0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(3):1174–1180
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doi: 10.1210/jc.2003-031467

Effects of Aromatase Inhibition in Elderly Men with Low or Borderline-Low Serum Testosterone Levels

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As men age, serum testosterone levels decrease, a factor that may contribute to some aspects of age-related physiological deterioration. Although androgen replacement has been shown to have beneficial effects in frankly hypogonadal men, its use in elderly men with borderline hypogonadism is controversial. Furthermore, current testosterone replacement methods have important limitations.

We investigated the ability of the orally administered aromatase inhibitor, anastrozole, to increase endogenous testosterone production in 37 elderly men (aged 62–74 yr) with screening serum testosterone levels less than 350 ng/dl. Subjects were randomized in a double-blind fashion to the following 12-wk oral regimens: group 1: anastrozole 1 mg daily (n = 12); group 2: anastrozole 1 mg twice weekly (n = 11); and group 3: placebo daily (n = 14). Hormone levels, quality of life (MOS Short-Form Health Survey), sexual function (International Index of Erectile Function), benign prostate hyperplasia severity (American Urological Association Symptom Index Score), prostate-specific antigen, and measures of safety were compared among groups.

Mean ± SD bioavailable testosterone increased from 99 ± 31 to 207 ± 65 ng/dl in group 1 and from 115 ± 37 to 178 ± 55 ng/dl in group 2 ($P < 0.001$ *vs.* placebo for both groups and $P = 0.054$ group 1 *vs.* group 2). Total testosterone levels increased from 343 ± 61 to 572 ± 139 ng/dl in group 1 and from 397 ± 106 to 520 ± 91 ng/dl in group 2 ($P < 0.001$ *vs.* placebo for both groups and $P = 0.012$ group 1 *vs.* group 2). Serum estradiol levels decreased from 26 ± 8 to 17 ± 6 pg/ml in group 1 and from 27 ± 8 to 17 ± 5 pg/ml in group 2 ($P < 0.001$ *vs.* placebo for both groups and P = NS group 1 *vs.* group 2). Serum LH levels increased from 5.1 ± 4.8 to 7.9 ± 6.5 U/liter and from 4.1 ± 1.6 to 7.2 ± 2.8 U/liter in groups 1 and 2, respectively ($P = 0.007$ group 1 *vs.* placebo, $P = 0.003$ group 2 *vs.* placebo, and P = NS group 1 *vs.* group 2). Scores for hematocrit, MOS Short-Form Health Survey, International Index of Erectile Function, and American Urological Association Symptom Index Score did not change. Serum prostate-specific antigen levels increased in group 2 only (1.7 ± 1.0 to 2.2 ± 1.5 ng/ml, $P = 0.031$, compared with placebo).

These data demonstrate that aromatase inhibition increases serum bioavailable and total testosterone levels to the youthful normal range in older men with mild hypogonadism. Serum estradiol levels decrease modestly but remain within the normal male range. The physiological consequences of these changes remain to be determined. (*J Clin Endocrinol Metab* 89: 1174–1180, 2004)

IN WOMEN, THE dramatic fall in estrogen production is the biochemical hallmark of the menopause. Whereas no such event occurs in men, the male aging process is associated with a slow, steady decline in gonadal androgen production (1–10). Circulating levels of estrogens also decrease as men age, although this decrease is less dramatic than the decrease in serum androgens (11–13). Thus, testosterone/estradiol ratios are reduced in elderly men, presumably due to increased aromatase activity (14), and there is a high incidence of frank hypogonadism (7, 10).

The clinical significance of the decline in androgens in aging men remains controversial. Unequivocal hypogonadism is associated with a variety of symptoms and physiological alterations that are similar to changes that occur with normal aging in men including decreased libido, fatigue, decreased intellectual ability, decreased lean body mass, increased fat mass, and osteoporosis (15–20). Several studies have explored the role of androgen replacement in elderly men. Whereas most have reported increases in general sense of well-being, libido, muscle size, and lean body mass/body fat ratios, effects on strength and bone density have been more variable (21–26).

