all entry criteria and provided written informed consent were randomly assigned a study number that corresponded with individually numbered drug supplies. To assess the adequacy of blinding, subjects were asked at the end of the treatment period to decide whether they had received active or placebo. The randomization code was not broken until all data were collected and the resulting database was cleaned and locked. Fasting blood samples were taken between 0830 and 1030 h. Participants were asked not to vary their diet or exercise patterns.

Participants were studied twice at baseline before commencing treatment, monthly during the 3-month treatment period, and then 1 month after cessation of treatment. A single observer following a standard protocol that replicated order, timing, and instruction of test procedures performed all study procedures throughout the study period. Treatment consisted of self-administration of sc r-hCG (Ovidrel, Serono Australia, French’s Forrest, Sydney, Australia). At each monthly visit, participants were supplied with vials containing either 250 μg (5000 IU) r-hCG or placebo sufficient until the next visit. Volunteers were taught mixing and injection procedures and were instructed to self-infuse one mixed vial sc on Tuesday and Friday mornings. Injection sites were rotated around the abdomen. A monthly diary was kept noting the date and time, and whether any adverse event (stinging, bruising, or spillage) occurred with each injection. Boxes and diaries were returned at each monthly visit, and medication compliance was based on diary entries and the number of unused vials returned. Adverse events or intercurrent illness and their likely relationship with drug administration were noted at each visit. These were coded while blinded to treatment allocation.

**Assays**

Hormones and biochemical variables were measured as described previously (34–38). Briefly, serum LH [coefficient of variation (CV), 5.0–7.4%], FSH (CV, 3.5–7.4%), total testosterone (CV, 7.8–12.7%), SHBG (CV, 6.1–7.9%), and osteocalcin (CV, 3.9–7.1%) were measured by commercial autoanalyser immunoassays (LH and FSH assayed by Assym, Abbott Laboratories, Abbott Park, IL; total testosterone, SHBG, and osteocalcin assayed by Immulite, Diagnostic Products Corp., Los Angeles, CA). The percentage of unbound testosterone was determined by an in-house centrifugal ultrafiltration assay (CV, 9.6–11.7%) using Centrifree columns (Millipore Corp., Bedford, MA) and tritiated testoster-

-one. Free testosterone was calculated from this percentage being unbound to simultaneously directly measured total testosterone (39). Estradiol was measured from unextracted serum samples using a Delfia assay (Perkin-Elmer Life Sciences, Rokvillie, Australia; CV, 1.2–5.8%). Hormones were measured within the same assay when feasible. Biochemical variables (hemoglobin, urea, creatinine, osteocalcin, and prostate-specific antigen) were measured by routine autoanalyser methods.

**Muscle strength**

Muscle strength was measured as PT estimated from repetitive isokinetic and isometric contractions on a Cybex NORM dynamometer (Cybex, Ronkonkoma, NY). Testing sessions occurred at baseline, at the end of the treatment period, and 1 month after the end of the treatment period. Each testing session evaluated two joints (knee and shoulder) isokinetically in extension and flexion for both dominant and nondominant sides as previously described (14). This was followed by isometric testing that evaluated only the dominant knee, first in extension and then in flexion. The order of testing was standardized: first the dominant shoulder, then the nondominant shoulder; next the nondominant knee, and then the dominant knee were evaluated isokinetically; and last, the dominant knee was tested isometrically. Subjects were positioned comfortably with proper alignment of the limb and dynamometer axes as recommended by the manufacturer. Verbal encouragement and visual reinforcement were provided throughout the testing period and consistently throughout the study. Joints are tested isokinetically through their full range of motion with gravity correction for the effect of limb weight on torque production calculated by proprietary software. For each joint movement, the isokinetic testing comprised five repetitions of submaximal extension-flexion at 90° followed by rest of 1 min, then five maximal repetitions at 90°, rest for 30 sec, and finally five maximal repetitions at 120°. Isometric knee testing consisted of six repetitions of 5-sec duration, each separated by a rest period of 25 sec. The first three repetitions were in extension at 60°, and the last three were in flexion at...
30°. The PT was recorded as the test outcome for isokinetic and isometric contractions.

