

Editorial: Time for (More Research on) Testosterone

In this issue of *JCEM*, Amory *et al.* (1) present the most impressive results yet published from a placebo-controlled clinical trial evaluating the effect of testosterone therapy on hip and spine bone density in older men with low testosterone levels.

To determine whether bone benefit could be achieved with little or no effect on prostate size, symptoms, or prostate-specific antigen (PSA) levels, the investigators compared placebo with 200 mg of im testosterone enanthate every 2 wk, given alone or with finasteride. After 36 months, the addition of finasteride did not significantly modify the marked increase in bone mineral density (BMD) observed with testosterone. There was a 9–10% increase in BMD at the lumbar spine and a 2–3% increase in BMD at the hip, as determined by dual-energy x-ray absorptiometry, with each increase significantly better than the observed changes in the placebo group and not significantly different from each other.

This trial offers proof of the principle that testosterone treatment preserves bone in older men with low testosterone levels, but are the results clinically relevant? The study was generally well designed, and the key elements of good clinical trials are clearly described: the sample, the computer-generated randomization process, the blind (which included a dual-energy x-ray absorptiometry reader unaware of treatment assignment), the main entry criteria (total testosterone levels < 350 ng/dl on two occasions and a PSA < 4 ng/ml), the primary outcome (BMD at the spine and hip), the compliance rate (95% for completers), the completion rate (71%), and the sophisticated analysis plan.

Unfortunately, the testosterone regimen used in this trial was associated with a high frequency of erythrocytosis. In the present study, 30% of the men assigned to the testosterone group required a reduction of the dose of testosterone to manage a hematocrit increase of 52% or greater. These men then received a testosterone dose of about 150 mg every 2 wk, suggesting that the 200-mg dose may not be necessary for bone benefit.

The dose is important because the BMD changes observed in the present study are much more impressive than those reported in other placebo-controlled trials of testosterone and bone density, most likely because of the lower dose of testosterone delivered. For example, there were no significant changes in BMD in another controlled trial at half the dose (100 mg testosterone enanthate every 2 wk) (2). Kenny *et al.* (3) reported less bone loss at the femoral neck but not at the spine in 44 men treated with placebo or 5 mg of testosterone administered daily by patch for 12 months. Snyder *et al.* (4) reported no significant differences in BMD at any

site after 36 months of 6 mg of daily testosterone by scrotal patch compared with placebo, although a subset analysis showed significantly better bone density in the men who had the lowest testosterone levels at baseline.

The large increase in spine BMD observed here is similar to that achieved in postmenopausal women after 3 yr of treatment with a bisphosphonate (5). Increases in BMD, however, only incompletely predict reductions in fracture risk (5, 6).

As Morley (7) has pointed out, fear of prostate disease is the 800-lb gorilla confounding decisions about the use of testosterone replacement therapy. In animal models, testosterone and dihydrotestosterone (DHT) therapy can cause prostate hypertrophy and cancer, but the relevance of these studies for humans is uncertain (8). Evidence is limited that higher doses of testosterone are more likely than lower doses to have adverse effects on the prostate, at least in younger men (9).

Testosterone undergoes conversion to DHT by steroid 5 α -reductase within the prostate, an effect blocked by finasteride, a 5 α -reductase inhibitor. In a recent clinical trial, finasteride reduced prostate cancer risk by 25% (10). A novel addition to the present clinical trial was the comparison of testosterone alone with testosterone plus finasteride. The former but not the combination increased PSA significantly compared with placebo, and prostate volume increased significantly less in the testosterone plus finasteride group compared with the testosterone-only or placebo groups.

As the authors note, men treated with the combination of testosterone and finasteride reduced their DHT by 50%, but not completely, and some DHT may be required for bone benefit. Further, testosterone plus finasteride increased serum estradiol and testosterone levels more than testosterone alone, reflecting the increase in LH secretion due to inhibition of 5 α -reductase in the pituitary. In observational studies, endogenous estradiol appears to be as important, or more important, than testosterone in bone maintenance (11). Just how testosterone works to preserve bone is not clear, but the results of this study raise the possibility that a bone-sparing, prostate-sparing testosterone regimen may be feasible. But just as improved bone density is insufficient to show fracture prevention, short trials showing modest PSA changes will be unsatisfactory to ensure prostate safety.

It is important to get answers to these risk-benefit issues before we make assumptions based on biological plausibility and intermediate outcomes, a mistake dramatically illustrated by the unexpected, unfavorable risk-benefit ratio for estrogen plus progestin therapy in postmenopausal women shown in the Women's Health Initiative (12). Recently, the Institute of Medicine (13) has recommended a consortium of smaller trials to determine the optimal regimens for the intermediate outcomes of testosterone therapy, acknowledging the ultimate need for a Men's Health Initiative (if benefit greater than risk for intermediate outcomes can be shown in the short term).

Abbreviations: BMD, Bone mineral density; DHT, dihydrotestosterone; PSA, prostate-specific antigen.

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The potential market is huge, which means that the potential benefit and harm are also large. In the Rancho Bernardo cohort (11), nearly half of the apparently healthy community-dwelling men aged 60 and older had a total testosterone level less than 288 ng/dl, below the less than 350 ng/dl level used to define hypogonadism in the trial reported here (13). This large target for treatment and the lure of remaining "forever young" are already irresistible. Testosterone product sales in the United States, which had been stable at \$18 million until 1988, were projected to reach \$400 million before the end of 2002 (14). The Institute of Medicine (13) recommendation for more research on testosterone is welcome and timely.

Elizabeth Barrett-Connor and Shalender Bhasin
Department of Family and Preventive Medicine (E.B.-C.), University of California, San Diego, La Jolla, California 92093; School of Medicine (S.B.), University of California, Los Angeles, Los Angeles, California; and Division of Endocrinology, Metabolism, and Molecular Medicine (S.B.), Charles Drew University, Los Angeles, Los Angeles, California

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Address all correspondence and requests for reprints to: Elizabeth Barrett-Connor, M.D., University of California, San Diego, Department of Family and Preventive Medicine, 9500 Gilman Drive, Mail Code 0607, La Jolla, California 92093-0607. E-mail: ebarrettconnor@ucsd.edu.

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