The safety of testosterone administration in elderly men, especially with regard to possible effects on the prostate, lipids, and red blood cell production remains a concern despite evidence suggesting that androgen replacement is generally quite safe in healthy aging men (27). Furthermore, although testosterone has been used pharmacologically since the 1940s, available androgen preparations are still not optimal. In particular, oral androgen replacement is limited by both toxicity and lack of efficacy. Anastrozole (Arimidex, AstraZeneca Pharmaceuticals) is a potent and selective orally administered aromatase inhibitor used in the treatment of breast cancer in women (28, 29). Because estradiol is a crucial mediator of hormonal feedback at the pituitary and hypothalamus in men (30–33), aromatase inhibition would be expected to promote pituitary stimulation of testicular testosterone production in men. Thus, anastrozole administration may be a novel means of normalizing testosterone levels in elderly men. To test this hypothesis, and to explore the physiologic effects of short-term aromatase inhibition in el-

Abbreviations: DHT, Dihydrotestosterone; PSA, prostate-specific antigen.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

derly men, we administered anastrozole in a placebo-controlled, double-blind study to elderly men with low levels of circulating testosterone and measured serum androgen, estrogen, and gonadotropin levels. Measures of prostate-related and other safety parameters, libido, and quality of life were also obtained.

Subjects and Methods

Study subjects

Forty-one men between the ages of 62 and 74 yr were recruited by advertisement in accord with institutional guidelines for clinical studies. All subjects were required to have screening serum testosterone levels between 150 and 350 ng/dl and normal serum LH and prolactin levels. Subjects were also required to have normal renal and hepatic function and a hematocrit between 35 and 50%. Subjects were excluded from participation if they had a history of malignancy (except basal cell carcinoma), a prostate nodule on digital rectal examination, a serum prostate-specific antigen (PSA) level greater than 4 ng/ml, a clinical history of acute urinary retention, a history of sleep apnea, significant cardiopulmonary disease, major psychiatric disease, or excessive alcohol or substance abuse. Additionally, subjects were excluded if they were taking any medication known to affect steroid hormone levels or steroid hormone binding protein levels (including androgens, estrogens, glucocorticoids, phenytoin, and carbamazepine).

A total of 126 individuals responded to our recruitment efforts and were screened by an initial blood sampling. Forty-one of these individuals were found to be eligible based on the laboratory criteria listed above. Of these 41, three subjects were found to be ineligible by physical examination and were excluded at that point. One additional subject voluntarily withdrew 3 wk before he completed the protocol due to a decrease in libido and other nonspecific symptoms, leaving 37 men who form the basis of this report. The study was approved by the Human Subject Committee of Partners Healthcare System, and all subjects provided written informed consent.

Randomization and methods

Subjects were randomized by computer-generated assignment to one of three treatment groups. Subjects in group 1 received one 1-mg anastrozole tablet daily for 12 wk. Subjects in group 2 received one 1-mg anastrozole tablet on Monday and Thursday of each week and placebo tablets on the remaining days for 12 wk. Subjects in group 3 received a placebo tablet daily for 12 wk.

Subjects were seen on the General Clinical Research Center at Massachusetts General Hospital every 4 wk for a total of four visits: wk 0 (baseline), wk 4, wk 8, and wk 12. All visits occurred on either a Monday or Thursday, and subjects were instructed to refrain from taking that day's medication until after the visit. Thus, subjects in group 1 would have taken the study drug approximately 24 h before each postbaseline visit (and blood sampling), and subjects in group 2 would have taken the study drug approximately 72–96 h before each postbaseline visit. At the conclusion of each visit, sufficient anastrozole (or placebo) was given to each subject to last until the following visit in weekly dose packs. Compliance was assessed by drug diary and inspection of empty drug containers.

Serum gonadal steroid, gonadotropin, and SHBG levels, routine chemistries, and complete blood count were measured at each visit between 8 and 10 h. Serum PSA was measured at wk 0 and 12. The following questionnaires were also administered at wk 0 and 12: American Urological Association Symptom Index Score (an index of benign prostatic hyperplasia severity) (34), the MOS Short-Form Health Survey (35), and the International Index of Erectile Function (index of male sexual function) (36).

