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EDITORIAL

Should testosterone be added to estrogen-progestin therapy for breast protection?

The therapeutic use of testosterone in women is a topic of considerable current interest and controversy.[1-4] The major reason to consider such use has been for the management of decreased sexual function, in particular hypoactive sexual desire disorder.[5] Earlier studies, although demonstrating substantial improvements in sexual function in symptomatic women, used regimens of administration that resulted in mainly supraphysiological levels of the steroid.[6-8] More recently, a number of randomized, controlled trials of testosterone administration, usually of 6 months duration, have been conducted in symptomatic, concomitantly estrogen-treated women, in whom the free testosterone concentrations achieved have been in the normal physiological range for young, reproductive-aged controls.[9-14] Testosterone administration has produced statistically significant benefits in terms of sexual function. A major concern that has currently limited the acceptance of such treatment is the lack of long-term safety data. In general, parenteral administration of physiological doses of testosterone seems to have few adverse effects in the short term, but an important and so far completely unanswered question is whether there may be long-term adverse effects on the cardiovascular system and on breast cancer risk.

Several studies have addressed the relationships between androgens, breast cell proliferation, and breast cancer.[15-17] There is a considerable body of evidence that both testosterone and its reduced derivative dihydrotestosterone exert inhibitory influences on the growth-promoting effects of estradiol on the breast, though the evidence is not uniform.

Of interest have been in vivo experimental studies in primates, in which the effects of testosterone on breast cell proliferation have been examined. Zhou et al[18] administered placebo, estradiol, estradiol and progesterone, estradiol and testosterone, or tamoxifen for 3 days to groups of four to seven ovariectomized rhesus monkeys. They determined the extent of mammary epithelial proliferation using the proliferation-specific Ki-67 antigen, detected immunohistochemically. The resulting circulating steroid levels were clearly supraphysiological. Estradiol alone caused a sixfold increase in proliferation and a modest increase in the expression of estrogen receptor α (ER-α) mRNA. Although progesterone had no effect on the proliferative influence of estradiol, testosterone reduced this by approximately 40% and abolished the augmentation of ER-α expression. Interestingly, tamoxifen also produced a threefold increase in proliferation but reduced ER-α expression below placebo levels. Androgen receptor mRNA was detected in the breast epithelial cells, and its levels were not altered by estradiol alone. However, it was reduced by the addition of testosterone and by treatment with tamoxifen. The authors concluded that "androgen-induced down-regulation of mammary epithelial proliferation and ER expression suggest that combined estrogen/androgen hormone replacement therapy might reduce the risk of breast cancer associated with estrogen replacement."

In a subsequent study[19] the same group of investigators examined the possible role of endogenous androgen in regulating epithelial proliferation and examined the effects of physiological testosterone treatment on the responses to estradiol given alone. The androgen receptor blocker Flutamide was used to investigate the influence of endogenous androgen levels in regularly cycling animals and was shown to cause a twofold increase in Ki-67 antigen expression in the mammary epithelium. Ovariectomized animals were again used to examine the effects of physiological testosterone supplementation in estradiol-treated animals. Circulating estradiol levels were in the periovulatory range, but testosterone concentrations achieved were in the physiological range. There was a 3.5-fold increase in proliferation index in the estradiol- and estradiol/progesterone-treated animals but no significant increase in the estradiol/testosterone-treated

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group. There was a significant reduction in mammary epithelial ER-α and increased ER-β expression in the estradiol/testosterone-treated groups as compared with the estradiol-treated group. In an accompanying editorial[20] it was suggested that the study "should lead to further investigations into the use of androgens for women with ovarian failure."

In this issue of *Menopause,* Hofling and colleagues[21] report the results of a 6-month prospective, randomized, double-blind, placebo-controlled study conducted in 99 postmenopausal women given the continuous combined regimen of estradiol and norethisterone acetate, which has been commonly used in Europe. The doses of steroids in this preparation (estradiol 2 mg, norethisterone acetate 1 mg) are somewhat higher than those currently advised for menopausal hormone therapy, but this has been a widely used preparation in the past. The subjects were randomized equally to receive additional treatment with a testosterone patch releasing 300 μg per 24 hours or a placebo patch. Fine needle aspirates were taken from the upper outer quadrant of the breast at baseline and after 6 months of therapy. Of the 88 women completing the study, 47 received testosterone and 41 placebo. Subjects receiving estradiol and norethisterone alone showed a fivefold increase in total breast cell proliferation from baseline to 6 months, whereas no significant increase was noted in those additionally treated with testosterone in amounts that gave total and free testosterone levels in the normal or only slightly supraphysiological range. The investigators separated breast epithelial from breast stromal cells, both of which showed the same effects. The investigators concluded that the results "support the concept that androgens may counteract the proliferative effect of estrogen and progestogen in the mammary gland."