CV for isokinetic PT measurements (within-observer, between-day) were 3.9–7.6% for knee extension, 6.6–8.6% for knee flexion, 6.1–8.6% for shoulder extension, and 6.6–14.3% for shoulder flexion (25). For isometric knee testing, CV was 6.4–7.4%.

**Functional assessment tests**

Physical functioning was evaluated by functional tests of static and dynamic balance, functional reach, chair rise, and self-selected and fast gait (40, 41). All tests were modified to increase difficulty to minimize possible ceiling effects in a high-functioning population. All timed tests were measured by stopwatch to the nearest 0.1 sec. Participants were asked to wear the same comfortable shoes for each testing session (42). To reduce learning effects, only a single attempt was allowed for balance measurements, and participants were asked not to practice at home.

Static (standing) balance was assessed in three positions, sequentially in order of presumed difficulty. The time each position could be maintained (0–60 sec) was measured. First, the feet were positioned in tandem (Sharpen Romberg) with the dominant foot forward; the second position was standing on one leg (the dominant leg) with eyes opened; and the final position was standing on the dominant leg with eyes closed (40, 41, 43). Due to ceiling effects, only time standing on one leg with eyes closed was analyzed.

Dynamic balance was measured by tandem gait (walking 10 steps heel-to-toe so that the heel of the front foot touches the big toe of the rear foot), with participants instructed to complete the task as quickly but also as accurately as possible. The time taken and the number of steps incorrectly performed heel-to-toe were both recorded (43, 44). The product of these two variables was defined as the composite measure of dynamic balance, and this variable in addition to each individual variable was also analyzed.

Gait was measured in a long corridor with no obstruction for an additional 2 m at either end to reduce the impact of terminal deceleration. Participants were initially asked to walk at their usual pace for 18 m at a self-selected gait speed with no terminal deceleration. The time to walk the first 2.4 m (8 feet) (41) as well as the entire 18 m were both recorded. Two trials were performed, and the average of each was analyzed. In addition, two trials walking 18 m at a maximal speed (without running) were performed, and the fastest trial was analyzed.

Functional reach test was measured (in millimeters) as the maximum of two trials of the maximal horizontal forward reach of the outstretched right arm without losing balance (45). Five-time chair rise was measured (in seconds) as the fastest of two trials of the time to stand up and sit down five times from a standard 43 cm high chair without hand support (41).

Physical activity was determined objectively by accelerometry (TriTrac R3D Ergometer, ZMD Reining Inc., Madison, WI) (46, 47) using the manufacturer’s proprietary software (TriTrac R3D software V6.05) as well as by the Physical Activity Scale of the Elderly (PASE), which relies on a manufacturer’s computer program. The Trac R3D Ergometer, ZMD Reining Inc., Madison, WI) (46, 47) was used for the physical activity scale of the elderly (PASE), a computer program that does not cause fluid retention (54). Using bioelectric impedance analysis, CV for body weight (52). Bioelectric impedance analysis has been successfully used in studies of androgen therapy (12, 14, 53), and testosterone supplementation over a wide dosage range does not cause fluid retention (54). Using bioelectric impedance analysis, CV was 6.4–7.4%.

