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Testosterone, estradiol and aromatase inhibitor therapy in elderly men☆

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1. Introduction

Aging in men is associated with a steady decline in gonadal androgen production [1]. This decline leads to incidences of hypogonadism of 30% in men over 70 and 50% in men over 80 years of age [2]. Estrogen production also decreases as men age, but less so than testosterone, resulting in typical testosterone-to-estradiol (T/E) ratios that are significantly higher in older versus younger men [3–6]. The clinical significance of the decline in androgen production with aging is controversial. Unequivocal hypogonadism is associated with many symptoms and physiological alterations that are similar to changes that occur with normal aging. For example, both aging and hypogonadism are associated with loss of strength and muscle mass, decreased libido and erectile function, decreased cognitive function, and loss of bone mineral density [7–12]. Furthermore, androgen replacement in elderly men increases muscle mass, lean body mass/body fat ratios, well-being, libido, and bone density [13–18].

While many physicians encourage the use of testosterone replacement in older hypogonadal men, enthusiasm is often tempered by long-term safety concerns and sub-optimal androgen preparations. Specifically, oral androgen preparations are limited by their toxicity and lack of efficacy, and intramuscular testosterone provides supraphysiologic peak levels followed by sub-therapeutic troughs. Topical testosterone preparations (gels and patches) are improved methods of hormone replacement, but both topical and intramuscular testosterone administration cause concomitant increases in serum estradiol levels (via peripheral aromatization), and thus may contribute additional potential physiological effects or toxicities.

Several potent and selective orally-administered aromatase inhibitors are currently used in the treatment of breast cancer in women. Because estradiol is a crucial mediator of hormonal feedback at the pituitary and hypothalamus in men [19–22], aromatase inhibition would be expected to promote pituitary stimulation of testicular testosterone production in men while reducing estrogenic production. Thus, aromatase inhibition, with its unique properties, may be an efficacious method of hormone replacement in older men. Specifically, aromatase inhibition would be expected to support the beneficial effects of testosterone while reducing the effects of estradiol. Currently, effects of estradiol in men are not as well defined as those of testosterone. Recent data suggest, however, that estradiol may mediate many effects originally attributed to androgens. While estrogen's effects on muscle mass and strength are not defined and may be dominated by those of androgens, estrogen's effects on skeletal homeostasis, cognition, cardiovascular risk, and prostate health are becoming increasingly clear and are reviewed briefly below.

1.1. Skeletal physiology

The preponderance of the *in vitro*, animal, and human data currently suggest crucial roles for both androgens and estrogens in male bone metabolism. This conclusion is based on the fundamental observation that both androgen and estrogen receptors are expressed on osteoblasts [23–25], and is extended by various animal models [26–31]. In humans, case reports have shown that men with mutations in either the estrogen receptor-α gene or the aromatase gene are osteoporotic [32–34], and numerous studies have reported associations between serum estradiol levels and BMD or fracture in adult men [35]. Using combinations of GnRH analogs, testosterone, and aromatase inhibitor administration, we compared the bone turnover response in young men with either no hormone deficiency, combined andro-

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gen and estrogen deficiency, or selective estrogen deficiency, and found that both classes of hormones independently regulate bone resorption [36]. Because the administration of aromatase inhibitors to older men with hypogonadism will simultaneously increase serum testosterone levels and decrease serum estradiol levels, the net effect of this interaction on bone metabolism will thus reflect these two opposing stimuli. In an uncontrolled study of 15 eugonadal elderly men, the aromatase inhibitor anastrozole (2-mg daily) modestly increased one of the two bone resorption markers measured [37], suggesting that the assessment of bone metabolism will be an important end point for any study of aromatase inhibitors in hypogonadal men.

1.2. Cognitive function

Various *in vitro* and animal studies have demonstrated that the brain is a steroidogenic organ able to produce both androgens and estrogens from steroid precursors [38]. Hypogonadal men have impaired cognitive function and memory and serum testosterone levels correlate positively with several aspects of cognitive function [8,39–41]. In older men, higher levels of estradiol are associated with lower scores on certain tests of memory, whereas higher levels of testosterone are associated with better scores, suggesting a positive effect of androgens and a negative effect of estrogens [42]. Androgen replacement in older men has had inconsistent effects on cognition, with beneficial effects most commonly seen in the cognitive domains relating to memory and spatial tasks. Because most studies used aromatizable androgens, however, discerning androgenic versus estrogenic affects is not possible [14,43–46]. The specific effects of estrogen on cognition in older men have not been investigated. And while there was initial enthusiasm regarding the effects of estrogens on cognition in women based on animal and epidemiological studies, the results from randomized controlled trials suggest a deleterious effect [47,48]. Thus, it is conceivable that if testosterone administration does have positive effects on cognition in men, these effects may be extended by aromatase inhibition.

