Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women\textsuperscript{1-3}

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ABSTRACT

Background: In older people, undernutrition is associated with increased hospitalization rates and mortality. Because weight loss in older people often reflects a disproportionate reduction of skeletal muscle, anabolic treatments may be beneficial.

Objective: Our aim was to evaluate the hypothesis that testosterone treatment and a nutritional supplement have additive benefits.

Design: Oral testosterone undecanoate (40 mg daily for women, 80 mg twice daily for men) and an oral nutritional supplement (475 kcal/d) were administered, alone or combined, for 1 to 49 community-dwelling, undernourished people [Mini Nutritional Assessment score <24 and low body weight (body mass index, in kg/m\(^2\): <22) or recent weight loss (>7.5% over 3 mo) aged >65 y (mean age: 77 y; 26 women and 23 men). Hospital admissions and other variables were assessed.

Results: In subjects receiving combined testosterone and nutritional supplements (\(n = 11\)), there were no hospital admissions, whereas there were 9 admissions (2 elective) in 13 subjects in the no-treatment group, 4 in the testosterone-treated group (\(n = 12\)), and 5 in the supplement-treated group (\(n = 13\)); \(P = 0.06\) with no-treatment compared with combined treatment. When compared with the no-treatment group, the combined-treatment group had significantly fewer subjects admitted to hospital (0 compared with 5, \(P = 0.03\)), fewer days in hospital (0 compared with 74, \(P = 0.041\)), and a longer time to hospital admission (\(P = 0.017\)).

Conclusions: In undernourished older people, combined treatment with testosterone and nutritional supplementation reduced the number of people hospitalized and the duration of hospital admissions, which are important endpoints in this group. Larger, confirmatory studies are now needed. This trial was registered before commencement at clinicaltrials.gov as NCT00117000. Am J Clin Nutr 2009;89:880–9.

INTRODUCTION

Aging is associated with a physiologic reduction of appetite and food intake (1, 2). Mean body weight decreases after \(\sim 60\) y (3, 4), which is largely due to muscle loss (5). When severe, muscle loss results in sarcopenia (6, 7), which is associated with an increased risk of falls, disability, and mortality (8–11). The combination of muscle loss and reduced food intake predisposes older people to undernutrition, which occurs in up to 10–15% of community-dwelling older people and in many more nursing home residents (2). Low body weight (13) and weight loss, particularly if involuntary, are major markers of harmful undernutrition in older people (12, 14).

Hospitalization is common in older people and imposes major burdens on both the individual and the community. Hospitalizations constitute a substantial part of undernutrition-related morbidity in older people. We have reported that 45% of undernourished, community-dwelling older people were hospitalized in 1 y, which is significantly more than in well-nourished controls, with a 3-fold higher rate of hospitalization for >1 mo (15).

Meta-analyses indicate that nutritional supplements can reduce mortality in selected undernourished older people (16). There is little evidence of other functional benefits (17). Administration of testosterone has been shown to increase muscle strength and, inconsistently, function and quality of life in older people (18–20). Longer-term testosterone administration to older people has produced only minor functional benefits and perhaps only in men with testosterone deficiency (20). To our knowledge, the effects of androgen administration or nutritional supplementation on hospital admission rates in older people have not been reported. Frail undernourished older people, with their associated sarcopenia, may have more to gain from such anabolic treatments, particularly when administered in combination.

This study was conducted to determine the effects, particularly on hospital admissions, of a nutritional supplement and testosterone, alone and combined, in undernourished older people.

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SUBJECTS AND METHODS

Subjects

Undernourished men and women, aged ≥65 y and living independently in the community, were recruited by advertisement between February 2003 and February 2006. Undernutrition was defined by a Mini Nutritional Assessment (MNA) score of <24 of 30 (21) (<17: malnourished; 17–23: at risk for malnutrition) and a body mass index (in kg/m²) of <22 or a self-reported weight loss of ≥7.5% in the 3 mo before enrolling in the study (Figure 1).