Statistical analysis

Analysis was performed blinded to the treatment group allocation. Response variables were calculated as the difference from baseline. r-hCG effects on continuous response variables were estimated by the main effects of treatment (1-hCG vs. placebo), time and treatment × time interaction terms in a repeated measures ANOVA model. r-hCG treatment effects were identified from treatment main effects or interactions and reversibility of treatment effects by an appropriate linear contrast. Missing data were not imputed. Where significant missing data were present, analysis of correlated data using generalized estimating equations was also performed (63). Repeated measures analysis of covariance of baseline and changes in testosterone and/or estradiol were performed where appropriate. Gait was normalized for height (64). To further delineate the overall effect of r-hCG on global strength, each of the 18 strength measurements was standardized, then pooled (65). Categorical variables were analyzed by exact contingency table methods. Data were analyzed and graphed by using StataXact version 4 (Cytel Software Corp., Cambridge, MA), SPSS version 10 (SPSS, Inc., Chicago, IL), and SigmaPlot 2000 (SPSS, Inc.). ToxTools version 1.0 (Cytel Software Corp.) was used to perform analyses based on generalized estimating equations. P value less than 0.05 (two-tailed) was considered significant.

**Results**

**Characteristics and disposition of participants**

After receiving initial information, 96 men attended initial screening, during which time a morning serum testosterone level was obtained. Of these, 23 declined further involvement, and 33 were excluded due to: high testosterone level

by subtraction from body weight (52). Bioelectric impedance analysis has been successfully used in studies of androgen therapy (12, 14, 53), and testosterone supplementation over a wide dosage range does not cause fluid retention (54). Using bioelectric impedance analysis, CV was 6.4–7.4%.
(21 men), prostate disease (4 men with prostate cancer and 3 with elevated PSA), unstable medical or psychiatric disease (4 men), and recent androgen use (1 man).

Ultimately, 40 eligible men aged 67.5 ± 0.8 (SEM) yr were recruited by public advertisement (18), by referral (14), or from prior contact with this department (8), with 20 being randomized to each group. Reflecting Australian demographics, these men were predominantly Caucasian (39), born in Australia or New Zealand (36), currently (32) or previously (7) married/de facto, and had retired from active employment (30). All lived in privately owned individual homes, and none required regular home assistance of any kind (from family, friends, or government agencies), indicating a high-functioning population. Groups were well matched for concomitant medical illnesses and medication (Table 1, only common diagnoses and medications are shown). The commonest prescribed medications were angiotensin-converting enzyme inhibitors for the treatment of hypertension, although calcium antagonists, diuretics, and β-blockers were also used.

The treatment groups were well matched by randomization for all response variables (Table 1, not all data shown) except that men in the placebo group had a lower serum urea concentration.

Compliance. Drug dispensed was calculated so as to finish on the morning of the next appointment when subjects were asked to return unused drug and empty drug vials. Compliance was assessed by counting the amount of unused drug in comparison to the subject’s diary. Noncompliance to treatment occurred in less than 1% for all participants and was due to spillage of drug during the injection procedure.

Data and adequacy of blinding. All 40 men completed the study. There were no missing appointments, and the minimal missing data (<1%) arose predominantly from equipment failure. Accelerometry was not performed during the recovery visit in nine men who were unable. For all other variables, missing data were minimal.

Subjects were unable to correctly identify their treatment assignments at the end of the treatment period (only 40% guessed correctly; \( P = 0.26 \)), confirming adequate blinding.

