Clinical Use of Aromatase Inhibitors in Adult Males

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ABSTRACT

Introduction. There is a growing interest in the treatment of late-onset hypogonadism, another name for the study of testosterone deficiency in an older age group. Initial attempts at testosterone replacement have also brought attention to the possible adverse effects on the patients' cardiovascular risk factors and their prostate health. The "female" hormone estradiol is no longer considered as the feminizing hormone, as it has been identified to have an effect on the sexual and general well-being of adult males. Urologists and endocrinologists alike have started to pay attention to the serum T/E_2 (testosterone : estradiol) ratio that appears to be more important than the respective individual hormonal levels. Therein lies the possible role of aromatase inhibitors (AIs) in restoring the normal balance of serum testosterone and estradiol levels for the adequate treatment of late-onset hypogonadism, while limiting the potential adverse effects. Currently, other established clinical indications of AIs include the treatment of breast cancer in female patients and developmental growth problems in pediatric patients.
Aim. This review evaluates the role of AIs as a treatment option for late-onset hypogonadism and the evidence for its other clinical uses in men, including its possible adverse effects.
Methods. A literature review was performed with regards to the use of aromatase inhibitors in adult males, the role of estrogens in adult males, as well as adverse effect of AIs on bone health in adult males.
Main Outcome Measures. To evaluate the evidence for the use of AIs in adult males to treat late-onset hypogonadism, obesity-related hypogonadotropic hypogonadism, gynecomastia, and male subfertility.
To evaluate the evidence for the possible adverse effects on the bone health of adult males with the use of AIs.
Results. Currently there is no literature to recommend the use of AIs in adult males to treat late-onset hypogonadism, obesity-related hypogonadotropic hypogonadism, gynecomastia, or male subfertility, although some positive effects have been reported. The adverse effects on bone health seen in females treated with AIs are not seen in males.
Conclusions. With the better understanding of the T/E_2 ratio in adult males, the lack of scientific data to show that bone health is adversely affected by AI usage in adult males, the positive effects of AIs on the treatment of conditions like late-onset hypogonadism and male subfertility encourages conducting large-scale, multicenter, randomized controlled trials for the clinical use of AIs in adult males. **Tan RBW, Guay AT, and Hellstrom WJG. Clinical use of aromatase inhibitors in adult males. Sex Med Rev 2014;2:79–90.**

Key Words. Late-Onset Hypogonadism; Testosterone Deficiency; Aromatase Inhibitors; Testosterone : Estradiol Ratio; T/E_2 Ratio; Low Testosterone

Introduction

Interest in the benefits of androgen replacement in males began as early as the end of the 19th century. Dr. Charles E. Brown-Sequard, Professor of Experimental Medicine at the College de France, made a presentation to the Societe de Biologie in June of 1889 with reports of his own observations on improved physical strength, intellectual capacity, and sexual vigor after repeated self-administration of a watery extract *liquide testiculaire* prepared from animal gonads [1]. Although we now know that Dr. Brown-Sequard's perceived clinical improvements were probably

due to a placebo effect (as testosterone is not water soluble), his presentation did ignite the first flames for the continued research of testosterone replacement in males. It was not until 1935, when three independent research teams led by Adolf Butenandt, Karoly Gyula, and Leopold Ruzicka (sponsored by Schering, Organon, and Ciba, respectively) were successful in its synthesis, that this powerful testicular hormone that "when injected into castrated animals would restore their maleness" [2] was ultimately named testosterone. Subsequently, Butenandt and Ruzicka received the Nobel Prize for Chemistry in 1939 for their seminal work on androgens.

Testicular function declines with advancing age [3], but unlike in menopause, where the ovary undergoes rapid functional involution, the change is incremental and of the same magnitude as that of other organs of the body [4]. The rate of serum testosterone decline is approximately 1% per year [5,6], once a man reaches his third decade of life. Understanding of the hypothalamic–pituitary–gonadal (HPG) axis brings to light the negative feedback that testosterone exerts on the hypothalamus and pituitary gland. In normal adult males, neurons in the preoptic area and the medial basal region of the hypothalamus secrete gonadotropin releasing hormone (GnRH), which in turn determines the pattern of secretion of the gonadotrophins, luteinizing hormone (LH), and follicle stimulating hormone (FSH), from the anterior pituitary gland. LH acts on the Leydig cells in the testis to produce testosterone whereas FSH regulates spermatogenesis in the basal aspect of the plasma membrane of Sertoli cells in the testis. Testosterone, along with its aromatized product, estradiol, then acts in a negative feedback mechanism on the anterior pituitary as well as the hypothalamus. Contrary to the traditional belief that estradiol is only important to female physiology, there is evidence that estradiol signaling via the HPG axis plays an important role in controlling GnRH and gonadotropin secretion in men. There are as many estradiol receptors as testosterone receptors in the hypothalamus and pituitary gland. This came from the observation of suppressed gonadotropins and low testosterone in men with estrogen-secreting tumors [7] and the profound inhibition of gonadotropin secretion via decreased pituitary response to GnRH with pharmacologic administration of estrogen or industrial exposure to diethylstilbesterol (DES) [8]. Estradiol is 200 times more potent as an inhibitor of gonadotropins when compared with testosterone. In males,

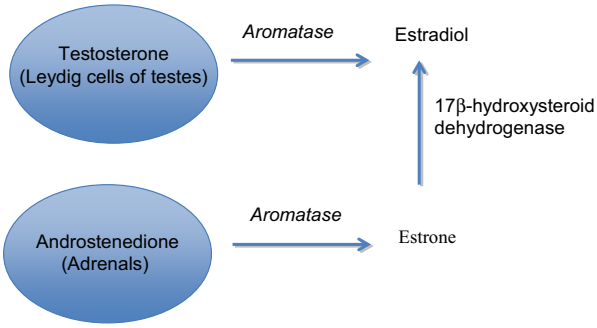

Figure 1 Sources of estradiol in men.