Exclusion criteria were as follows: the inability to comply with the protocol; increased risk of cognitive impairment [Folstein’s Mini Mental State Examination score ≤23 (22)]; elevated hematocrit (>50%); history of prostate cancer, prostate-specific antigen (PSA) concentrations greater than the age-related normal range, or an irregular prostate on examination; breast cancer; preexisting androgenic signs or symptoms of concern (deep voice, hirsutism, acne, or androgenic hair loss) in women; risk of depression [Yesavage Geriatric Depression Scale score >11 (23)]; cardiac failure corresponding to New York Heart Association class III and above; abnormal liver function tests (alanine aminotransferase, γ-glutamyltransferase, bilirubin, or alkaline phosphatase >2 times the upper limit of normal; serum creatinine >0.2 mmol/L); any disease that, in the opinion of the investigator, was likely to lead to death within 1 y; and testosterone or other androgen therapy within 4 mo of starting the study. Women had to be off or on a stable dose of estrogen or other hormone replacement therapy for at least 3 mo before starting the study. This treatment was not changed during the study.

The study was approved by the Ethics Committee of the Royal Adelaide Hospital. All subjects gave written informed consent. Subjects were able to withdraw from the study at any time.

Study design

At baseline subjects underwent a physical examination and measurement of the following: fasting blood for glucose, hematocrit, PSA, electrolytes, liver function, testosterone, sex hormone binding globulin (SHBG), free androgen index [FAL: (testosterone/SHBG) × 100], all measured by routine assays at the Institute of Medical and Veterinary Science, Adelaide, Australia; and C-reactive protein (CRP) with standard enzymatic kits (Roche, Indianapolis, IN). In addition, the following were assessed; Mini Mental State Examination score (22), geriatric depression score (23), Fried frailty score (24), the 36-Item Short Form-36 Health Survey (SF-36) (25), a “retrospective falls” diary for the previous 3 mo, 24-h food recall, record of hospital admissions over the previous year, whole-body fat and lean mass by dual-energy X-ray absorptiometry (Norland Densitometer XR36; Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, Australia), strength by using a hand dynamometer (Stoelting Hand Grip Dynamometer; Stoelting Co, Wood Dale, IL), and International Prostate Symptom Score (26).

Subjects were told that they had been assessed as undernourished and were given advice on increasing their energy intake. They were advised to eat 3 full meals/d and given specific recommendations on what to eat (eg, ≥2 servings of fruits or vegetables/d) on the basis of their responses to the MNA questionnaire. This constituted “standard care.” The subject’s general practitioner was notified of their participation in the study.

Subjects were randomly assigned to 1 of 4 groups by using a stratification system to ensure a close to equal ratio of “at-risk of malnutrition” (MNA score: 17–23.5) to “malnourished” (MNA score: <17) subjects and of men to women in the 4 treatment groups. The treatment groups were as follows:

No treatment (NT): standard care + placebo testosterone capsule
Testosterone (T): standard care + oral testosterone undecanoate [Andriol Testocaps (Organon Ltd, Oss, Netherlands) 40-mg capsules: 40 mg orally once a day in women, 80 mg orally twice a day in men]
Supplement (SUP): standard care + placebo testosterone + nutritional supplement [237 ml/d Nova Source 2 (Novartis Pharmaceuticals, North Ryde, Australia; 475 kcal, 18% protein, 43% carbohydrate, 39% fat, and orange or vanilla flavor)]
Combined-treatment (COM): standard care + testosterone undecanoate + nutritional supplement

Andriol and placebo capsules were provided by Organon Ltd, and Nova Source was purchased from Novartis Ltd. There was no placebo nutritional supplement drink. Subjects were advised to take their testosterone/placebo tablets with meals and the nutritional supplement several hours after a meal in divided doses if desired.

Subjects were provided with phone numbers to inform the investigators of any hospitalization. At home visits and phone contacts, subjects were asked to provide details of any hospitalization. The protocol was continued during, and after, any hospitalization if this did not result in adverse effects or interfere with any medical treatment. Subjects were visited at home at 3, 6, and 12 mo for measurements of weight, anthropometry, and grip strength and at 1, 2, 3, 4, 5, 6, 8, 10, and 12 mo for assessment of dietary and medication compliance (tablet and empty packet count) and documentation of any change in medical conditions, medications, living arrangements, or hospitalizations. Details of hospital admissions were obtained from the subject and, with their written permission, from their general practitioner. Where possible, hospital records, including copies of discharge letters, were obtained. Compliance was reinforced and assessed by phone calls every 2 wk for the first 6 mo and then every 4 wk. The occurrence of any adverse events was actively sought during these calls and visits. PSA, hematocrit, electrolytes, glucose, CRP, and androgen blood tests were repeated at 3 (hematocrit and PSA only), 6, and 12 mo. The frailty, SF-36, and MNA measures were repeated at 6 mo. At the end of the study all measures were repeated.