### TABLE 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>( \text{r-hCGn = 20} ) (mean ± SEM or number)</th>
<th>( \text{Placebo = 20} ) (mean ± SEM or number)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>68.7 ± 1.3</td>
<td>66.3 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176 ± 2</td>
<td>174 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.6 ± 2.8</td>
<td>82.0 ± 3.6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 ± 0.7</td>
<td>27.2 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Physical functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-paced walking speed (m/sec)</td>
<td>0.7 ± 0.0</td>
<td>0.7 ± 0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Physical activity (kcal/h)</td>
<td>102 ± 4</td>
<td>106 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Body composition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.98 ± 0.01</td>
<td>0.96 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Midthigh skinfold thickness (mm)</td>
<td>14.7 ± 1.0</td>
<td>15.1 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
<td>60.8 ± 2.2</td>
<td>61.1 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>23.2 ± 1.5</td>
<td>24.3 ± 2.2</td>
<td>NS</td>
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<tr>
<td><strong>Ultrasound</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Testis volume (ml)</td>
<td>13.7 ± 0.8</td>
<td>12.3 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td>37.5 ± 3.1</td>
<td>42.8 ± 4.1</td>
<td>NS</td>
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<tr>
<td><strong>Hormones</strong></td>
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<td></td>
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</tr>
<tr>
<td>Total testosterone (nmol/liter)</td>
<td>11.1 ± 0.5</td>
<td>11.8 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Free testosterone (pmol/liter)</td>
<td>173 ± 12</td>
<td>186 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>LH (IU/liter)</td>
<td>5.3 ± 1.0</td>
<td>5.7 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>FSH (IU/liter)</td>
<td>9.3 ± 2.5</td>
<td>9.8 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>SHBG (nmol/liter)</td>
<td>35.4 ± 2.7</td>
<td>29.4 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol (pmol/liter)</td>
<td>127 ± 5</td>
<td>125 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA (µg/liter)</td>
<td>1.9 ± 0.4</td>
<td>2.0 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Osteocalcin (µg/liter)</td>
<td>0.8 ± 0.2</td>
<td>0.7 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/liter)</td>
<td>44 ± 1</td>
<td>44 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Urea (mmol/liter)</td>
<td>7.0 ± 0.4</td>
<td>6.1 ± 0.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**NS**, Not significant; BMI, body mass index; ACE, angiotensin-converting enzyme; HMG CoA, hydroxy-3-methylglutaryl coenzyme A; NSAID, nonsteroid anti-inflammatory drug.
Hormonal and biochemical effects

Hormones. r-hCG treatment produced a marked increase in plasma total and free testosterone and estradiol. LH and FSH were markedly suppressed (Fig. 1). Because our young reference range for serum testosterone is 11.0–35.0 nmol/liter, two subjects had single serum testosterone levels above that limit (one being 37.8 nmol/liter, and the other 47.0 nmol/liter); however, even in these two men, the remaining testosterone determinations were all within the young reference range. Estradiol was raised above our young reference range (80–180 pmol/liter) in all but one man treated with r-hCG. All hormonal changes had returned to baseline by 1 month after cessation of treatment. There was no significant treatment effect on SHBG (Fig. 1) or osteocalcin (Fig. 2). Figure 3 illustrates the same steroidal response data according to time since the last r-hCG injection, confirming stable pharmacological response.

Biochemistry and hematology. Hemoglobin was unchanged by r-hCG treatment, and no participant became polycythemic. r-hCG resulted in a significant fall in albumin and urea (Fig. 2) but had no significant effect on creatinine (data not shown).

There were no significant differences in any biochemical or hormonal findings using either baseline total or free testosterone or estradiol as covariates.

Efficacy parameters

Muscle strength. PT developed during isokinetic dynamometry (knee and shoulder, extension and flexion, dominant and nondominant limb) and isometric dynamometry (dominant knee) increased with time, but not differently between the treatment and placebo groups, consistent with a practice effect (Fig. 4). Significant treatment × time interactions were observed in both isokinetic nondominant knee extension measurements, consistent with greater reduction in strength into the recovery period for the treatment group, but not for any other measure (data not shown). The mean pooled effect size was 0.17 (95% confidence interval, 0.02–0.32) sd units, which corresponds to a mean relative increase in overall strength due to treatment of approximately 3%. Re-analysis of the data according to the baseline testosterone concentration as covariate did not alter the findings.

Reflecting the measurement reproducibility, the power of this study was greater for knee (than shoulder) and extension (than flexion). It was 91–93% to exclude a 20% increase, and 72–96% to exclude a 15% increase, in knee contractions; it was 72–96% to exclude a 20% increase, and 31–82% to exclude a 15% increase, for shoulder contractions. Assuming a treatment effect size of 3%, a sample size of over 1000 subjects would have approximately a 70% power to detect this difference.