estradiol is primarily produced via peripheral aromatization of serum testosterone with the Leydig cells contributing 20% of the total serum estradiol. The adrenals contribute an even smaller percentage from the aromatization of androstenedione into estrone, of which a small portion is converted to estradiol [9]. The enzyme responsible for the peripheral conversion of testosterone to estradiol is known as the aromatase (Figure 1). The important contribution of estrogens to male health and the possible clinical use of aromatase inhibitors (AIs) in men derive from observations from case reports of men with aromatase deficiency and aromatase excess. Adult aromatase-deficient men demonstrate a remarkably low bone mass and unfused epiphyses leading to linear growth into adulthood and above-average body length. Bone has both testosterone and estradiol receptors. Both need to be stimulated to have normal bone metabolism. Estradiol regulates bone resorption and testosterone stimulated fibroblastic bone matrix formation. Once treated with estradiol, epiphyses close, bone mineral density (BMD) increases, and related metabolic disturbances improve in most of these patients [10]. Conversely, men with aromatase excess have the phenotype of gynecomastia, accelerated growth, and premature bone maturation during puberty due to excessive peripheral estrogen synthesis.

AIs could then be used to treat or prevent gynecomastia and increase gonadotropin secretion. Thereby stimulating Leydig and Sertoli cell function and prevent or delay epiphyseal closure, which increases adult height [11].

Estrogens in Males

Demographic factors that influence serum estradiol levels in males include age, body mass index (BMI), and race. Most studies report an

overall significant decrease in estradiol with age, including a greater decrease in testosterone compared with estradiol, which then leads to a decreased T/E_2 ratio [12]. There appears to be a direct relationship between estradiol and BMI with higher estradiol levels in obese men in many studies [13,14]. In Muller et al. [13], total testosterone, bio-available testosterone, and dehydroepiandrosterone-sulfate levels were noted to decrease with increasing age in 400 independently living men aged between 40 and 80 years. These levels were associated with increased BMI and waist circumference, along with increasing estradiol levels. It was also noted in this study that the general health status modified the effect between sex hormones and age. Some may argue that the endogenous testosterone levels are influenced by physical exercise, but Swerdoff et al. [15] show that endogenous testosterone levels are acutely and substantially influenced by physical exercise. This noted increase is less, transient, and tends to fade away after a short while in the elderly. On the contrary, low testosterone level itself could induce reduced physical fitness. The physical activity measured in Muller et al. [13] represents physical activity during the past year. Therefore, the increase in total testosterone (TT), bioavailable testosterone (BT), and sex hormone binding globulin (SHBG), found in the high-activity group, is probably a reflection of a favorable general health state rather than a high acute physical activity level.

However, in the osteoporotic fracture in men (MrOS) study [16], BMI did not influence the age-related decrease in estradiol, although there was a weak relationship with free estradiol. BMI reflects both visceral fat and subcutaneous, gluteal fat. The latter is known to have 10-fold higher aromatase activity as compared with the former [17]. In this study, the authors obtained subcutaneous abdominal adipose tissue as well as visceral (omental) adipose tissue from men, premenopausal women, and postmenopausal women who were either undergoing elective surgery or cosmetic surgery to investigate the aromatase expression in male and female subcutaneous and visceral fat. A study using computed tomography to measure subcutaneous fat in obese men aged 30–60 years [18] strongly associated free estradiol with subcutaneous fat, but not intra-abdominal fat or visceral fat. This could explain the differences in observation from the MrOS study. A large multinational study of sex steroid levels in 5,003 men reported 10–16% higher estradiol levels in African and African-American men compared with Asian and Caucasian men independent of age, BMI, and geography. T/E_2 ratios were also lower, suggesting that increased aromatase activity may mediate racial differences in sex-hormone levels [19].

Even in males, estradiol is necessary for normal bone development, with testosterone affecting radial bone growth [10]. There is growing interest in the synergistic effects of testosterone and estradiol facilitating endothelial-dependent vasodilation [20] and prevention of atherogenesis [21], thereby recognizing the importance of estrogens in cardiovascular health and metabolism.

The role of estrogens in male sexual function is poorly understood in humans, until Finkelstein's latest study shed some new light [22]. Animal studies suggest that estrogens play a role in male sexual function and behavior from the observation of mating behavior restoration in castrated male lizards [23], quails [24], rats, and hamsters [25] with estrogen administration, either by systemic or by intracranial routes. Now we have human data, especially because of the synergy between testosterone and estradiol in the central nervous system [22]. Systemic administration of estrogen to castrated rats even maintains erections during copulation [26]. Data from observational studies, e.g., Olmstead County, failed to find any relationship between estradiol levels and the Brief Male Sexual Function Inventory (instrument used to assess libido and erectile function) [27] or in the International Index of Erectile Function [28]. As exogenous testosterone therapy is known to suppress spermatogenesis and the HPG axis, clomiphene citrate, a selective estrogen receptor modulator, has been used for treatment of testosterone deficiency in men who still desire fertility. A 25-mg daily dose of oral clomiphene citrate has shown to increase serum testosterone levels and improve the T/E_2 ratio [29]. This led to the hypothesis that interaction between the hormones, as reflected in the T/E_2 ratio, may play an important role in male sexual function.

Castration, be it surgical or medical, causes a significant drop in the serum levels of testosterone and estradiol; however, estradiol decreases by a smaller amount. This is due to the aromatization of androstenedione, which is produced by the adrenals, into estrone, which is subsequently converted into estradiol. Gynecomastia in castrated men is postulated to be due to the relative excess of estrogenic activity over androgenic activity, i.e., T/E_2 ratio. It is interesting to note that from studies of castrated men [30], in the absence of testosterone, estradiol is sufficient for sexually

stimulated erections, but not for maintaining sexual interest and nocturnal erections. This suggests that estradiol plays a role in male sexual function. A recent randomized control trial [22] compared the changes in percentage of body fat and lean mass as well as muscle strength and sexual function between groups of healthy men aged 20–50 years of age who have received varying doses of testosterone gel, placebo gel, with or without anastrozole (an AI) for testosterone replacement after being administered goserelin acetate to induce a hypogondal state. In general, sexual desire declined as the replacement dose of testosterone was reduced. Both testosterone and estrogen contributed to the maintenance of normal libido, and erectile function and estrogen had a fundamental role in the regulation of body fat and sexual function. This suggests that estrogen deficiency is responsible for some consequences of male hypogonadism. Therefore, the authors recommend that measurement of estradiol levels might be useful in assessing the risk of sexual dysfunction, bone loss, or adipose accumulation.