Study drug dose adjustment

The study drug dose was halved to one tablet twice a day in men and to one tablet on alternate days in women if either of the following occurred (confirmed by repeat test): hematocrit >54% and PSA >10% above the upper end of the age-related normal range. The test was repeated in 6 wk for subjects with these abnormal results. If the value had normalized, the subject continued the halved dose. If the result remained elevated, the study medication was ceased permanently (the abnormal value was re-measured 6 wk later and after that according to the study schedule) and the subject continued in the nutritional supplement arm of the study. Women who developed androgenic side effects had the option of stopping the drug or halving the dose. If the dose was halved, the full dose was not reinstituted later and the subject had the option of stopping the study drug at a later time.
Statistical analyses

The primary endpoints were hospital admissions and SF-36 quality of life scores. Secondary endpoints were measures of body composition, muscle strength, falls, frailty score, walk time, and mortality. We aimed to recruit 200 subjects, the number needed for a 48% reduction in hospital admissions with treatment to achieve significance, according to power calculations based on our previous study (15). Recruitment was slower than anticipated and was stopped early due to exhaustion of funds and time. All analyses were performed according to the intention-to-treat principle. The distribution of the number of hospitalizations in each group was compared by using Fisher’s exact test. Times to admission were analyzed by using the Cox proportional hazards regression with account taken of within-subject correlation for subjects with multiple admissions; tests were based on a grouped jackknife variance estimator. The numbers of days spent in hospital were compared by using Mann-Whitney tests (R statistical software; R Foundation for Statistical Computing, Vienna, Austria). Other data were analyzed with a linear mixed model by using residual maximum likelihood and including all available time points (GenStat 10th edition; VSN International Ltd, Hemel Hempstead, UK). A \( P \) value < 0.05 was considered statistically significant.

RESULTS

Two hundred eighty-one people were screened and 49 were recruited. Their characteristics are summarized in Table 1. There were no significant differences among the subjects allocated to the 4 treatment groups in any characteristic, including the number (\( P = 0.83 \)) and duration (\( P = 0.84 \)) of hospital admissions in the year before the study.

Hospital admissions

Hospital admissions are detailed in Tables 2 and 3. Thirteen subjects (26.5%; 7 men and 6 women), had 18 hospital
admissions, with no subject admitted more than twice. All admissions were nonelective except 2 admissions for one man in the no-treatment group for replacement of each hip. Results were analyzed with and without these elective admissions.

The number of hospitalizations was greatest in the NT group (9 with and 7 without elective admissions), the least (zero) in the COM group, and intermediate in the T (4) and SUP (5) groups (P = 0.06: number of hospitalizations of NT compared with COM groups). Fewer subjects in the COM group were hospitalized than in the NT group (all admissions: 5 compared with 0 subjects, P = 0.03; nonelective admissions: 4 compared with 0, P = 0.07). There were significant differences among groups in the distribution of the number of all hospitalizations (P = 0.03), with the reduction in admission number in the COM compared
with the NT group just failing to achieve statistical significance ($P = 0.06$). For nonelective hospitalizations, the differences among groups were nearly significant ($P = 0.08$).

The SUP group spent the most days in hospital and the COM group the fewest. The COM group spent fewer days in hospital than the NT group (0 compared with 71 d, $P = 0.041$ with elective admissions; 0 compared with 48 d, $P = 0.098$ without elective admissions) with no other significant differences between groups.

The mean time to admission for the NT group was 3.9 and 3.8 mo for those with nonelective admissions and all admissions, respectively. The equivalent time for the SUP and T groups was 2.7 and 6.7 mo, respectively. Survival analysis showed a significant difference between the NT and COM groups ($P = 0.038$ for nonelective admissions and $P = 0.017$ for all admissions).