Laboratory measurements

Serum bioavailable testosterone was measured by RIA after ammonium sulfate precipitation as described previously (37, 38). The intra- and interassay coefficients of variation were 8 and 9%, respectively. Serum total testosterone was measured by immunoradiometric assay (Diagnostic Products Corp., Los Angeles, CA). The intra- and interassay coefficients of variation were 10 and 12%, respectively. Serum dihydrotestosterone (DHT) was measured by column chromatography/RIA as described previously (2). The intra- and interassay coefficients of variation were 3 and 8%, respectively. Serum estradiol was measured by RIA (Diagnostic Systems Laboratory, Webster, TX). The intra- and interassay coefficients of variation were 2 and 8%, respectively. Serum estrone was measured by RIA (Diagnostic Systems Lab). The intra- and interassay coefficients of variation were 2 and 6%, respectively. Serum SHBG was measured using an immunometric technique (Immulite, Diagnostic Products Corp.). The intra- and interassay coefficients of variation were 6 and 8%, respectively.

Data analysis

End points were compared between groups by repeated-measures ANOVA with the baseline value included as a covariate. If significant differences were found, pairwise tests were performed to compare individual treatment groups. All P values are two-sided, and $P < 0.05$ was considered statistically significant.

Results

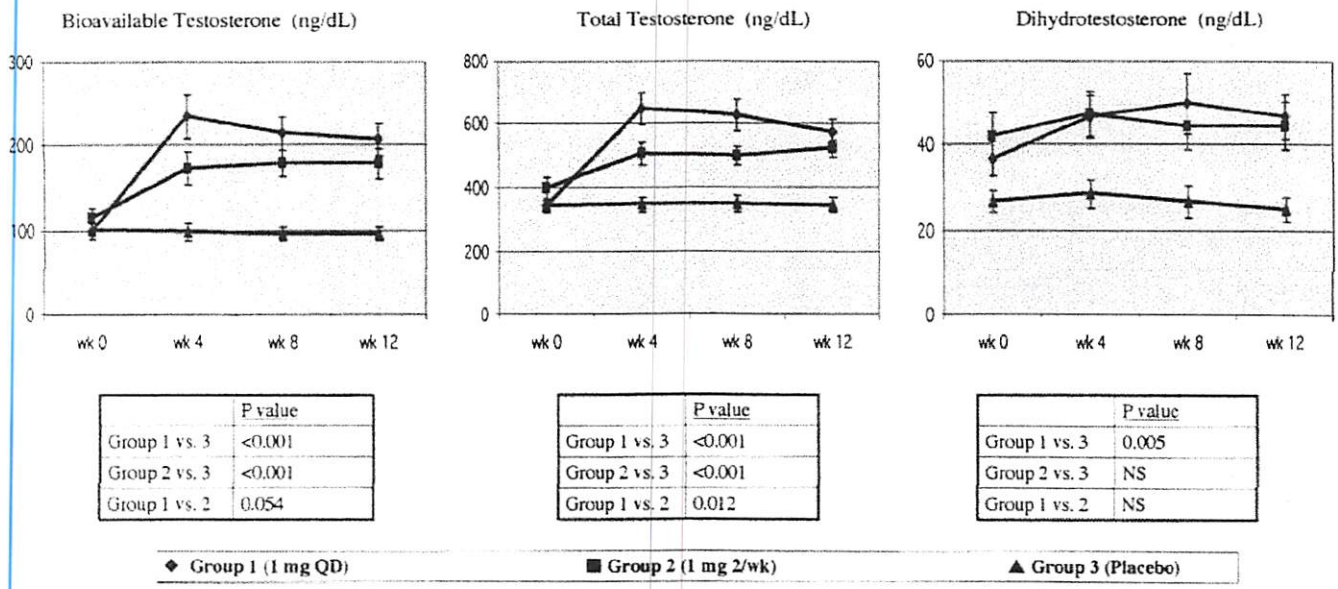
Table 1 shows the baseline clinical characteristics, gonadal steroid levels, and SHBG levels of the study subjects. There were no significant differences among groups.