At this point in time, we acknowledge potential problems with estradiol level monitoring in men. The main limitation of current commercially available assays (for determining female serum estradiol levels) for the detection of male serum estradiol levels lies in their poor accuracy with the normal range, as male levels are generally very low compared with female levels. In a recent editorial [31] regarding the requirement for mass spectrometry sex steroid assays in *Journal of Clinical Endocrinology and Metabolism*, the inaccuracy of former steroid immunoassays has prompted clinicians and scientists to move away from the initially overpriced and difficult methods of mass spectrometry steroid assays. The recent improvements of benchtop mass spectrometers have improved our abilities to measure the sex steroid levels accurately due to their sensitivity matching the best immunoassays while retaining reference level specificity and introducing multianalytic capability. In view of this change in the method of evaluating the hormone levels, it is understood that the publications and studies along the way may not have the same "normal" ranges, not to mention the sensitivity and specificity of these different tests. The gold standard test for measurement of such low serum estradiol levels is the gas chromatography/tandem mass spectrometry [32], which has shown to be superior compared with radioimmunoassay methods for monitoring levels of estradiol for the evaluation of AI therapy.

Brief Introduction to the AIs

The enzyme aromatase is found in the endoplasmic reticulum of the estrogen-producing cell and is the key enzyme in estrogen biosynthesis. The enzyme aromatase is able to convert testosterone into estradiol and androstenedione into estrone. Aromatase activity has been demonstrated in gonads, placenta, brain [33], adipose tissue [34,35], muscle [36], hair [37], bone [38], and vascular tissue [39].

AIs were first used for the treatment of metastatic breast cancer. They are now the standard adjuvant endocrine treatment for postmenopausal estrogen-receptor-positive breast cancers, but not without severe atrophic vaginitis. The concept of aromatase inhibition for breast cancer therapy started from the observation of adrenocortical toxicity with the use of aminogluethimide, originally developed as an antiepileptic. Aminoglutethimide inhibits the enzymatic conversion of cholesterol to 5-pregnenolone, resulting in a decrease in the production of adrenal glucocorticoids, mineralocorticoids, estrogens, and androgens. It was not until 1978 that there was a confirmatory study that aminogluethimide acted as an AI in vivo [40].

AIs are classified as either type 1 (steroidal) or type 2 (nonsteroidal). Examples of steroidal AIs are testolactone, formestane, and exemestane, which inhibit aromatase activity by mimicking the substrate androstenedione. They irreversibly inhibit the aromatase enzyme by covalently binding to it; as such they are also known as "suicidal inhibitors."

Nonsteroidal AIs inhibit enzyme activity by reversibly binding with the heme iron of the enzyme, resulting in competitive inhibition. Examples of nonsteroidal AIs are aminoglutethimide, fadrozole, anastrozol, letrozole, and vorozole (Table 1).

AIs are further classified into generations based on their efficacy. First generation inhibitors (e.g., aminoglutethimide) are relatively weak and nonspecific, whereas third generation AIs (e.g., letrozole and anastrozole) are most potent, most specific, and least toxic. Their pharmacokinetic properties ($t_{1/2}$ of 48 hours for ansatrozole and letrozole and $t_{1/2}$ of 27 hours for exemestane) allow for a once-daily dosing schedule. Their selective inhibitory properties negate the need for corticosteroidal or mineralocorticoid supplementation, which is essential for the nonspecific AI aminogluthimide. The second generation AIs are

Table 1 Classification of aromatase inhibitors

Generation	Type 1 (steroidal)	Type 2 (nonsteroidal)
First	None	Aminoglutethimide
Second	Formestane	Fadrozole
Third	Esemestane	Anastrozole
		Letrozole
		Vorozole

in between with regard to potency, specificity, and toxicity (e.g., formestane and fadrozole). Third generation AIs have been reported to have close to 100% inhibition of the enzyme, but this is not the case in males. In men, third-generation AIs will decrease the mean plasma estradiol/testosterone ratio by 77% [41,42]. This can be explained by the higher plasma concentration of testosterone in eugonal adult men compared with women. Because inhibition of aromatase is dose-dependent, aromatase is less suppressed in the testis compared with adipose and muscle, thus explaining the incomplete efficacy of aromatase inhibition in males. The molar ratio of testosterone to AI and testicular aromatase activity is higher compared with adipose and muscle tissue. As mentioned earlier in this article, low estradiol levels are detrimental to bone health and sexual function. Thus, this incomplete suppression may be advantageous to men, and this lowers the risk of the potential side effects of AIs. Long-term use of potent AIs reduces circulating estradiol levels by 88% [43]. This is associated with adverse effects on bone [44,45] and could possibly be associated with increased body fat in men [22].

Evidence for Its Use for Treatment of Late-Onset Hypogonadism

AIs lower estradiol levels, which negates the negative feedback mechanism of estradiol at the level of the pituitary gland, resulting in an increase in levels of gonadotrophins, e.g., LH, FSH, and a rise in serum testosterone [41,42]. This makes AIs a potential option to increase testosterone levels in men with low testosterone levels. However, we should note that for AIs to work, the patient must have normal function of the HPG axis. This is due to the fact that GnRH release is in a pulsatile manner, and the periodicity and amplitude of GnRH secretion determines the pattern of secretion of LH and FSH from the anterior pituitary. One pulse per hour of GnRH sustains gonadotrophin synthesis and secretion. Wildt [46] has demonstrated that deviation from normal pulse frequencies results in different effects on LH and FSH secretion in Rhesus monkeys. Adult men with late-onset secondary hypogonadism might find this to be effective, especially if gynecomastia or mastalgia is present. AIs appear to be a potential answer to the problems associated with current testosterone replacement preparations due to its ease of use (orally once daily), fast onset (may result in physiological 24 hours testosterone profile), without its potential misuse (supra-physiological testosterone levels cannot be achieved with use of AIs alone).