**Quality of life measures**

There was no significant effect of any treatment on the SF-36 mental scores (Table 4). SF-36 physical scale scores increased more from baseline to 12 mo in the combined-treatment group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>All hospital admissions</th>
<th>Nonelective hospital admissions</th>
<th>Total days in hospital—all admissions</th>
<th>Total days in hospital—nonelective admissions</th>
<th>Total days in hospital—nonelective admissions</th>
<th>Total days in hospital—nonelective admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>9 [1 × 1; 4 × 2]</td>
<td>7 [1 × 1; 3 × 2]</td>
<td>71 (0–36)</td>
<td>90 (0–42)</td>
<td>90 (0–42)</td>
<td>90 (0–42)</td>
</tr>
<tr>
<td>(n = 13)</td>
<td>(2 men, 3 women)</td>
<td>(1 man, 3 women)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplement</td>
<td>5 [3 × 1; 1 × 2]</td>
<td>0.27</td>
<td>5</td>
<td>0.43</td>
<td>11 (0–4)</td>
<td>11 (0–4)</td>
</tr>
<tr>
<td>(n = 13)</td>
<td>(3 men, 1 woman)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>4 [4 × 1; 0 × 2]</td>
<td>0.08</td>
<td>4</td>
<td>0.10</td>
<td>0.49</td>
<td>0.83</td>
</tr>
<tr>
<td>(n = 12)</td>
<td>(2 men, 2 women)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined treatment</td>
<td>0</td>
<td>0.06</td>
<td>0</td>
<td>0.15</td>
<td>0.041</td>
<td>0.098</td>
</tr>
</tbody>
</table>

$^{1}$ Distribution of number of hospitalizations was compared by using Fisher’s exact test. Numbers of days in hospital were compared by using Mann-Whitney tests.

$^{2}$ Distributions are shown in brackets.

$^{3}$ Ranges per subject are shown in parentheses.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Reason for admission/duration</th>
<th>Time of admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Hip replacement (11)</td>
<td>0.5</td>
</tr>
<tr>
<td>Male</td>
<td>Hip replacement (12)</td>
<td>7.3</td>
</tr>
<tr>
<td>Male</td>
<td>Lethargy/weakness (4)</td>
<td>8.1</td>
</tr>
<tr>
<td>Male</td>
<td>Suicide attempt (33)</td>
<td>10.4</td>
</tr>
<tr>
<td>Female</td>
<td>Exacerbation COAD (2)</td>
<td>5.2</td>
</tr>
<tr>
<td>Female</td>
<td>CVA (5)</td>
<td>3.6</td>
</tr>
<tr>
<td>Female</td>
<td>Anxiety/situational crisis (1)</td>
<td>3.9</td>
</tr>
<tr>
<td>Female</td>
<td>Lower gastrointestinal bleed (4)</td>
<td>7.0</td>
</tr>
<tr>
<td>Female</td>
<td>Colonoscopy/gastrointestinal tests (2)</td>
<td>7.7</td>
</tr>
</tbody>
</table>

| Supplement-treated group |                               |                   |
| Male            | Spinal surgery for acute pain (42) | 8.0               |
| Male            | Pulmonary aspergillosis (27)     | 0.6               |
| Male            | Myocardial infarction (12)       | 3.5               |
| Male            | Ischemic chest pain (7)          | 4.6               |
| Female          | Exacerbation of COAD (3)         | 0.4               |

| Testosterone-treated group |                               |                   |
| Male            | Gout (3)                        | 6.2               |
| Male            | Shoulder effusion (1)           | 11.4              |
| Female          | Exacerbation of COAD (5)        | 2.3               |
| Female          | Motor vehicle accident (4)      | 6.8               |

| Combined-treatment group |                               |                   |
| No admissions          |                               |                   |

$^{1}$ CVA, cerebrovascular accident; COAD, chronic obstructive airways disease.

$^{2}$ Number of days is shown in parentheses.

$^{3}$ Results were analyzed with and without these 2 elective admissions.

