CORRESPONDENCE

# Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men

**TO THE EDITOR:** Finkelstein et al. (Sept. 12 issue)[1] conclude that estrogen deficiency induced by an aromatase inhibitor primarily accounts for an increase in fat mass in men. However, it should be recognized that testosterone action is not limited to androgen receptors and aromatization of testosterone to estradiol; other hormone systems are also influenced by testosterone.

Testosterone stimulates growth hormone secretion by means of aromatization to estrogen. This is supported by observations that nonaromatizable androgens do not stimulate growth hormone secretion,[2] whereas aromatase inhibitors reduce testosterone-stimulated growth hormone secretion in men.[3] Moreover, in men with aromatase deficiency, growth hormone secretion is reduced — an effect that is not rescued by systemic estrogen replacement.[4] Thus, the local production of estrogen centrally by means of aromatization is crucial for the stimulation of growth hormone secretion in men. Because growth hormone significantly reduces fat mass,[5] in the study by Finkelstein et al. reduced growth hormone secretion, rather than estrogen deficiency per se, may be linked to the detrimental effects on fat mass.

Thus, androgen replacement requires testosterone rather than synthetic androgens to induce the full spectrum of testosterone effects by means of androgen receptors, aromatization to estradiol, and consequent effects on the growth hormone system.

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**TO THE EDITOR:** Finkelstein et al. imply that boosting estrogen levels (by means of testosterone supplementation) may decrease cardiovascular risk by decreasing body fat. Unfortunately,

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previous trials strongly suggest that just the opposite is true. The administration of estrogen was associated with an increase in cardiovascular risk in three large randomized, controlled trials: the Coronary Drug Project,[1] the Women's Health Initiative,[2] and the Veterans Administration Cooperative Urological Research Group studies in prostate cancer.[3] Moreover, a recent meta-analysis showed that testosterone therapy as much as doubled cardiovascular risk.[4] Surely, the leading hypothesis must be that both testosterone and estrogen therapies increase, rather than decrease, cardiovascular risk.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** When I read the report by Finkelstein et al., I was both reassured and concerned: reassured, because as a uro-oncologist with metastatic castration-resistant prostate cancer, I have found supplemental estrogen to be a boost to my own quality of life and to that of my patients; and concerned, because this study may not reach the urologists and oncologists who treat prostate cancer with androgen-deprivation therapy (ADT).

The benefits of estrogen in treating men with hypogonadism apply profoundly to the iatrogenic hypogonadal state induced by ADT when it is used to treat prostate cancer.[1,2] Estrogen can now be delivered transdermally to minimize the cardiovascular morbidity associated with oral estrogens, a complication that has greatly limited the use of estrogen therapy in prostate cancer.[3]

The findings of Finkelstein et al. suggest it is very likely that patients with prostate cancer will be better served when ADT is indicated with single, rather than dual, hormonal deprivation. It is time to revisit the role of estrogen in therapy for prostate cancer.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** The recent article by Finkelstein et al. raises ethical concerns. The methods included the administration of goserelin acetate to suppress endogenous gonadal steroids for a 16-week period. This form of treatment is similar to chemical castration, can have side effects that can affect the quality of life of the participants, and might have adverse effects on muscle mass and bone density.[1] Furthermore, the use of ADT in men with prostate cancer is associated with an increase in cardiovascular morbidity.[2] In our view, this study, although important, has a troubling adverse-effect profile that raises the question of whether Good Clinical Practice guidelines were followed.

In addition, to protect the best interests of the participants, we think that bone density should have been measured at the end of treatment. This approach would have permitted a per-protocol treatment if deemed necessary. The safety and best interests of patients should be first and foremost in clinical trials.

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No potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** Birzniece postulates that the decreased secretion of growth hormone was associated with an increase in fat mass in our participants with hypogonadism. As she notes, both estrogen deficiency and estrogen blockade reduce growth hormone secretion. Our study was not designed to examine mechanisms whereby estrogen deficiency increases body fat; however, we agree that diminished growth hormone secretion is a potential mechanism.

Schooling et al. state that we implied that "boosting estrogen levels . . . may decrease cardiovascular risk." We wrote that "the marked increase in intraabdominal fat with aromatase inhibition could portend an increase in cardiovascular disease with long-term estrogen deficiency," not that estrogen administration would reduce such risk. Moreover, the studies they cited as evidence that estrogen administration increases the risk of cardiovascular disease among men[1,2] used doses far higher than those needed for physiologic replacement.

Schellhammer cites personal experience, published urologic literature, and our article as evidence that estrogen therapy is beneficial in men with prostate cancer who are receiving ADT. As noted above, we did not study the effects of estrogen administration in men receiving ADT. Nevertheless, the finding that estrogen deficiency is responsible for several of the undesirable consequences of ADT raises the possibility that the administration of low-dose estradiol might benefit men with prostate cancer who are receiving ADT. Randomized, controlled trials are needed to determine whether estradiol administration is effective and safe in such patients.

Finally, Malnick et al. question the ethics of using a gonadotropin-releasing hormone agonist to investigate reproductive physiology. We[3] and others[4] have used this approach in studies for many years, and no safety issues have been observed. Our study was specifically designed to be sufficiently brief so that clinically important bone loss, as assessed by means of dual-energy x-ray absorptiometry (DXA), would not occur. We measured bone mineral density (BMD) by means of DXA at baseline and study completion. As predicted, changes in the BMD of the spine and hip were 1% or less, and there were no significant differences between the hypogonadal group and the eugonadal (control) group. The major side effects of ADT, hot flashes and decreased sexual function, resolve with medication discontinuation and have no known residual effect on health. Moreover, because most of the men in our study received some testosterone, most participants did not report such ADT-related side effects. Participants were informed that if they had troubling side effects, they could withdraw from the study and receive testosterone replacement until the ADT wore off. Finally, ethical concerns were not raised by our institutional review board, our data and safety monitoring board, or the National Institutes of Health.

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Since publication of their article, the authors report no further potential conflict of interest.

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# Cystatin C versus Creatinine for Kidney Function–Based Risk

**TO THE EDITOR:** The meta-analysis by Shlipak et al. (Sept. 5 issue)[1] shows that a cystatin C–based estimated glomerular filtration rate (eGFR) offers improvements in predicting risks of death and end-stage renal disease across diverse populations. In their editorial, Ingelfinger and Marsden[2] caution that "results cannot be applied to Asian and Hispanic patients except by extrapolation." Also, diabetes was underrepresented in the sample of patients with chronic kidney disease; it was pres-