Leder demonstrated a doubling in bioavailable testosterone levels in elderly men, aged 62–74 years, being treated with 12 weeks of oral anastrozole (an AI) 1 mg daily [47]. This is one of the first few randomized control trials that looked at the use of AI in the treatment of late-onset hypogonadism. In this study, the side effects associated with traditional testosterone replacement therapy were not seen with use of anastrozole, e.g., rise in hematocrit, worsening of lower urinary tract symptoms (LUTS) as measured by the American Urological Association Symptoms Index Score. A statistically insignificant increase in serum prostate-specific antigen (PSA) levels was observed in the group treated with oral anastrozole 1 mg twice weekly when compared with placebo.

Another randomized controlled trial from the Netherlands [48] investigated whether hormone replacement with dehydroepiandrosterone (DHEA) and/or atamestane (AI) would improve the course of frailty in older men. A total of 100 non-institutionalized, healthy, independently living men aged 70 years and older with low scores on strength test were recruited and randomized to atamestane 100 mg daily and placebo, DHEA 50 mg daily and placebo, a combination of atamestane 100 mg daily and DHEA 50 mg daily, or two placebo tablets. These subjects were treated for 36 weeks, and physical frailty was measured by isometric grip strength, leg extensor power, and physical performance. Seventeen subjects did not complete the study. However, there were no differences between the treatment arms and the placebo group in any of the outcome measurements after intervention.

After the pilot study by Leder et al. in 2004, which showed anastrozole increases testosterone production and normalizes serum testosterone in older men with mild hypogonadism, investigators from Massachusetts General Hospital and Harvard Medical School carried out a 1-year, double-blind, randomized, placebo-controlled trial to assess the

effects of daily anastrozole administration on gonadal steroid hormone levels, body composition, strength, and prostate-related and other safety parameters in men aged 60 years or older with mild-to-moderate hypogonadism [49]. Men aged 60 years and older with total serum testosterone levels from 150 to 300 ng/dL on a single measure or from 300 to 350 ng/dL on two consecutive measures, symptomatic for hypogonadism were recruited and given either anastrozole 1 mg daily or placebo. Testosterone levels and bioavailable testosterone levels peaked at month 3 (322.8 ± 95.1 ng/dL to 524.5 ± 49.0 ng/dL and 77.8 ± 23.1 ng/dL to 155.6 ± 49.0 ng/dL, respectively), and this was statistically significant. However, these levels declined by month 12, albeit they were still significantly higher than baseline and greater than placebo. Estradiol levels, on the other hand, decreased significantly from 55.8 ± 15.4 pmol/L to 42.2 ± 13.6 pmol/L at month 3, and the levels stayed stable. Despite the changes in the hormonal levels, these alterations did not improve body composition or strength. There were also no changes in serum PSA, LUTS, hematocrit, or lipid levels. Sixty-nine patients completed the study. Eleven subjects in the anastrozole group and eight subjects in the placebo group withdrew during the study. Six subjects withdrew consent for nonmedical reasons. Five serious adverse events resulted in withdrawal: prostate cancer, pancreatic cancer, hepatitis A, pulmonary embolism, and embolic stroke. The patient who was diagnosed with prostate cancer came from the placebo group, and the rest of the adverse events were noted in the treatment group. Compliance with the drug was excellent as measured by pill counts and medication diaries. Although 12 months of anastrozole therapy resulted in restoration of testosterone levels into the mid-normal range for healthy young men, the lack of clinical benefit in terms of improved body composition or strength was disappointing. A possible explanation may be acquired resistance to aromatase inhibition or due to the influence of reduced estradiol production. The other explanation to the lack of clinical effects could be due to the fact that the mean baseline testosterone levels of the treated groups were slightly lower than the normal range for young adult men. Hence, the relative increase in testosterone levels may have been too small to elicit a clinically apparent response [11].

This observation that men with lower pretreatment baseline serum testosterone levels will benefit more from testosterone replacement therapy was evident in a study on the effect of testosterone treatment on BMD in men over the age of 65. The authors found that increasing the serum testosterone levels of a normal man over 65 years of age to the mid-normal range of young men did not increase lumbar BMD overall, but an increase in BMD was observed in those men with low pre-treatment serum testosterone levels [50].

A study was conducted on a small group of subjects to evaluate the effect of letrozole on gonadotropin response in young men when compared with old men [42]. Both groups were given placebo and letrozole 2.5 mg daily for 28 days with a 2-week washout in between and subsequently challenged with an intravenous 2.5 mcg GnRH bolus. Letrozole, 2.5 mg daily for 28 days, significantly increased LH levels by 339% in the young and 323% in the elderly with a corresponding clinically insignificant 146% increase and 99% increase in testosterone levels, respectively. This was associated with a clinically significant lowering of estradiol levels by 46% in young men and 62% in old men. Peak LH response to GnRH was a significant 152% increase and 52% increase from baseline in young and old men, respectively. Although AIs do affect their ability to restore serum testosterone level to that in of a normal young adult, in addition to lowering estradiol levels, these changes have failed to result in any clinically relevant improvements. Therefore, at this point, AIs are not recommended to treat patients with late-onset hypogonadism.