It is now well established that long-term combined oral estrogen and progestogen therapy moderately increases breast cancer risk. The combined continuous treatment arm of the Women's Health Initiative randomized, controlled clinical trials of hormone therapy demonstrated no statistically significant increase in risk in subjects previously untreated with menopausal hormone therapy (hazard ratio, 1.02; 95% CI, 0.77-1.36).[22] However, among 4,301 prior users in that study, the adjusted hazard ratio for estrogen+ progestogen vs placebo was 1.96 (95% CI, 1.17-3.27). This figure may be artifactually high because of the declining risk in prior hormone users assigned to placebo.[23] Treatment with oral estrogen alone resulted in an apparent reduction in breast cancer risk that did not quite reach statistical significance (hazard ratio, 0.77; 95% CI, 0.59-1.01).[24] The effects of postmenopausal estrogen therapy on circulating androgens has been subjected to limited investigation. Casson et al[25] examined the effects of oral micronized estradiol 2 mg daily given for 12 weeks and observed a 42% decrease in total testosterone and a 160% increase in sex hormone–binding globulin (SHBG). Free testosterone concentrations were not calculated but would have declined substantially more than 42%. Vehkavaara et al[26] also documented the effects of 2 mg oral estradiol and compared them with those of 50 μg transdermal estradiol. In the orally treated group SHBG increased from 72 to 168 nmol/L at 12 weeks, total testosterone was unchanged (0.99 vs 0.74 nmol/L at 12 weeks after oral therapy), and free testosterone concentrations decreased in the oral group from 11 to 4 pmol/L. Concentrations of SHBG and total and free testosterone did not change in the transdermally treated group despite comparable levels of free estradiol after 12 weeks of treatment. Systematic study of the effects of combined oral estrogen and progestin on total and free testosterone levels have not been reported, though oral contraceptive use is known to increase SHBG and decrease free testosterone substantially.[27] The suppression of circulating androgens results from both the inhibition of circulating gonadotropin concentrations and the increase in SHBG. Whether androgen suppression contributes to the greater risk of breast cancer from combined estrogen plus progestogen therapy, as compared with estrogen alone, has not been established. Whether transdermal estradiol is associated with the same increase in breast cancer risk also is unclear.

There are no prospective, randomized, long-term trials from which effects of testosterone added to hormone therapy can be determined. Two observational studies merit comment. Dimitrakakis et al[28] reported the results of a retrospective, observational study of 508 postmenopausal women treated with testosterone implants in addition to usual hormone therapy. The incidence of invasive breast cancer was 238 per 100,000 women-years for all groups combined. In the estradiol/progestogen/testosterone group the incidence was higher, at 293 cases per 100,000 women-years and lower in the estradiol plus testosterone group (115 per 100,000 women-years). These rates were compared with those for several other studies, including the combined treatment arm of the Women's Health Initiative (380 cases per 100,000 women-years[29]) and the Million Women Study (521

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per 100,000 women-years[30]). The rate was closest to that reported for hormone therapy never users in the Million Women Study (283 per 100,000 women-years), and their age-standardized rate was the same as for the general population of South Australia, where the study was conducted. An accompanying editorial was entitled "It might be wise to consider adding androgen to the estrogen or estrogen-progestin regimens in the appropriate patients."[31] Tamimi et al[32] recently reported an increased risk of breast cancer in women in the Nurses' Health Study using a combination of systemic estrogen and androgen, primarily methyltestosterone (multivariate relative risk, 2.48; 95% CI, 1.53-4.04). These results must be interpreted cautiously, however. It is likely that the majority of women who used testosterone had used other hormones, and in fact, in 1998, only 2.4% of estrogen plus testosterone users had not previously used other hormones. The analysis did not allow for the type or duration of prior hormone use in testosterone users. Users were also younger, more likely to have had benign breast disease, had a higher percentage of relatives with breast cancer, and were heavier alcohol users than those who had used estrogen alone. Because more patients had benign breast disease in the testosterone group, it is likely that more breast examinations and mammograms would have been done with the possibility of ascertainment bias. It was also paradoxical that the increased risk of breast cancer was noted in users of less than 5 years, but not in those who had used testosterone for more than 5 years.

It is to be hoped that as experience with physiological testosterone therapy, particularly in women with low libido, becomes wider, data will gradually accumulate regarding possible increase or reduction in breast cancer risk, as compared with women not so treated. It should be noted that the recently published clinical practice guideline of the US Endocrine Society[4] will undoubtedly cause some confusion as its initial recommendation is "against making a diagnosis of androgen deficiency in women at present." This is a surprising recommendation given the now extensive demonstration of the efficacy of administered testosterone in the treatment of low libido and in particular the clear-cut demonstration of benefit in women with organic testosterone deficiency as occurs in hypopituitarism.[33]

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