$^{4}$ Onset of pain occurred during the study period.
than in other groups, but this difference was not significant. SF-36 physical scores were higher in subjects on testosterone than in subjects not on testosterone at 6 mo (46.6 ± 1.67 compared with 41.8 ± 1.87), but not at 12 mo (44.5 ± 1.67 compared with 45.2 ± 2.07, P = 0.017, time × testosterone interaction; no other interactions significant).

### Secondary endpoints

#### Body weight and composition

Body weight increased in both men and women in all treatment groups. Overall, weight increased 3.1 ± 0.57 kg (~6%) from baseline to 12 mo (P < 0.001) because of an increase in absolute fat mass (P < 0.001) without a change in lean tissue mass (P = 0.74; Table 4). The weight increase was greater in subjects receiving the nutritional supplement than in those not (4.2 ± 0.94 compared with 1.8 ± 0.46 kg, P = 0.012), whereas those receiving testosterone gained nonsignificantly less weight than those not receiving testosterone (2.5 ± 0.67 compared with 3.8 ± 0.91 kg, P = 0.46). There was no interaction between the effects of the 2 treatments (P = 0.88).

Percentage of body fat increased in all groups, except in the men treated with testosterone alone (decreased 1.2%). There was a greater increase in percentage of body fat in those taking the supplement than in those not taking it (+4.9 ± 1.24% compared with +1.1 ± 0.02% P = 0.027) and a nonsignificantly smaller increase in those receiving testosterone than in those not receiving it (+2.1 ± 1.24% compared with +4.1 ± 1.14%, P = 0.27), with no interaction between the effects of the 2 treatments (P = 0.82). Percentage of lean tissue decreased in all groups, except in subjects taking testosterone alone (+1.1%). Percentage of lean tissue decreased more in subjects receiving the supplement than in those not receiving it (~4 ± 1.19% compared with −0.8 ± 1.13%; P = 0.052). There was a nonsignificant trend for a smaller reduction in subjects receiving testosterone than in subjects not receiving it (~0.9 ± 1.23% compared with −3.9 ± 1.08%; P = 0.094), with no interaction between the effects of the 2 treatments (P = 0.684).
**Muscle strength**

Grip strength increased with the supplement treatment (+1.56 ± 0.85 kg compared with −0.32 ± 0.77 kg; \( P = 0.029 \)) but was not affected by testosterone (+0.65 ± 0.83 kg compared with +0.3 ± 0.89 kg; \( P = 0.73 \)). These effects were different in men and women. Grip strength increased more in men on the supplement (+2.5 ± 1.39 kg on the supplement compared with −1.6 ± 0.91 kg off the supplement) than it did in women (+0.66 ± 1.0 kg on the supplement compared with +0.98 ± 1.14 kg off the supplement; sex × supplement interaction; \( P = 0.015 \)), whereas it increased more in women on testosterone (+1.77 ± 1.23 kg on testosterone compared with −0.13 ± 0.79 kg off testosterone) than it did in men (−0.93 ± 1.21 kg compared with +1.8 ± 1.45 kg; sex × testosterone interaction; \( P = 0.011 \)). There was no interaction between the effects of the 2 treatments.

**Frailty scale scores, walk time, and falls**

Fried frailty scores were higher throughout the study in women than in men (1.0 ± 0.1 compared with 0.7 ± 0.1; \( P = 0.046 \)) and decreased, indicating a reduction in frailty, during the study in both men and women in all 4 treatment groups (1.1 ± 0.15 baseline to 0.69 ± 0.12 at 12 mo; \( P = 0.007 \)), with no difference between the effects of the treatments or interactions between treatments. Walk time did not change during the study and did not differ between treatment groups. There were 24 reported falls during the 12-mo study compared with 26 falls recalled for the 3 mo before the study (Table 1). There was no difference between the reported number of falls in the 4 treatment groups during the study (NT, 8 falls; T, 3 falls; SUP, 4 falls; COM, 9 falls; \( P = 0.19 \)).

**Mortality and living arrangements**

Two subjects died during the study, both outside hospital. A woman in the supplement-treated group died of respiratory disease 6 d after a 4-d hospitalization (included in analysis of hospital admissions) for severe chronic airway obstruction. A man in the testosterone group with known heart disease died in hospital admissions) for severe chronic airway obstruction. A man in the testosterone group with known heart disease died suddenly of a myocardial infarction. All surviving subjects continued to live in the community throughout the study.