Evidence of Its Use in Obesity-Related Hypogonadotropic Hypogonadism

Metabolic syndrome (MS) refers to a clustering of various medical conditions, with a risk for development of diabetes mellitus and of cardiovascular disease. The components of the National Cholesterol Education Program—Adult Treatment Panel III and International Diabetes Federation definitions of MS include hyperinsulinemia, hyperglycemia, increased body size measured by waist circumference, serum high density lipoprotein (HDL) cholesterol levels, serum triglyceride levels, and blood pressure. Observations from the Massachusetts Male Aging Study [51] and Baltimore Longitudinal Aging Study [52] have confirmed that the prevalence of MS increases with age and is related to hypogonadism. The relationship of hypogonadism to MS remains even when using different definitions of MS (even adjusting for the individual components), and when follow-

ing patients prospectively for more than 10 years [53]. Obesity is a core element of MS and studies have shown that central obesity is associated with reduced testosterone levels [54], and that increasing waist circumference predicted low testosterone levels [50,55] better than BMI [56]. The association between obesity and testosterone is complicated. Obese men have lower levels of SHBG, and this should increase the serum total testosterone, while decreasing serum free testosterone. However, due to increased inflammatory cytokine production and increased aromatization of testosterone into estradiol in peripheral adipose tissue, this causes a fall in gonadotropins, thus resulting in a decrease in testicular production of testosterone. Elevated leptins in these obese men also interfere with LH and human chorionic gonadotropin (HCG) stimulation of androgen production [57], which again results in decreased androgen levels. Insulin resistance, which is present in patients with MS, also contributes to the decreased levels of serum total and free testosterone, by direct negative effect on the Leydig cells [58]. Testosterone has a suppressive effect on the expression of estrogen receptor β, which, in the presence of high levels of estradiol, suppresses the expression of glucose transporter type 4 (GLUT-4), resulting in insulin insensitivity [59].

Letrozole or testolatone has been used in morbidly obese men to improve their testosterone levels. In one study [60], a 6-week treatment with letrozole ranging from 7.5 to 17.5 mg per week significantly decreased serum estradiol from 120 ± 20 to 70 ± 9 pmol/L and increased serum testosterone from 216.1 ± 28.8 to 685.9 ± 86.5 ng/dL. Another study [61] showed that administration of testolactone 1 g daily for 6 weeks resulted in an increase in 24-hour mean serum testosterone from a mean of 290 ± 165 ng/dL to 403 ± 170 ng/dL as well as a decrease in 24-hour mean serum estradiol from a mean of 40 ± 10.8 pg/mL to 29 ± 6.7 pg/mL. A more recent study [62] showed that letrozole 2.5 mg once a week produced a sustained normalization of serum total testosterone in obesity-related hypogonadotropic hypogonadism. Unfortunately, this was not translated into decreased obesity, possibly due to the fact that estrogen deficiency may cause increased fat stores [22].

Evidence for Its Use in Treatment of Gynecomastia

Gynecomastia is postulated to be due to the imbalance between testosterone and estradiol. The rationale of using AI to treat gynecomastia draws its evidence from the treatment of hormone-responsive breast carcinoma in postmenopausal women using AI [63]. In the treatment of bicalutamide-induced gynecomastia and breast pain in patients with prostate cancer, tamoxifen 20 mg daily significantly reduced the incidence of gynecomastia or breast pain when used prophylactically and therapeutically in a randomized controlled trial, but anastrozole 1 mg daily failed to do so. AIs have shown to be efficacious in the treatment of gynecomastia of other etiologies, and the authors were unable to explain the ineffectiveness of anastrozole for the treatment of bicalutamide-induced gynecomastia [64]. A recent meta-analysis [65] also showed that prophylactic tamoxifen 20 mg daily as the first-line preventive measure and radiotherapy as the first-line treatment option for bicalutamide-induced gynecomastia and that AIs were not recommended. There are no randomized controlled studies with regard to the treatment of testosterone-induced gynecomastia with AIs, and the evidence is only from a case report [66] of successful treatment of gynecomastia in two patients on testosterone replacement therapy using anastrozole 1 mg daily. This is weak evidence, but it does correlate with the clinical experience of many practitioners. Both patients reported complete resolution after 1 month of treatment with anastrozole combined with cessation of testosterone therapy. There was no recurrence of gynecomastia even after restarting their previous testosterone replacement regimens.

Evidence for Its Use in Treatment of Male Subfertility

In 1934, Zondek [67] described the presence of an estrogenic compound in stallion urine. Thirty years later, Jayle et al. [68] confirmed that the human testis synthesizes estrogens under HCG control. Patients with congenital estrogen deficiency or estrogen resistance are noted to be infertile [69], and aromatase deficient men have impaired sperm motility and germ cell arrest at the spermatid stage [70]. It has been observed that men with severely impaired sperm production have a decreased T/E_2 ratio due to relative excess of estradiol to testosterone. The testis are the source of excess aromatase activity, where there is excess Leydig cell conversion of testosterone to estradiol [71]. Men with normal spermatogenesis have a mean T/E_2 ratio of 14.5 (calculated using

testosterone in ng/dl and estradiol in pg/mL), whereas men with severe male subfertility have a T/E_2 ratio of 6.9 [72].

In animals, evidence of the important role of estrogen in sperm production is seen in the local expression of aromatase. Estrogens play an important role in the reabsorption of fluid within the rete testis [73] and may have direct adverse effects on the germinal epithelium. High estrogen levels in combination with low testosterone levels have shown to impair spermatogenesis [74], confirming earlier data.

The first AI used for treatment of male subfertility was testolactone. In 1989, a randomized, controlled cross-over trial [75] investigated the use of testolactone, a steroidal AI, in men with idiopathic infertility. However, there was no improvement in semen parameters, and no pregnancies occurred in the treatment group or the placebo group. However, it was later discovered that the relatively high dose of testolactone (at 2 g per day) in this study might have resulted in suppression of testosterone production [76]. Other authors [72] treated subfertile males with a lower dose of testolactone (50–100 mg twice a day) and showed a statistically significant increase in T/E_2 radio and an improvement in sperm parameters. Testolactone is no longer clinically available in the United States.