1.3. Prostate disease

The effect of testosterone on prostate health, particularly prostate cancer, has been a dominant issue in the androgen replacement field. While it is clear that androgens are necessary for normal prostate development, the roles that androgens play in initiating and supporting prostate cancer have not been defined. Testosterone is metabolized to DHT and estrogen within the prostate gland [49]. In humans, prostate carcinoma is an androgen-responsive tumor and androgen deprivation therapy is a commonly prescribed treatment for advanced disease [50]. Nonetheless, prospective studies have not shown a relationship between prostate cancer incidence and endogenous androgen levels whereas the case controlled Physicians Health Study did report increased prostate cancer risk in men with higher testosterone levels [51–53].

Though androgens have been the main focus of research investigating the effects of gonadal steroids on the prostate, *in vitro* and animal studies suggest that estrogens also play a role in the pathogenesis of both prostatic hyperplasia and prostate cancer [54–58]. Furthermore, studies in humans have shown that genetic polymorphisms in genes involved in estrogen metabolism and action (including estrogen receptor-α) are associated with prostate carcinoma development [59–61]. For these reasons, it is conceivable that the prostate-related risk profile of androgen replacement via aromatase inhibition is different than that for standard androgen replacement therapy.

1.4. Metabolism and cardiovascular risk

The influence of gonadal steroids on cardiovascular disease (CVD) and atherosclerotic disease has been investigated in both observational and interventional studies, though the latter have necessarily focused on surrogate markers of CVD. In observational studies, androgens are generally associated with beneficial lipid profiles and hypogonadism with adverse lipid profiles (low HDL, high LDL, total cholesterol and triglycerides) [62–65]. Conversely, some androgen administration studies have demonstrated deleterious effects on lipid profiles (reduced HDL and increased LDL), particularly with supraphysiologic doses [13–15,43,66–72].

Just as in postmenopausal women, oral estrogens raise serum HDL and triglycerides levels, and decrease total cholesterol and LDL levels in older men [73–75]. In women, these changes do not appear to provide any CVD benefit, however [76,77]. Increasingly, inflammation is recognized as an important mediator of all phases of arteriosclerosis, and interleuken-6 (IL-6) and C-reactive protein (CRP) are potent markers of cardiovascular risk [78–80]. Hormone replacement therapy (HRT) elevates CRP levels in women [81], but the effects of androgens or estrogens on CRP levels in men have not been extensively studied.

The effects of gonadal steroids on insulin sensitivity in men have been evaluated through observational and interventional methods. In contrast to the findings reported in women with polycystic ovarian syndrome, higher testosterone levels in men appear to be associated with increased insulin sensitivity [82–84] and lower levels of testosterone are associated with the metabolic syndrome of obesity and type 2 diabetes [85–88]. The effects of testosterone administration on insulin sensitivity have been mixed. In a small randomized, double blind, controlled trial of mildly-hypogonadal middle-aged men treated with either testosterone, DHT, or placebo, insulin sensitivity improved in both androgen treated groups but to a greater degree in the group treated with the nonaromatizable androgen DHT [89]. Conversely, in a case report describing a man with congenital aromatase deficiency, testosterone therapy increased and estradiol therapy decreased insulin resistance [90]. Estrogen administration had no direct effect on insulin sensitivity in hypogonadal men [91].

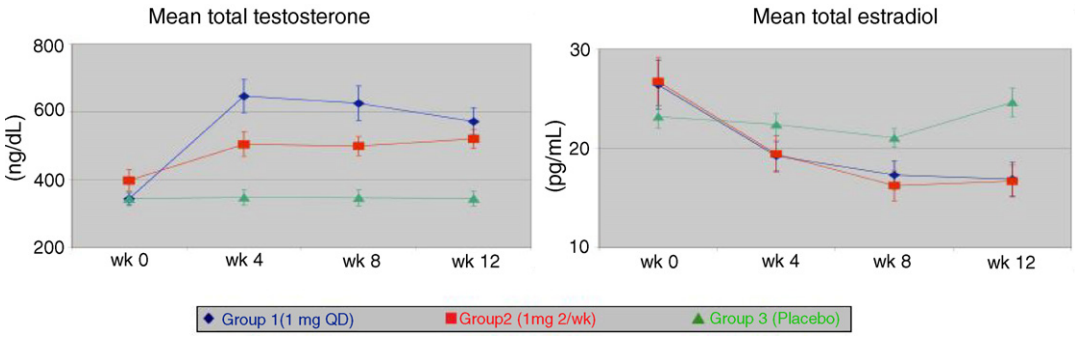

Fig. 1. Mean (+S.E.) serum testosterone and estradiol levels during the 12-week study period. Adapted from Ref. [94].