**Laboratory measures**

**Testosterone**

All men had a serum total testosterone concentration within the young-adult normal range (8–31 nmol/L) at baseline. In men, total testosterone concentrations decreased during the study from 18.8 ± 1.2 to 15.8 ± 1.2 nmol/L (\( P = 0.002 \)), with no significant differences between treatments, but a trend toward the decrease was greater in the testosterone-treated group than in other groups (−7.0 ± 0.7 (T), −0.1 ± 1.2 (NT), −3.8 ± 1.1 (SUP), and −1.6 ± 2.3 (COM) nmol/L). SHBG decreased (60.1 ± 3.8–51.45 ± 3.7 nmol/L; \( P = 0.018 \)) with no significant difference between treatments, but a trend toward the decrease was greatest in the T group (−17 ± 7.4 (T), −13 ± 3.3 (NT), −9.5 ± 7.2 (SUP), and −6 ± 9.3 (COM) nmol/L). Calculated FAI did not change (33.5 ± 2.5–32.5 ± 2.6%; \( P = 0.72 \)) with no difference between treatments.

In women, total testosterone concentration increased during the study from 0.8 ± 0.1 to 1.25 ± 0.2 nmol/L (\( P = 0.01 \)), with increases in all treatment groups nonsignificantly greater in those receiving testosterone than in those not receiving testosterone (+0.76 ± 0.3 compared with + 0.14 ± 0.2 nmol/L; \( P = 0.057 \)). SHBG decreased (87.2 ± 6.9–68.6 ± 6.6 nmol/L; \( P = 0.005 \)), with nonsignificantly greater decreases in women receiving testosterone than in those not receiving testosterone (−29 ± 10.8 compared with −7.8 ± 3.2 nmol/L; \( P = 0.068 \)). Calculated FAI increased from 1.0 ± 0.2% to 2.4 ± 0.4% (\( P = 0.0017 \)), with increases in all treatment groups, but greater increases in women receiving testosterone than in those not receiving testosterone (−2 ± 0.6% compared with +0.58 ± 0.3%; \( P = 0.038 \)). FAI increased =3-fold in women taking testosterone (from 1.0 ± 0.3% to 3.15 ± 0.8%; \( P = 0.007 \)).

**CRP**

CRP concentrations were nonsignificantly higher at baseline in the COM group (Table 1) because 2 subjects had high values of 54 and 88 mg/L without apparent cause. Overall CRP concentrations did not change during the study (4.9 ± 2.2–3.56 ± 0.7 mg/L; \( P = 0.57 \)) but decreased significantly (\( P = 0.026 \)) in the COM group and increased nonsignificantly in the other groups to become lowest at 12 mo in the COM group (NT group: 3.1 ± 1.5 mg/L; T group: 5.6 ± 1.9 mg/L; SUP group: 3.3 ± 0.7 mg/L; and COM group: 2.3 ± 0.8 mg/L). There was no decrease with combined treatment when the 2 subjects with high baseline CRP concentrations were excluded from analysis; there was then an overall increase in CRP concentrations during the study (1.85 ± 0.4–3.63 ± 0.7 mg/L; \( P = 0.006 \)).

**Adverse effects, reductions in study treatment, and compliance**

Seventeen of the subjects (35%) reduced or ceased 1 of the 2 components of their treatment: 5 in the NT group, 2 in the SUP group, 4 in the T group, and 6 in the COM group. No subject ceased both components. Although most reasons for treatment reduction were probably not related specifically to the treatments, 2 women taking testosterone developed hirsutism, which resolved with dose reduction; 4 subjects ceased the supplement because of nausea; and one man taking testosterone had an increase in PSA above the age-related normal range, which was corrected by halving the testosterone dose. No subject developed a hematocrit level that required dose reduction. On an intention-to-treat basis (including the 2 deceased subjects until their deaths), subjects reported taking 87.8% of the assigned supplement drinks and 83.1% of the testosterone/placebo capsules during the study. There was no effect of any treatment on PSA or prostate symptom score.