Treatment with anastrozole 1 mg daily significantly increased T/E_2 ratios and improved sperm parameters [76] in subfertile men with abnormal T/E_2 ratios after a mean duration of 4.7 months.

Letrozole, 2.5 mg daily, induced spermatogenesis [77], documented on testis biopsy, in a man after treatment of 4 months. This was also associated with marked increase in serum testosterone levels and FSH levels. Another case series [78] of four patients with FSH levels less than 10 IU/L with non-obstructive azoospermia demonstrated return of sperm in their ejaculate after being treated with letrozole 2.5 mg daily. Similarly, mean FSH levels and serum testosterone levels were increased. This return of sperm is attributed to an increase in gonatrophins and testosterone with a paralleled decrease in estradiol. Other studies [79] have also shown improvement in sperm parameters in oligospermic men with letrozole treatment. Common side effects from treatment of AI include decreased libido (estradiol has a fundamental role in sexual function and a deficiency related to decreased libido [22]) and transient liver enzyme derangments, which were self-limiting after cessation of treatment.

Currently, there have been no large-scale randomized controlled trials to evaluate the role of AI in the treatment of male subfertility.

Adverse Effect on Bone Health in Men

The main concerns of AIs use lie in their possible adverse effects on bone health. Increased bone resorption and decreased BMD has been described in long-term use of AIs in postmenopausal women [44,45]. Both testosterone and estradiol are known to be critical for normal bone development and maintenance in men [80], as bone contains both testosterone and estradiol receptors. A randomized, double-blind, placebo-controlled trial [49] was conducted to assess the effects on aromatase inhibition on BMD in older men with low testosterone levels. Anastrozole 1 mg daily increased serum testosterone levels, decreased estradiol levels, and appears to decrease BMD. However, bone turnover markers, i.e., bone-specific alkaline phosphatase, octeocalcin, N-terminal propeptide of type 1 procollagen, C-terminal telopeptide of type 1 collagen, N-telopeptide of type 1 collagen, osteoprotegrin, were not affected. It is interesting to note that in this study, the BMD actually increased in the placebo group, making interpretation and validation of these results rather confusing. This finding was definitely not expected in these hypogonadic men over the age of 60. In this study, the apparent loss of BMD at the posterior–anterior spine suggests that the observed increase in testosterone, with aromatase inhibition, was insufficient to overcome the effects of selective estrogen deficiency on the skeleton. Alternatively, it is possible that if aromatase inhibition had produced higher serum testosterone levels, then BMD would have been maintained. Evidence to support this hypothesis comes from studies demonstrating that testosterone and estradiol have independent roles in maintaining normal bone turnover [81–83]. In some studies, there was greater association between estradiol and BMD in older men [84–86], whereas there was greater association between testosterone and BMD in others [87–89]. We traditionally equate bone health to BMD. Interestingly, bone strength is also impacted by the quality, mass, and geometry of the bone. Differential periosteal apposition can result in bone of different diameters. Because testosterone stimulates periosteal apposition and estradiol inhibits it, aromatase inhibition should change bone geometry and subsequently improve bone health [85,90]. However, in a study [91] looking at the relationship between

gonadal steroids and skeletal geometry in 808 men aged 30–79 years, estradiol was positively associated with hip strength parameters, whereas testosterone was not. This suggests that it is not the absolute levels of each hormone that are important, but perhaps the T/E_2 ratio. The long-term effects of AIs on bone health in males have also not been studied.

Recommendations

Current evidence from studies on AIs for the treatment of late-onset hypogonadism and MS shows an increase in testosterone levels and decreased in estradiol levels. Change in gonadal hormonal levels fails to result in any change in clinical outcome, except in the area of subfertility, but it shows promise and requires further studies. Although the improvement in sperm parameters seen in the case series is encouraging, there has also been no randomized controlled study for the use of AIs to treat male subfertility. However, improvement in sperm parameters does not necessarily equate to successful conception, which is multifactorial.

The evidence for AIs in the treatment of testosterone-replacement-related gynecomastia as well as bicalutamide-induced gynecomastia is weak and currently not recommended as standard treatment, until there are further studies.

Conclusions

AIs have their established use in the treatment of breast cancer in postmenopausal women. There are no scientific data that bone health appears to be adversely affected by AI use in adult men. AIs appear to reduce masalgia and gynecomastia, but more controlled trials are necessary. AIs may have a place in secondary hypogonadism, especially in older men, but better data are needed here also. Hence, additional large-scale, multicenter, randomized controlled studies to evaluate the benefit of AIs in the treatment of various conditions in adult men are warranted.

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References

1 Brown-Sequard CE. Note on the effects produced on man by subcutaneous injections of a liquid obtained from the testicles of animals. Lancet 1889;2:105–7.
2 Gallager TF, Koch FC. The testicular hormone. J Biol Chem 1929;84:495–500.
3 Lamberts SW, van den Beld AW, van der Lely AJ. The endocrinology of aging. Science 1997;278:419–24.
4 Perheentupa A, Huhtaniemi I. Aging of the human ovary and testis. Mol Cell Endocrinol 2009;299:2–13.
5 Wu FC, Tajar A, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva F, Forti G, Giwercman A, Huhtaniemi IT, Kula K, Punab M, Boonen S, Vanderschueren D; European Male Aging Study Group. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: The European Male Aging Study. J Clin Endocrinol Metab 2008;93:2737–45.
6 Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: Longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 2002;87:589–98.
7 Veldhuis JD, Sowers JR, Rogol AD, Klein FA, Miller N, Dufau ML. Pathophysiology of male hypogonadism associated with endogenous hyperestrogenism. Evidence for dual defects in the gonadal axis. N Engl J Med 1985;312:1371–5.
8 Finkelstein JS, O'Dea LS, Whitcomb RW, Crowley WF, Jr. Sex steroid control of gonadotropin secretion in the human male. II. Effects of estradiol administration in normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab 1991;73:621–8.
9 Saez JM, Morera AM, Dazord A, Bertrand J. Adrenal and testicular contribution to plasma oestrogens. J Endocrinol 1972;55:41–9.
10 Clarke BL, Khosla S. Androgens and bone. Steroids 2009;74:296–305.
11 de Ronde W, de Jong FH. Aromatase inhibitors in men: Effects and therapeutic options. Reprod Biol Endocrinol 2011;9:93.
12 Kacker R, Traish AM, Morgentaler A. Estrogens in men: Clinical implications for sexual function and the treatment of testosterone deficiency. J Sex Med 2012;9:1681–96.