2. Studies of aromatase inhibitor therapy in men

Given the data discussed above, we hypothesized that aromatase inhibitor therapy:

(1) May be a novel means of normalizing testosterone levels in elderly men.
(2) May have unique beneficial efficacy and safety properties when compared to standard testosterone replacement.

To test the initial hypothesis, we performed a 12-week placebo-controlled double-blind study of the aromatase inhibitor anastrozole (Arimidex®, AstraZeneca Pharmaceuticals), in elderly men with low levels of circulating testosterone. The primary endpoints of this study were changes in gonadal steroid hormone levels. Realizing that testing the second hypothesis would require a longer-term study, we attempted to use the initial study to obtain early information regarding some of the biological and safety endpoints using surrogate markers of functional endpoints.

The details of the study protocol have been published [92–94]. Briefly, we randomly assigned 37 subjects to one of three double-blinded 12-week treatment groups. Subjects in group 1 received one 1-mg anastrozole tablet daily, subjects in group 2 received one 1-mg anastrozole tablet twice weekly, and subjects in group 3 received a placebo tablet daily. Subjects were seen every 4 weeks during the study and gonadal steroid hormone levels as well as the secondary endpoints discussed below were measured at each visit.

Baseline characteristics of our subjects are found in the above references and reveal a well-matched population. Mean baseline serum testosterone levels were in the mildly-hypogonadal range (274–290 ng/dL), whereas estradiol levels were normal (23–27 pg/mL). As shown in Fig. 1, aromatase inhibition proved to be an effective means of increasing testosterone production in elderly men with low or borderline low serum testosterone levels. Specifically, both doses of anastrozole normalized serum total testosterone (and to even greater degree bioavailable testosterone [94]) into the mid-normal range for healthy young men. Aromatase inhibition reduced estradiol levels modestly (<40%). Importantly, the 12-week 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). As expected, mean serum LH levels increased from 5.1 + 4.8 to 7.9 + 6.5 U/L and from 4.1 + 1.6 to 7.2 + 2.8 U/L in the lower and higher dose groups, respectively (Fig. 2).

To assess the effects of anastrozole on bone metabolism, we measured biochemical markers of bone resorption (serum *N*-telopeptide and urinary deoxypyridinoline) and biochemical markers of bone formation (osteocalcin and amino-terminal propeptide of type 1 collagen) in the subjects every 4 weeks during the study. None of these markers changed significantly [93]. Similarly neither lipid profiles (total cholesterol, HDL, LDL, triglycerides), markers of insulin sensitivity, nor pro-inflammatory markers of cardiovascular risk (C-reactive protein and interleukin-6) were altered by anastrozole therapy [92].

Mean PSA levels also did not change during therapy as measured by overall ANOVA, but a significant increase was observed when the lower dose group was compared with the control group (1.7 ± 1.0 to 2.2 ± 1.5 ng/mL, $P = 0.031$) [94]. This increase was largely driven by two patients, both

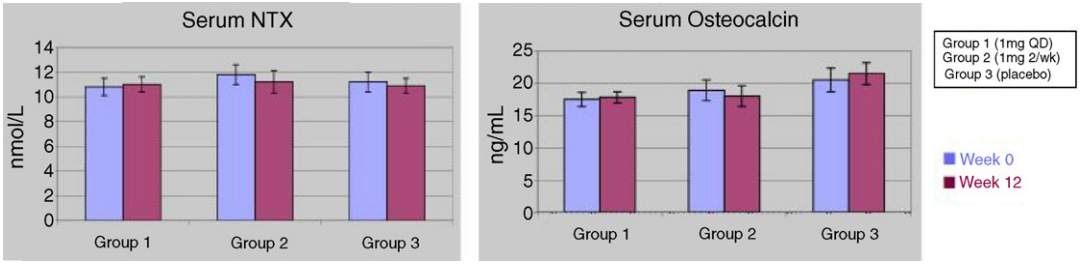

Fig. 2. Mean (+S.E.) serum *N*-telopeptide (NTX and osteocalcin (OC) at weeks 0 and 12. Adapted from Ref. [93].

of whom had increases in PSA levels from below to above 4 ng/mL (our cut-off for subject inclusion) during the 12-week study. Both of these men 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 without incident.

3. Conclusion

Hypogonadism in elderly men is an extremely common condition. Moreover, the recognition of hypogonadism in the elderly as an important clinical concern is likely to continue to expand as our population ages. Early studies suggest that aromatase inhibition increases androgen production and normalizes serum testosterone levels in older men with mild hypogonadism while reducing estradiol levels modestly. Short-term assessment, using early biological markers of physiological endpoints, suggests that this approach will be safe in older men. Longer-term studies are clearly needed, however, to assess the overall physiologic consequences and safety of this combined hormonal alteration.

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