Functional tests. There were no significant changes in maximal reach, static or dynamic balance, gait, or chair rise (Fig. 5). Using height-normalized gait did not alter the results (data not shown). The Frailty and Injuries: Cooperative Studies of Intervention Techniques version 4 (40) composite global measure of overall function could not be meaningfully analyzed because only four people failed to reach the maximum score. The results of the self-selected walk, dynamic balance, and chair rise were significantly improved over time (data not shown) but equally in both groups, consistent with a training effect. No time effect was seen in functional reach, tests of static balance, or fast walk.

There was no significant effect on physical activity measured objectively by accelerometry or by self-reported PASE questionnaire (Fig. 5).

Anthropometric measures. During treatment, r-hCG significantly increased weight and lean mass (determined by bioimpedance and calculated anthropometrically) (Fig. 6). Cal-
culated fat mass fell significantly (bioimpedance) with a similar nonsignificant trend detected anthropometrically (Siri equation). Midthigh skinfold thickness fell (Fig. 6, treatment × time interaction; \( P < 0.02 \)), with similar nonsignificant trends in all other skinfold thicknesses. No effect on any circumferences or waist/hip ratio was detected (data not shown). There were no significant differences in findings using either baseline testosterone or testosterone plus r-hCG as covariates.

Sexual function. No significant r-hCG effect was seen on sexual activity during treatment. Sexual activity was increased in 12 (5 r-hCG, 7 placebo), unchanged in 27 (15 r-hCG, 12 placebo), and decreased in 1 (placebo) man (\( P = 0.50 \), extended exact Fisher’s test). No significant r-hCG effect was seen on sexual activity 1 month after ceasing treatment. Sexual activity was not increased in any man, was unchanged in 5 (3 r-hCG, 2 placebo) and decreased in 35 (17 r-hCG, 18 placebo) men (\( P = 0.50 \), extended exact Fisher’s test).

Safety parameters

Testicular volume. Three months of r-hCG treatment significantly reduced testicular volume measured ultrasonographically (\( P = 0.003 \)). Similar trends were seen by Prader orchidometer, but these results did not reach statistical significance (\( P = 0.06 \)). Testicular volume had not returned to baseline 1 month after the end of treatment (Fig. 2).

![Fig. 2. Plot of changes in fasting biochemical, prostate, and testis volume variables before, during, and after twice weekly sc injection of 250 µg (5000 IU) r-hCG for 3 months. Note significant decrease in testis volume, albumin, and urea but no consistent changes in prostate variables or hemoglobin. Data are plotted as mean and SEM of differences from each individual’s own baseline. In some instances the error bar is smaller than the data point symbol. Dashed lines indicate no change from baseline. Significant differences between the treatment (black circles) and placebo (white circles) groups are indicated by the asterisk that appears next to the variable name. For more details, see text.](image)

![Fig. 3. Plot of changes in serum hormone concentrations among 60 serum samples (3 samples from each of 20 men who received r-hCG) collected after r-hCG injections according to days since last injection. Data are plotted as mean and SEM of differences from each individual’s own baseline. n, Number of samples at each time point.](image)
Blood pressure and pulse. No significant difference in systolic or diastolic blood pressure, pulse, or pulse pressure was detected between the two treatments at any stage during the study period (data not shown).

Prostate symptoms. Lower urinary tract symptoms measured by the International Prostate Symptom Score did not differ between the two treatment groups throughout the study period (Fig. 2).

PSA. Plasma PSA levels of the two treatment groups were not different during the study period and did not significantly change with time (Fig. 2).

Adverse events. The number of adverse events was not different between treatment groups overall; nor was it different when subjects were grouped according to severity or by likelihood of association with treatment. The only serious adverse event was injection related. However, less than 3% of all visits. Approximately half of these were due to infection (upper respiratory tract infections or diarrheal illnesses), with another one third being musculoskeletal.