13 Muller M, den Tonkelaar I, Thijssen JH, Grobbee DE, van der Schouw YT. Endogenous sex hormones in men aged 40–80 years. Eur J Endocrinol 2003;149:583–9.
14 Vermeulen A, Kaufman JM, Goemaere S, van Pottelberg I. Estradiol in elderly men. Aging Male 2002;5:98–102.
15 Swerdloff RS, Wang C. Androgens and aging in men. Exp Gerontol 1993;28:435–46.
16 Middle JG, Kane JW. Oestradiol assays: Fitness for purpose? Ann Clin Biochem 2009;46(Pt 6):441–56.
17 McTernan PG, Anderson LA, Anwar AJ, Eggo MC, Crocker J, Barnett AH, Stewart PM, Kumar S. Glucocorticoid regulation of p450 aromatase activity in human adipose tissue: Gender and site differences. J Clin Endocrinol Metab 2002;87:1327–36.
18 Vermeulen A, Goemaere S, Kaufman JM. Sex hormones, body composition and aging. Aging Male 2002;2:8–11.
19 Orwoll ES, Nielson CM, Labrie F, Barrett-Connor E, Cauley JA, Cummings SR, Ensrud K, Karlsson M, Lau E, Leung PC, Lunggren O, Mellström D, Patrick AL, Stefanick ML, Nakamura K, Yoshimura N, Zmuda J, Vandenput L, Ohlsson C; Osteoporotic Fractures in Men (MrOS) Research Group. Evidence for geographical and racial variation in serum sex steroid levels in older men. J Clin Endocrinol Metab 2010;95:E151–60.
20 Sader MA, Celermajer DS. Endothelial function, vascular reactivity and gender differences in the cardiovascular system. Cardiovasc Res 2002;53:597–604.
21 Van Pottelbergh I, Braeckman L, De Bacquer D, De Backer G, Kaufman JM. Differential contribution of testosterone and estradiol in the determination of cholesterol and lipoprotein profile in healthy middle-aged men. Atherosclerosis 2003;166:95–102.
22 Finkelstein JS, Lee H, Burnett-Bowie SA, Pallais JC, Yu EW, Borges LF, Jones BF, Barry CV, Wulczyn KE, Thomas BJ, Leder BZ. Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med 2013;369:1011–22.
23 Crews D, Morgentaler A. Effects of intracranial implantation of oestradiol and dihydrotestosterone on the sexual behaviour of the lizard *Anolis carolinensis*. J Endocrinol 1979;82:373–81.
24 Cornil CA, Dalla C, Papadopoulou-Daifoti Z, Baillien M, Balthazart J. Estradiol rapidly activates male sexual behavior and affects brain monoamine levels in the quail brain. Behav Brain Res 2006;166:110–23.
25 Arteaga-Silva M, Marquez-Villanueva Y, Martinez-Garcia R, Hernandez-Gonzalez M, Bonilla-Jaime H, Retana-Marquez S. Effects of hormonal replacement with androgens and estrogens on male sexual behavior and plasma levels of these steroids in gonadectomized golden hamsters (*Mesocricetus auratus*). Physiol Behav 2005;85:571–80.
26 Christensen LW, Clemens LG. Intrahypothalamic implants of testosterone or estradiol and resumption of masculine sexual behavior in long-term castrated male rats. Endocrinology 1974;95:984–90.
27 Gades NM, Jacobson DJ, McGree ME, St Sauver JL, Lieber MM, Nehra A. The associations between serum sex hormones, erectile function, and sex drive: The Olmsted County Study of Urinary Symptoms and Health Status among Men. J Sex Med 2008;5:2209–20.
28 Basar MM, Aydin G, Mert HC, Keles I, Caglayan O, Orkun S. Relationship between serum sex steroids and Aging Male Symptoms score and International Index of Erectile Function. Urology 2005;66:597–601.
29 Shabsigh A, Kang Y, Shabsign R, Gonzalez M, Liberson G, Fisch H. Clomiphene citrate effects on testosterone/estrogen ratio in male hypogonadism. J Sex Med 2005;2:716–21.
30 Bettocchi C, Palumbo F, Cormio L, Ditonno P, Battaglia M, Selvaggi FP. The effects of androgen depletion on human erectile function: A prospective study in male-to-female transsexuals. Int J Impot Res 2004;16:544–6.
31 Handelsman DJ, Wartofsky L. Requirement for mass spectrometry sex steroid assays in the *Journal of Clinical Endocrinology and Metabolism*. J Clin Endocrinol Metab 2013;98:3971–3.
32 Santen RJ, Demers L, Ohorodnik S, Settlage J, Langecker P, Blanchett D. Superiority of gas chromatography/tandem mass spectrometry assay (GC/MS/MS) for estradiol for monitoring of aromatase inhibitor therapy. Steroids 2007;72:666–71.
33 Stoffel-Wagner B, Watzka M, Schramm J, Bidlingmaier F, Klingmuller D. Expression of CYP19 (aromatase) mRNA in different areas of the human brain. J Steroid Biochem Mol Biol 1999;70:237–41.
34 Schindler AE, Ebert A, Friedrich E. Conversion of androstenedione to estrone by human tissue. J Clin Endocrinol Metab 1972;35:627–30.
35 Bulun SE, Simpson ER. Competitive reverse transcription-polymerase chain reaction analysis indicates that levels of aromatase cytochrome P450 transcripts in adipose tissue of buttocks, thighs, and abdomen of women increase with advancing age. J Clin Endocrinol Metab 1994;78:428–32.
36 Longcope C, Pratt JH, Schneider SH, Fineberg SE. Aromatization of androgens by muscle and adipose tissue in vivo. J Clin Endocrinol Metab 1978;46:146–52.
37 Schweikert HU, Milewich L, Wilson JD. Aromatization of androstenedione by isolated human hairs. J Clin Endocrinol Metab 1975;40:413–7.
38 Schweikert HU, Wolf L, Romalo G. Oestrogen formation from androstenedione in human bone. Clin Endocrinol (Oxf) 1995;43:37–42.
39 Harada N, Sasano H, Murakami H, Ohkuma T, Nagura H, Takagi Y. Localized expression of aromatase in human vascular tissues. Circ Res 1999;84:1285–91.
40 Santen RJ, Santner S, Davis B, Veldhuis J, Samojlik E, Ruby E. Aminoglutethimide inhibits extraglandular estrogen production in postmenopausal women with breast carcinoma. J Clin Endocrinol Metab 1978;47:1257–65.
41 Raven G, de Jong FH, Kaufman JM, de Ronde W. In men, peripheral estradiol levels directly reflect the action of estrogens at the hypothalamo-pituitary level to inhibit gonadotropin secretion. J Clin Endocrinol Metab 2006;91:3324–8.
42 T'Sjoen GG, Giagulli VA, Delva H, Crabbe P, De Bacquer D, Kaufman JM. Comparative assessment in young and elderly men of the gonadotropin response to aromatase inhibition. J Clin Endocrinol Metab 2005;90:5717–22.
43 Geisler J, Haynes B, Anker G, Dowsett M, Lonning PE. Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. J Clin Oncol 2002;20:751–7.
44 Perez EA, Josse RG, Pritchard KI, Ingle JN, Martino S, Findlay BP. Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: A companion study to NCIC CTG MA.17. J Clin Oncol 2006;24:3629–35.
45 Lonning PE, Geisler J, Krag LE, Erikstein B, Bremnes Y, Hagen AI. Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. J Clin Oncol 2005;23:5126–37.
46 Wildt L, Hausler A, Marshall G, Hutchison JS, Plant TM, Belchetz PE. Frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the rhesus monkey. Endocrinology 1981;109:376–85.
47 Leder BZ, Rohrer JL, Rubin SD, Gallo J, Longcope C. Effects of aromatase inhibition in elderly men with low or borderline-