Figure 1 shows the changes in serum bioavailable testosterone, total testosterone, and DHT during the 12-wk study period. Mean (± SD) serum bioavailable testosterone levels increased from 99 ± 31 to 207 ± 65 ng/dl in group 1 (anastrozole 1 mg daily) and from 115 ± 37 to 178 ± 55 ng/dl in group 2 (anastrozole 1 mg twice weekly) ($P < 0.001$ *vs.* placebo for both groups and $P = 0.054$ group 1 *vs.* group 2). Mean serum total testosterone levels increased from 343 ± 61 to 572 ± 139 ng/dl in group 1 and from 397 ± 106 to 520 ± 91 ng/dl in group 2 ($P < 0.001$ *vs.* placebo for both groups and $P = 0.012$ group 1 *vs.* group 2). Mean serum DHT levels increased from 37 ± 14 to 47 ± 18 ng/dl in group 1 ($P = 0.005$

TABLE 1. Baseline clinical characteristics and gonadal steroid concentrations

	Group 1 (anastrozole, 1 mg QD)	Group 2 (anastrozole, 1 mg twice weekly)	Group 3 (placebo)	Normal range
n	12	11	14	
Age (yr)	67 ± 3	67 ± 3	67 ± 4	
BMI (kg/m^2)	29 ± 5	29 ± 3	28 ± 5	
Bioavailable testosterone (ng/dl)	99 ± 31	115 ± 37	100 ± 34	70–320
Testosterone (ng/dl)	289 ± 37	290 ± 50	274 ± 51	270–1070
Estradiol (pg/ml)	26 ± 8	27 ± 8	23 ± 4	10–50

Values are reported as mean ± SD. No statistically significant differences between groups were observed. To convert values for bioavailable testosterone and testosterone to nmol/liter, multiply by 0.0347. To convert values for estradiol to pmol/liter, multiply by 3.67. BMI, Body mass index.



	P value
Group 1 vs. 3	<0.001
Group 2 vs. 3	<0.001
Group 1 vs. 2	0.054

	P value
Group 1 vs. 3	<0.001
Group 2 vs. 3	<0.001
Group 1 vs. 2	0.012

	P value
Group 1 vs. 3	0.005
Group 2 vs. 3	NS
Group 1 vs. 2	NS

FIG. 1. Mean (±SE) serum androgen levels during the 12-wk study period. To convert values for bioavailable testosterone and testosterone to nanomoles per liter, multiply by 0.0347. To convert DHT to nanomoles per liter, multiply by 0.0344.

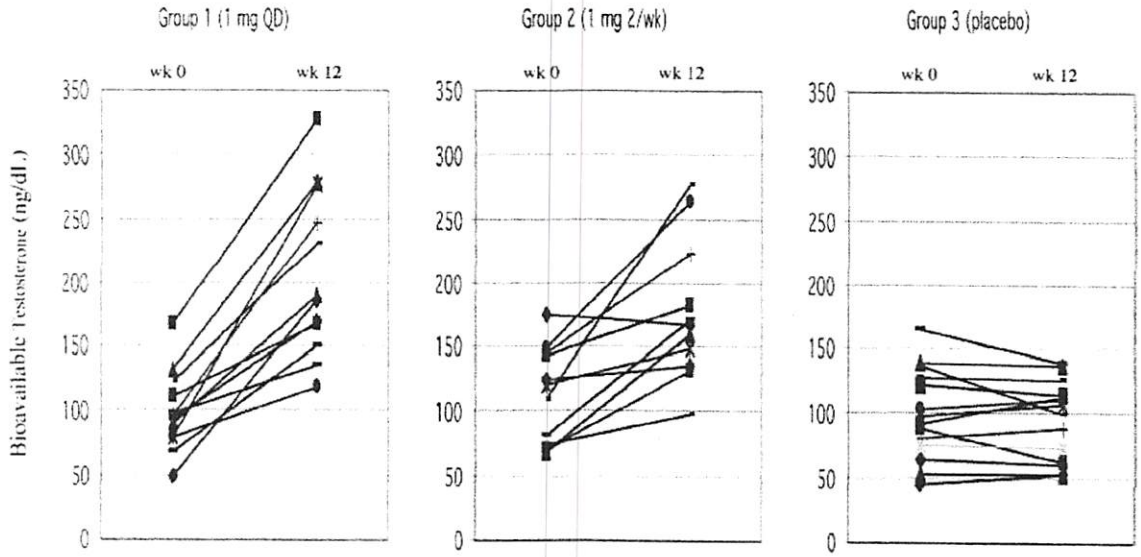


FIG. 2. Individual serum bioavailable testosterone levels at wk 0 and 12. To convert values for bioavailable testosterone to nanomoles per liter, multiply by 0.0347.

vs. placebo), but the increase in group 2 was not statistically different, compared with the placebo group.