**DISCUSSION**

In this study of community-dwelling, undernourished older people, treatment of 1 y with a combination of oral testosterone and a nutritional supplement drink was associated with a significant reduction in the number of people hospitalized, the time to hospital admission, and the number of days spent in hospital. When given alone, testosterone and the supplement were associated with intermediate hospitalization rates. These benefits were in addition to the increase in body weight and the reduction in frailty scores that occurred even in subjects receiving no active treatment, which was probably the result of all subjects receiving...
standard care that comprised regular follow-up visits and advice about increasing energy intake.

The effects of the study treatments in reducing hospital admissions were most marked when all hospital admissions, elective and nonelective, were included in the analysis, as prescribed by our prestudy hypothesis. The effects were less marked when nonelective admissions alone were considered. Although there was still a statistically significant increase in the time to hospital admission with combined treatment, the reductions in the number of subjects hospitalized \((P = 0.07)\) and in the number of days in hospital \((P = 0.098)\) did not reach statistical significance. The results, although identifying a treatment of considerable potential benefit, must therefore be classified as preliminary. They highlight the need for a larger trial of such combined therapy, which, if confirmatory, could justify a change in clinical practice.

During the 1-y study, 38% of the NT group were hospitalized at least once, compared with 57% of all subjects in the year before the study and 45% in a comparable group of untreated, undernourished, community-dwelling older people whom we studied previously \((15)\). These rates are substantially higher than those of their well-nourished, community-dwelling counterparts \((15)\) and highlight the poor outcomes associated with undernutrition in the elderly. Hospital admissions account for the majority of health care costs and predominantly occur in older people. People aged \(>75 \text{ y}\) spend 7–10 times as much time in hospital as adults \(<45 \text{ y}\) \((27, 28)\) and hospital bed days are predicted to double by 2050 because of the aging of the population \((27)\). As well as indicating the presence of illness sufficiently serious to require hospital admission, hospitalization in older people is frequently associated with complications, including delirium and muscle deconditioning, and is often followed by functional decline \((29)\). In older people, there is a strong relation between hospitalization and the subsequent development of disability, which often necessitates movement to residential care \((30, 31)\).

Previous studies indicated that nutritional supplements have modest benefits in older people, particularly in those who are more undernourished, who are in hospitals or other institutions, or who receive larger supplements for longer time periods \((16, 17)\). Testosterone administration to older men has been shown to increase muscle mass and decrease fat mass \((20, 32, 33)\) and to increase muscle strength, albeit modestly and variably, more with high doses and in men with low testosterone concentrations \((20, 32–34)\). In postmenopausal women, testosterone treatment increases lean body mass, energy, libido \((35, 36)\), and possibly muscle strength \((35)\).

The evidence for functional benefits of testosterone treatment in older people, other than increased strength, is limited. We are unaware of evidence that testosterone improves clinically relevant outcomes, such as physical performance or cognitive function, in older women \((35, 37)\). There have been few reports of functional benefits of testosterone administration to older men; testosterone in higher doses than that used in this study has been reported to improve standing ability after knee replacement surgery \((18)\), to improve timed walking \((20)\), and to increase of the Function Independence Measure and grip strength \((19)\). To our knowledge, the current study is the first to show that testosterone treatment reduces hospitalizations. This benefit occurred with a relatively low testosterone dose that did not increase testosterone concentrations in men but did in women.

Notably, the decreases in circulating concentrations of total testosterone and SHBG in men receiving testosterone in this study, which did not reach statistical significance due to small subject numbers, were consistent with statistically significant reductions observed in a recent study by Emmelot-Vonk et al \((38)\), in which the same dose of the same oral testosterone preparation was administered to older men for 6 mo. Total testosterone decreased 7 nmol/L with testosterone treatment alone in our study, compared with a 3.2 nmol/L reduction \((P < 0.001)\) in the Emmelot-Vonk et al \((38)\) study, probably in response to a proportionally greater reduction in SHBG concentrations \((28%)\) in our study and \(30\%)\) in Emmelot-Vonk et al \((P < 0.001)\). The doses used were based on our previous study in men, in which a 12-mo treatment with the same dose of testosterone undecanoate was associated with significant increases in lean mass and reductions in fat tissue in older men with low-normal gonadal status \((32)\). A quarter of the dose was used in women to allow for their lower circulating testosterone concentrations and greater propensity to develop testosterone-induced side effects. The same dose of testosterone undecanoate has been reported recently to not affect mobility or cognition in older men \((38)\). Indeed, there was only a clear benefit in our study when testosterone was combined with a nutritional supplement, perhaps because we targeted people on the basis of undernutrition, not age alone or testosterone deficiency, and administered a combination of anabolic treatments.