Discussion

r-hCG has theoretical advantages over existing steroidal preparations for use as androgenic supplementation in older men. First, it may be conveniently self-administered as a twice-weekly subcutaneous injection with minimal discomfort compared with implant oil-based steroids. Second, intermediary steroids, in addition to testosterone and estradiol, are also increased because overall steroidogenesis is promoted, which may possibly result in additional direct or indirect effects (as prohormones). In addition, direct effects mediated by the LH receptor (66) are possible. Finally, safety may be superior because the risk of overdosage is limited by Leydig cell capacity (31) and reversal is rapid upon drug cessation, which is advantageous in an older population where disease (such as prostate cancer) can supervene and contraindicate further androgen use.

Nevertheless, the available comparable randomized placebo-controlled prospective studies of androgenic supplementation in older men have generally used steroids, particularly testosterone or dihydrotestosterone (14). All of the larger/longer studies of at least 100 patient months duration have consistently described an increase in lean body mass and/or a reduction in fat mass (7–10, 12–14) with one exception (11). Our data confirms an increase in lean mass. A reduction in fat mass was also seen, particularly at the mid thigh but not elsewhere, suggesting an overall reduction in abdominal fat that was not, however, confirmed by a reduction in waist circumference. Which effects are mediated by further potentiation of 5α-reduction into dihydrotestosterone or via aromatization into estradiol in certain tissues has not been determined.

Despite an increase in lean mass, no significant r-hCG effect on proximal upper or lower limb strength was detected, although there was a definite practice effect. Studies that do not include a control group (67) or lack proper blinding with matched placebo (11, 19) cannot exclude a practice effect or effort-related effect. Using these criteria, none of the available studies have shown a clear increase in muscle strength, whether measured using isometric handgrip strength or via more sophisticated dynamometry (8, 12–14). It appears that the increase in overall lean mass is insufficient to cause a detectable increase in regional muscle strength, because no significant r-hCG effect was detected despite comprehensive assessment of regional strength that may differ (68) using isokinetic and isometric dynamometry. This is consistent with the most important of the published studies, incorporating almost the same number of patient months duration as all the other studies combined, which showed that 3 yr of transdermal testosterone did not significantly increase muscle strength (or bone density) compared with placebo (7, 8). To better delineate the effect size, we obtained a pooled estimate of a 3% increase in overall muscle strength. Such a small effect size is consistent with our data, and the literature and would require a large sample of over 1000 subjects to detect this difference.

Similarly, apart from some significant time-related (learn-


In some instances, the error bar is smaller than the data point symbol. Significant differences between the treatment (black circles) and placebo (white circles) groups are indicated by the asterisk that appears next to the variable name. Dashed lines indicate no change from baseline. For more details, see text.

Fig. 5. Plot of changes in physical activity, physical function, balance, and gait before, during, and after twice weekly sc injection of 250 μg (5000 IU) r-hCG for 3 months. No changes are significant. Data are plotted as mean and SEM of differences from each individual's own baseline. In some instances, the error bar is smaller than the data point symbol. Significant differences between the treatment (black circles) and placebo (white circles) groups are indicated by the asterisk that appears next to the variable name. Dashed lines indicate no change from baseline. For more details, see text.

Although we recruited partly through primary care physicians, the resultant population was still high functioning because all subjects lived in the community, none required home support services, all but four achieved the maximum Frailty and Injuries: Cooperative Studies of Intervention Techniques version 4 score, and baseline self-paced walking speed was brisk (64, 69). Either physical performance cannot be further improved in such a high-functioning population (70, 71), the testing performed was insensitive to subtle functional improvements, or treatment is more effective in a more disabled population (70). Although these scales lack sensitivity due to inherent variability in volunteer motivation and effort, they can predict short-term mortality and nursing home placement (41) as well as disability in activities of daily living or mobility (72) in low-functioning populations. Furthermore, improvements in these scores are associated with reduced falls and moderate injuries (73) in randomized controlled interventional studies. It therefore seems likely that androgen supplementation will have only minor effects on gait and balance in a high-functioning population because strength is a major determinant (71, 74), and detection will require larger sample sizes (12) or synergistic interventions to increase the effect size. Further investigation targeting more disabled populations (70) in whom even small improvements may have functionally important effects is warranted.