Figure 2 shows the individual changes in bioavailable testosterone between wk 0 and 12 in the study subjects divided by group. Levels increased by more than 100% in six of the 12 men in group 1 and in three of the 11 men in group 2 but in none of the men in group 3. In fact, no subject in the placebo group had an increase in bioavailable testosterone of more than 22%.

Figure 3 shows the changes in mean serum estrogens during the 12-wk study period. Mean serum estradiol levels decreased from 26 ± 8 to 17 ± 6 pg/ml in group 1 and from 27 ± 8 to 17 ± 5 pg/ml in group 2 ($P < 0.001$ *vs.* placebo for both groups and P = NS group 1 *vs.* group 2). Notably, the 12-wk serum estradiol levels remained in the normal male range (10–50 pg/ml) in all but one treated subject (group 1 subject, level 9 pg/ml). Mean serum estrone levels decreased from 38 ± 19 to 21 ± 9 pg/ml in group 1 and from 45 ± 16 to 23 ± 7 pg/ml in group 2 ($P < 0.001$ *vs.* placebo for both groups and P = NS group 1 *vs.* group 2). Mean serum SHBG levels decreased from 38 ± 12 to 34 ± 12 nmol/liter in group 1 ($P = 0.015$ *vs.* placebo) but did not decrease significantly in group 2, compared with the placebo group.

Figure 4 shows the change in serum LH levels during the 12-wk study period. Mean serum LH levels increased from 5.1 ± 4.8 to 7.9 ± 6.5 U/liter and from 4.1 ± 1.6 to 7.2 ± 2.8 U/liter in groups 1 and 2, respectively ($P = 0.007$ group 1 *vs.* placebo, $P = 0.003$ group 2 *vs.* placebo, and P = NS group

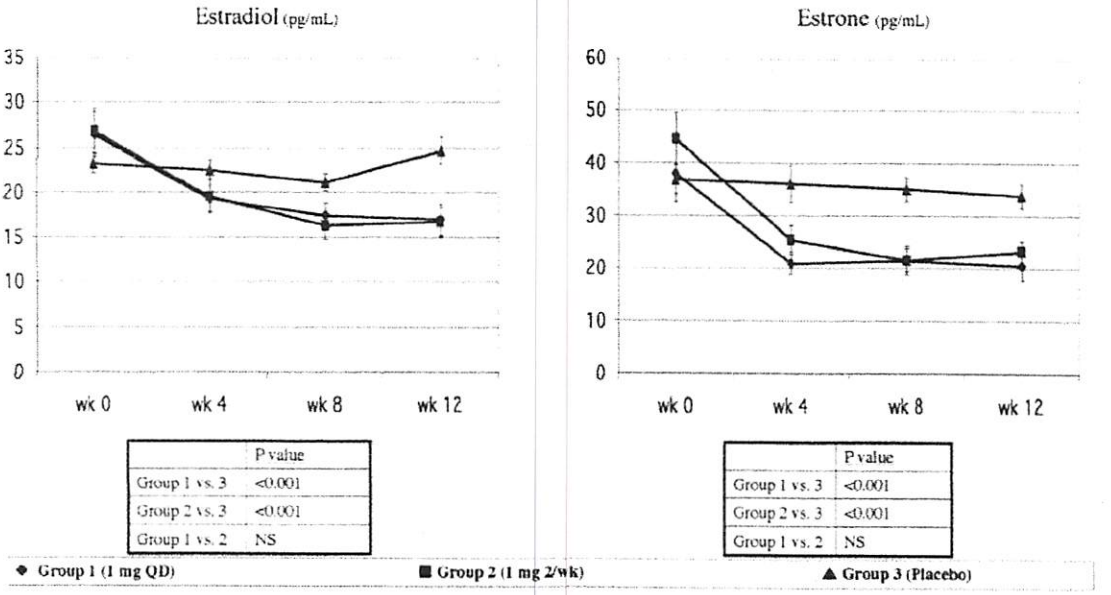


FIG. 3. Mean (±SE) serum estrogen levels during the 12-wk study period. To convert values for estrone and estradiol to picomoles per liter multiply by 37 and 3.67, respectively.