The mechanisms by which the combination treatment reduced hospitalizations are not clear. Testosterone treatment might reduce inflammation and stimulate feeding. Cytokines inhibit food intake and reduce body weight. Circulating cytokine concentrations increase with normal aging \((39)\), are further increased in older people with cachexia \((40)\), and correlate inversely with functional ability and circulating sex hormone concentrations \((41)\). Indeed, CRP concentrations decreased with combined treatment. This finding requires confirmation, however, as CRP concentrations did not decrease in subjects treated with testosterone alone, which is consistent with other reports \((42, 43)\). Furthermore, CRP decreased with combined treatment probably only because 2 subjects in that group had unexplained high baseline concentrations. When they were removed from the analysis, there was no change in CRP with testosterone treatment and an overall increase during the study, consistent with the positive relation of CRP with body weight and fat \((44)\), both of which increased during the study.

A limitation of our study was the lack of a supplement control treatment. We were unable to source a similarly packaged, low-energy “control” drink. We do not know how this affected the results, but it should not have altered the observed benefits of adding placebo-controlled testosterone to the other treatments. The number of subjects precluded a more conclusive examination of some of the endpoints and mechanisms of actions. A larger study is needed to confirm our findings.

Because of assay limitations, it is difficult to detect testosterone deficiency in women, so the baseline status of our female subjects is unclear. Although circulating testosterone concentrations in men decline on average with aging \((45)\) and ill-health \((46)\), none of the older men in this study were testosterone deficient by young adult standards. This is probably because they were undernourished with low body-fat stores; fat concentrations are inversely associated with circulating testosterone.
concentrations in older men (47). Hence, the beneficial effects of testosterone treatment on hospitalizations occurred in testosterone-sufficient men. Testosterone treatment influenced body composition similarly in men and women, with more weight gained as lean tissue and less as fat.

The treatments were well tolerated. Although approximately a quarter of testosterone-treated subjects reduced the dose or stopped this drug because of possible adverse effects, the number doing so was similar with the placebo (6 compared with 5). The increases in hemoglobin and hematocrit of ~9 g/L and 2.5%, respectively, with testosterone treatment were consistent with increases reported previously for this mode of testosterone administration (38). They were equated to an increase of ~6% from baseline, did not quite achieve statistical significance, and did not result in polycythemia requiring dose reduction in any subject. Nevertheless, these increases need to be monitored and some of the side effects of testosterone treatment (hirsutism in women and increased PSA in one man) were quite likely due to this treatment. Older people taking testosterone treatment, even in low doses, need to be monitored for such side effects.

In summary, combined treatment with testosterone and a nutritional supplement for 1 y significantly reduced hospitalizations in undernourished older people. Because hospitalizations are a common and serious event in undernourished older people, this is an exciting finding of considerable potential benefit to many people. Larger, confirmatory studies are now needed.

The authors' responsibilities were as follows—IMC and RV: conception and design of study, acquisition of data, analysis and interpretation of data, drafting and revising of the article, and final approval; JEM: conception and design of study, analysis and interpretation of data, drafting and revising of the article, and final approval; and JBFF and MH: analysis and interpretation of data, drafting and revising of the article, and final approval. IMC received a grant from Organon Ltd of €120,000 to conduct this study. Organon also supplied Andriol Testocaps and placebo capsules free of charge. The funding was used to pay for investigations (blood tests and body composition analyses), salary of a research assistant (AJH), and purchase of the Nova Source nutritional supplement. This was a single-center, investigator-initiated study for which Organon was approached for funding. Organon had no input into study design, the conduct of the study, or the analysis and reporting of the results. JEM has received research funding and grant support from Organon Ltd (makers of the study drug) and Novartis, the makers of the Nova Source nutritional supplement. None of the remaining authors had a conflict of interest.

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