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RESEARCH HIGHLIGHT

A role for dihydrotestosterone treatment in older men?

Mara Y Roth and Stephanie T Page

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Androgens play a vital role in the maintenance of health in normal men. Testosterone supports bone development and strength, provides anabolic effects for maintenance of lean muscle mass, and contributes to normal sexual function and libido. Circulating testosterone concentrations gradually decline as men age, rendering nearly 20% of men biochemically hypogonadal by age 60.[1] Current guidelines recommend androgen replacement, when indicated, using testosterone delivery *via* injection or transdermally.[2] However, due to a lack of large, long-term clinical trials, the risks of testosterone replacement are not clearly known. Exogenous testosterone can be associated with negative effects, such as polycythemia, and might be associated with prostate growth, such that it is currently contraindicated in men with prostate cancer.[2] Testosterone is metabolized *in vivo* to both estradiol, *via* aromatization, and dihydrotestosterone (DHT) *via* 5α-reduction, both of which are physiologically active. In particular, due to very high concentrations in the prostate, DHT is thought to play an important, yet unclear, role in prostate health. Moreover, DHT is a more potent androgen than testosterone, and might be clinically useful in treating hypogonadism. To determine the effects and safety of exogenous DHT in older men, a group from the ANZAC Research Institute (Australia) recently published a 2-year randomized, placebo-controlled trial in the *Annals of Internal Medicine* entitled, 'Long-term effects of dihydrotestosterone treatment on prostate growth in healthy, middle-aged men without prostate disease'.[3]

Idan and colleagues report results from a comprehensive trial in 114 healthy, eugonadal men who received 2 years of either DHT treatment with a transdermal, pharmacologic dose of 70 mg DHT gel daily, or matching placebo gel. The primary outcome was prostate volume measured by ultrasonography, and secondary outcomes included bone mineral density, body composition, serum lipids and hormones, and quality of life questionnaires. There were no serious adverse events and a high retention rate for such a long study (71% completed all study procedures). As expected, the DHT-treated group had a 10-fold increase in serum DHT levels, well above the normal range of circulating DHT, and a concomitant decrease in serum testosterone and estradiol concentrations which were all unchanged in the placebo group. In summary, they report no DHT-specific effects on prostate volume, with both the treatment and placebo groups experiencing a similar increase in prostate volume and prostate specific antigen during the study. Compared to placebo, the DHT group demonstrated a decrease in total body fat mass and in bone mineral density at the spine, but not at the hip, and increased lean body mass, serum hemoglobin and creatinine. Both groups experienced a similar rise in low-density lipoproteins and decline in high-density lipoproteins. None of the quality of life indicators differed between the treatment groups in this eugonadal cohort.

DHT is a highly potent, 'pure androgen' which cannot be aromatized, yet the authors hypothesized that exogenous DHT would reduce prostate size due to: (i) negative feedback on gonadotropin and testosterone production; and (ii) its metabolism to 3β-androstanediol-5α which has been suggested to inhibit prostate growth.[4] On the other hand, 5α-reducatase inhibitors which block testosterone conversion to DHT clearly decrease prostate volume, presumably by reducing serum and intraprostatic concentrations of DHT.[5] Prior, shorter-term studies of DHT gel in hypogonadal men reported no impact on prostate volume.[6,7] This study aimed to extend these findings and, if their hypothesis was correct, perhaps provide the basis for a clinical agent that could correct the signs and symptoms of hypogonadism while avoiding costly exacerbations of benign prostatic hypertrophy and prostate specific antigen elevations. The authors definitively demonstrate that high doses of exogenous DHT in healthy eugonadal men, resulting in substantial decreases in serum testosterone, do not change prostate volume or prostate specific antigen compared to placebo. Interestingly, the increase in prostate volume in both groups was remarkably high compared to prior studies. Subjects in this study had an average increase in prostate volume of nearly 30% over 2 years, compared to prior studies showing an average 10% increase in prostate volume over 2 years.[5] The mechanism whereby DHT acts as a 'prostate-sparing' androgen is unknown, but may be attributable to the observation that despite substantially raising serum DHT levels, exogenous DHT does not appear to increase intraprostatic androgen concentrations in healthy men (Page ST *et al.*, in press in *Journal of Clinical Endocrinology and Metabolism*).

The extremely high serum levels of DHT achieved in this study lead to significant gonadotropin suppression, thereby reducing circulating testosterone levels to nearly castrate levels and reducing circulating estradiol levels by 90%. The most concerning outcome of this study is the effect of high dose DHT gel on bone mineral density. Over 2 years, the subjects receiving DHT gel had a significant, progressive decrease in bone mineral density at the lumbar spine compared to placebo, despite expected anabolic effects on lean body mass. This effect on bone mineral density is in contrast to the effects of testosterone therapy, with or without a 5α-reductase inhibitor, which increases bone mineral density at the spine and hip when given to hypogonadal men.[8] The negative impact of DHT on bone mineral density in the spine is likely mediated by the marked reduction in serum estradiol

University of Washington Medical Center, 1959 NE Pacific St, Box 357138, Seattle, WA 98195, USA
Correspondence: Dr MY Roth (mylang@uw.edu)

levels and further demonstrates the importance of estradiol in bone health, particularly for trabecular bone, in both men and women. Interestingly, these effects on bone are similar to those reported for 7α-methyl-19-nortestosterone, a non-reducible androgen which, although aromatized, also markedly suppresses circulating gonadotropins and is associated with decreased vertebral bone density.[9] These results suggest that perhaps selective androgen receptor modulators that preserve endogenous gonadotropin production and estradiol levels might be more clinically useful anabolic agents for effectively treating androgen deficiency in men. Alternatively, lower doses of DHT than those used by Idan *et al.* that suppress gonadotropins and estradiol less completely[10] might avoid these negative bone effects. Of note, there was no impact of DHT treatment on bone mineral density at the femoral neck, illustrating the greater impact of estradiol on trabecular versus cortical bone.

Finally, regarding markers of cardiovascular disease risk, there were no treatment-related changes in serum lipoproteins, insulin or vascular reactivity. This is surprising given previous studies reporting the importance of estradiol on HDL levels in men[11] but perhaps such expected changes in lipid metabolism are offset by the changes in body composition, which also impact serum lipids, observed with DHT treatment. Systolic but not diastolic blood pressure was slightly increased in the DHT group only, although the clinical significance of this change is unclear.

In summary, this is an important, well-designed study evaluating the effect of high doses of exogenous DHT in normal men, demonstrating that supraphysiologic levels of DHT neither inhibit nor promote prostate growth in men. However, high-dosage exogenous DHT results in significant decreases in bone mineral density at the spine over 2 years likely by decreasing estradiol concentrations. While DHT may have beneficial effects on body composition, at least at supraphysiologic doses, the negative impacts on trabecular bone mineral density may limit its clinical utility. Future studies exploring the impact of lower doses of DHT in hypogonadal men will be of interest.

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