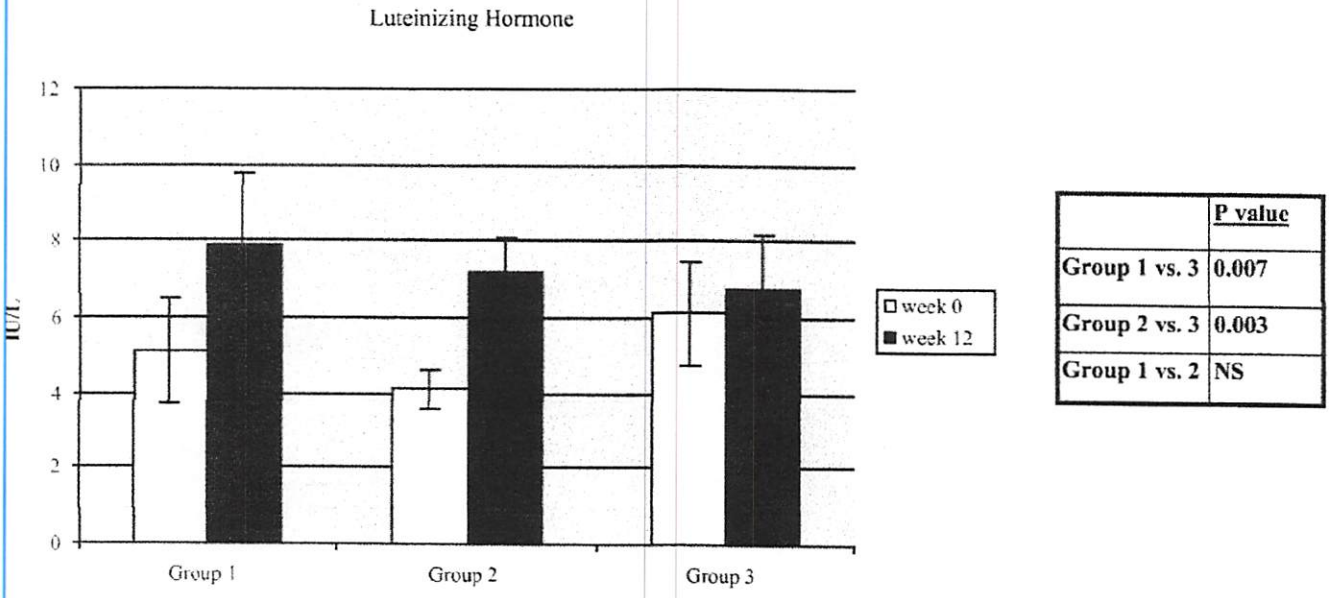


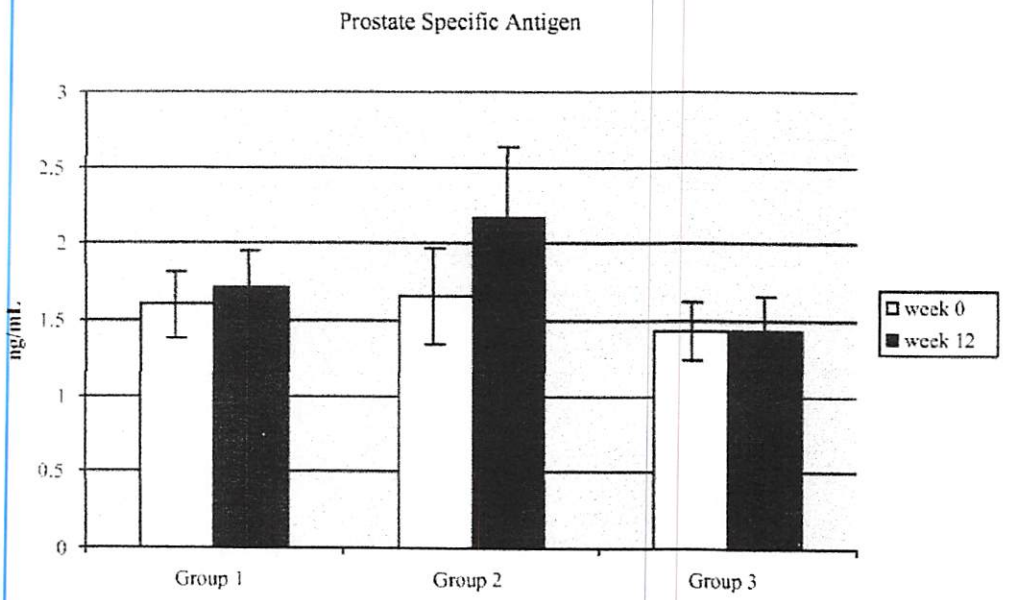
FIG. 4. Mean (±SE) serum LH levels at wk 0 and 12 in men receiving 1 mg of anastrozole daily (group 1), 1 mg of anastrozole twice weekly (group 2), or placebo (group 3).