In this study, twice weekly sc injections of 250 μg (5000 IU) r-hCG for 3 months produced expected hormonal changes of increased serum total and free testosterone and estradiol with negative feedback suppression of gonadotropins (LH, FSH). These changes were fully reversed 1 month after cessation of treatment. Estradiol was increased above the young reference range in all but one man treated with r-hCG, and three men complained of nipple tenderness that may have possibly progressed to gynecomastia with time, but was not present after 3 months. Importantly, this study confirms that medium-duration therapy with r-hCG can have sustained effects on steroidogenesis, indicating that older men retain sustained testicular responsiveness. Previous studies have
all been less than 1 wk in treatment duration, however the magnitude of our observed effects (a 150% increase of all measured steroids) is consistent with these acute studies (26–31). The magnitude of our observed effects (a 150% increase of all measured steroids) is consistent with those short-term studies that also recruited older men with lower serum total testosterone (29–31). However, in those studies that tended to recruit older men with higher serum total testosterone levels, only a 50% increase in steroids was observed (26–28). Although the stable pharmacological response to twice weekly sc r-hCG may be related to the biphasic response of testosterone to hCG (29), these short-term studies suggest that less frequent dose administration is unlikely to be possible, although dose titration may be feasible.

Treatment-related reductions in albumin and urea were detected, and similar changes have previously been described in eugonadal young men (75). The effect was small and not clinically important. Biochemical markers of bone turnover were unchanged, but longer studies would be required to determine the net effects of r-hCG on bone mass and fracture rates in older men. Unlike previous studies using testosterone (7, 18), there was no consistent effect of baseline testosterone on any outcome in this study. Nor did inclusion of baseline estradiol or change in testosterone or estradiol alter any finding.

r-hCG had no effect on sexual activity, and this lack of effect is consistent with the observation that young androgen-deficient men maintain libido except in the presence of marked androgen deficiency (5) and that sexual function in older men is not fully accounted for by hormonal factors (76). However, the use of a clinically meaningful composite measure that encompasses both libidinal and functional aspects, cannot fully exclude a purely libidinal effect. Testicular volume was reduced by r-hCG presumably due to the suppression of endogenous FSH resulting in a reduction in volume due to inhibition of spermatogenesis. Volumes had not returned to baseline 1 month after the cessation of therapy, and this is consistent with male hormonal contraceptive studies in young men in whom up to 6 months duration may be required before testicular volume returns to normal (77). This has not previously been documented and confirms that the aging testis remains structurally responsive to hormonal manipulation.

Any impact upon fertility arising from a r-hCG effect on spermatogenesis is speculative because semen analysis was not examined. However, a significant effect on fertility arising from changes in sexual activity was excluded. Even if spermatogenesis was impaired by r-hCG, this effect may be inconsequential if the female partner is postmenopausal or even beneficial in a population desiring contraception after the completion of progenitive desires. In any case, any effect is likely to be reversible (77).

There was no difference in the number or severity of clinical (polycythemia, sleep, lower urinary tract symptoms, blood pressure, pulse) or biochemical (hemoglobin, PSA) adverse events between r-hCG and placebo treatment groups. The lack of adverse effects on sleep and polycythemia could be due to the more stable pharmacological steroid response compared with injectable im steroid preparations with unfavorable pharmacokinetics featuring supraphysiological serum testosterone concentrations (78) or possibly due to a modulating effect of estradiol.

We conclude that 3 months of treatment with sc r-hCG at a relatively high dose demonstrates stable pharmacological features with consistent negative feedback effects on pituitary-testicular axis. Favorable body compositional effects were seen, but minimal effects on muscle strength, physical activity, or function were observed. The short-term prostatic safety of r-hCG in older men was supported by the lack of increase in PSA or lower urinary tract symptoms. Future studies should consider lower doses of r-hCG and combination with other synergistic interventions.
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