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Preliminary Communication

Effect of Testosterone Replacement Therapy on Prostate Tissue in Men With Late-Onset Hypogonadism

A Randomized Controlled Trial

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Context Prostate safety is a primary concern when aging men receive testosterone replacement therapy (TRT), but little information is available regarding the effects of TRT on prostate tissue in men.

Objective To determine the effects of TRT on prostate tissue of aging men with low serum testosterone levels.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial of 44 men, aged 44 to 78 years, with screening serum testosterone levels lower than 300 ng/dL (<10.4 nmol/L) and related symptoms, conducted at a US community-based research center between February 2003 and November 2004.

Intervention Participants were randomly assigned to receive 150 mg of testosterone enanthate or matching placebo intramuscularly every 2 weeks for 6 months.

Main Outcome Measures The primary outcome measure was the 6-month change in prostate tissue androgen levels (testosterone and dihydrotestosterone). Secondary outcome measures included 6-month changes in prostate-related clinical features, histology, biomarkers, and epithelial cell gene expression.

Results Of the 44 men randomized, 40 had prostate biopsies performed both at baseline and at 6 months and qualified for per-protocol analysis (TRT, n = 21; placebo, n = 19). Testosterone replacement therapy increased serum testosterone levels to the mid-normal range (median at baseline, 282 ng/dL [9.8 nmol/L]; median at 6 months, 640 ng/dL [22.2 nmol/L]) with no significant change in serum testosterone levels in matched, placebo-treated men. However, median prostate tissue levels of testosterone (0.91 ng/g) and dihydrotestosterone (6.79 ng/g) did not change significantly in the TRT group. No treatment-related change was observed in prostate histology, tissue biomarkers (androgen receptor, Ki-67, CD34), gene expression (including *AR*, *PSA*, *PAP2A*, *VEGF*, *NXK3*, *CLU* [*Clusterin*]), or cancer incidence or severity. Treatment-related changes in prostate volume, serum prostate-specific antigen, voiding symptoms, and urinary flow were minor.

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Conclusions These preliminary data suggest that in aging men with late-onset hypogonadism, 6 months of TRT normalizes serum androgen levels but appears to have little effect on prostate tissue androgen levels and cellular functions. Establishment of prostate safety for large populations of older men undergoing longer duration of TRT requires further study.

Trial Registration clinicaltrials.gov Identifier: NCT00161304

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