1 *vs.* group 2). Mean serum FSH levels increased from 10.0 ± 13.9 to 13.9 ± 14.8 U/liter in group 1 and from 7.8 ± 6.5 to 10.3 ± 5.8 U/liter in group 2 ($P < 0.001$ group 1 *vs.* placebo, $P = 0.005$ group 2 *vs.* placebo, and P = NS group 1 *vs.* group 2).

No significant between-group changes were observed in health-related quality of life (MOS Short-Form Health Survey), erectile function (International Index of Erectile Function), or benign prostatic hyperplasia symptoms (American Urological Association Symptom Index Score).

Changes in PSA levels are shown in Fig. 5. Whereas the overall ANOVA was of only borderline significance ($P = 0.076$), PSA levels did increase significantly in group 2 *vs.* the placebo group (1.7 ± 1.0 to 2.2 ± 1.5 ng/ml, $P = 0.031$ group 2 *vs.* controls). PSA did not increase significantly in group 1 *vs.* the placebo group (1.6 ± 0.8 to 1.7 ± 0.8 ng/ml, P = NS group 1 *vs.* placebo). Two patients (both in group 2) had increases in PSA levels from below to above 4 ng/ml during the 12-wk study. Both patients underwent prostate biopsy. In one case, adenocarcinoma was diagnosed and the patient began external beam radiation. In the other case, the biopsy was negative and the subject has since been followed up without incident.

No changes were observed in hematocrit or hemoglobin



	P value
Group 1 vs. 3	NS
Group 2 vs. 3	0.031
Group 1 vs. 2	NS

FIG. 5. Mean (±SE) serum PSA levels at wk 0 and 12 in men receiving 1 mg of anastrozole daily (group 1), 1 mg of anastrozole twice weekly (group 2), or placebo (group 3).

levels. Similarly, liver function tests did not increase nor were any other significant toxicities reported.

Discussion

This study demonstrates that aromatase inhibition is an effective means of increasing testosterone production in elderly men with low or borderline low serum testosterone levels. Specifically, in this study we have shown that anastrozole, even at low doses, increases serum LH and testosterone levels robustly while decreasing serum estrogen levels in a more modest fashion.

Current testosterone replacement methods have important limitations. Oral androgens are potentially hepatotoxic and injectable testosterone esters result in supraphysiological peaks of testosterone levels followed by hypogonadal troughs (39). Transdermal testosterone patches frequently cause local skin reactions and are associated with a decline in serum testosterone concentrations toward the end of the treatment period (40). Testosterone gels appear to cause fewer dermatological reactions but can be associated with transmission of testosterone from male patients to female partners (41). Thus, a well-tolerated orally administered agent may have unique potential as a means of androgen replacement therapy. Furthermore, gynecomastia is a common side effect of current modes of androgen administration (27) but does not occur with aromatase inhibition as estrogens are reduced.

Anastrozole's effect on androgen production is likely directly mediated by the reduction in estrogen production. By reducing estradiol synthesis (and hence estradiol's negative feedback on the pituitary and hypothalamus) (30–33), anastrozole appears to stimulate pituitary LH secretion sufficiently to increase endogenous testosterone production to the mid-normal range for young healthy men. Furthermore, this increase in gonadotropin secretion is also likely responsible for limiting the reduction in estrogen levels and maintaining normal (albeit reduced) estradiol levels in treated subjects. In support of this hypothesis, it has previously been shown that GnRH-analog-blocked, but testosterone-replaced, men have much lower serum estradiol levels when given similar doses of anastrozole (42). Thus, the feedback loop of the hypothalamic-pituitary-gonadal axis effectively limits the potency of anastrozole to decrease estradiol production to a degree that may be more physiologically significant.

Whereas it has been well documented that gonadal steroid levels decrease with age in men, the mechanism underlying this decrease has not been defined. In fact, unless testosterone levels are severely depressed or other hormonal abnormalities coexist, the etiology of the hypogonadism is rarely related to overt gonadal or pituitary pathology (43). This observation suggests that more subtle physiological alterations are responsible for the changes in androgen levels observed in aging. For example, it has been suggested that the increase in gonadotropin levels in older men is a result of Leydig cell resistance to pituitary stimulation (2, 5, 8, 10). Alternatively, it has also been hypothesized that the gonadotropin-suppressive activity of androgens are increased in elderly men (44). Finally, as aromatase activity increases with age, an alteration in the estrogen/testosterone ratio may contribute to decreased androgen production (45, 46). Importantly, the effects of aromatase inhibition that we observed in this study are consistent with (but do not prove) a role of increased aromatization in the androgen deficiency in the aging male syndrome.

Anastrozole has been given to men of various ages in several small uncontrolled studies (47–49). In these studies similar changes in gonadal steroid hormone levels were generally observed. Interestingly, in a study of 15 eugonadal elderly men given 2 mg of anastrozole daily for 9 wk, serum

estradiol levels decreased by 29% and total testosterone levels increased by 56% (49). These changes are no greater than those observed in our subjects receiving half the dose and suggest the lack of a continued testosterone dose response beyond the 1-mg level. In fact, serum estradiol levels changed similarly in the two treated groups in the present study, indicating that the optimal dose of anastrozole may depend on the desired end point (decreasing estradiol *vs.* increasing testosterone).

The long-term physiologic effects of the increasing bioavailable testosterone and decreasing estradiol levels in elderly men are unclear. The primary end points in this study were changes in serum testosterone and estradiol concentrations. Whereas quality of life and libido measures were obtained, this study was not sufficiently powered to detect clinically important changes in these end points. Longer-term studies of traditional androgen replacement in men with low or borderline low testosterone levels have shown beneficial effects on these parameters as well as on body composition and bone mineral density (21, 22, 24–26, 50, 51). Because aromatizable androgens were administered in these studies, however, it is possible that similar improvements would not be observed in men receiving anastrozole. This issue may be especially important with regard to bone metabolism, in which the importance of estrogens in maintaining normal bone turnover has been established (42, 52). Additionally, the relative roles of androgens and estrogens in the central nervous system, lipid metabolism, vascular physiology, and cardiovascular risk in general are areas of considerable interest and importance in this population currently, but ones in which no definitive relationship has yet been defined (53).

The safety of androgen replacement in elderly men is currently an area of considerable controversy. Androgen administration in elderly men can cause polycythemia, especially with high doses of parenteral testosterone (22–24). Hematocrit did not increase in the treated subjects in the present study. Prostate size and PSA levels increased in some studies of androgen replacement in elderly men although a causative relationship between testosterone replacement and prostate cancer has not been established (54, 55). In the present study, serum PSA levels increased in subjects receiving the lower anastrozole dose and symptoms related to prostatic obstruction did not worsen in any group. Notably the possibility that estrogens may play a role in the development of both prostate cancer and hyperplasia has recently been suggested from a variety of animal studies (56–59). Specifically, in mice with selective inactivation of the aromatase gene, there was no induction of prostate malignancy despite dramatically elevated androgen secretion from birth (60). Thus, it is conceivable that the prostate-related risk profile of androgen replacement via aromatase inhibition might be different from that for standard androgen replacement therapy.

We conclude that the aromatase inhibitor anastrozole increases androgen production and normalizes serum testosterone levels in older men with mild hypogonadism. Serum estradiol levels are reduced but generally remain within the normal range for men. Longer-term studies are needed to assess the overall physiologic consequences of this combined hormonal alteration in aging men.

Acknowledgments

We are grateful to the nursing staff of the Mallinckrodt General Clinical Research Center for their meticulous performance of the study protocol. We are also grateful to Ms. Charlene Franz, Dr. Ping Patrick, Dr. John Morley, and the Immunodiagnostics Laboratory at Massachusetts General Hospital for the analysis of the gonadal steroids.

Received August 27, 2003. Accepted November 23, 2003.

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This work was supported by National Institutes of Health Grant K23-RR16310 (to B.Z.L.), the Massachusetts General Hospital Clinical Research Center grant (RR-1066), and AstraZeneca Pharmaceuticals.

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