low serum testosterone levels. J Clin Endocrinol Metab 2004;89:1174–80.
48 Muller M, van den Beld AW, van der Schouw YT, Grobbee DE, Lamberts SW. Effects of dehydroepiandrosterone and atamestane supplementation on frailty in elderly men. J Clin Endocrinol Metab 2006;91:3988–91.
49 Burnett-Bowie SA, McKay EA, Lee H, Leder BZ. Effects of aromatase inhibition on bone mineral density and bone turnover in older men with low testosterone levels. J Clin Endocrinol Metab 2009;94:4785–92.
50 Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH. Effect of testosterone treatment on bone mineral densityin men over 65 years of age. J Clin Endocrinol Metab 1999;84:1966–72.
51 Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. J Clin Endocrinol Metab 2006;91:843–50.
52 Rodriguez A, Muller DC, Metter EJ, Maggio M, Harman SM, Blackman MR. Aging, androgens, and the metabolic syndrome in a longitudinal study of aging. J Clin Endocrinol Metab 2007;92:3568–72.
53 Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP. The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: A prospective cohort study. J Clin Endocrinol Metab 2005;90:712–9.
54 Osuna JA, Gomez-Perez R, Arata-Bellabarba G, Villaroel V. Relationship between BMI, total testosterone, sex hormone-binding-globulin, leptin, insulin and insulin resistance in obese men. Arch Androl 2006;52:355–61.
55 Svartberg J, Jorde R, Sundsfjord J, Bonaa KH, Barrett-Connor E. Seasonal variation of testosterone and waist to hip ratio in men: The Tromso study. J Clin Endocrinol Metab 2003;88:3099–104.
56 Svartberg J, von Muhlen D, Sundsfjord J, Jorde R. Waist circumference and testosterone levels in community dwelling men. The Tromso study. Eur J Epidemiol 2004;19:657–63.
57 Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A. Leptin and androgens in male obesity: Evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab 1999;84:3673–80.
58 Tsai EC, Matsumoto AM, Fujimoto WY, Boyko EJ. Association of bioavailable, free, and total testosterone with insulin resistance: Influence of sex hormone-binding globulin and body fat. Diabetes Care 2004;27:861–8.
59 Cohen PG. Obesity in men: The hypogonadal-estrogen receptor relationship and its effect on glucose homeostasis. Med Hypotheses 2008;70:358–60.
60 de Boer H, Verschoor L, Ruinemans-Koerts J, Jansen M. Letrozole normalizes serum testosterone in severely obese men with hypogonadotropic hypogonadism. Diabetes Obes Metab 2005;7:211–5.
61 Zumoff B, Miller LK, Strain GW. Reversal of the hypogonadotropic hypogonadism of obese men by administration of the aromatase inhibitor testolactone. Metabolism 2003;52:1126–8.
62 Loves S, Ruinemans-Koerts J, de Boer H. Letrozole once a week normalizes serum testosterone in obesity-related male hypogonadism. Eur J Endocrinol 2008;158:741–7.
63 van Landeghem AA, Poortman J, Nabuurs M, Thijssen JH. Endogenous concentration and subcellular distribution of estrogens in normal and malignant human breast tissue. Cancer Res 1985;45:2900–6.
64 Saltzstein D, Sieber P, Morris T, Gallo J. Prevention and management of bicalutamide-induced gynecomastia and breast pain: Randomized endocrinologic and clinical studies with tamoxifen and anastrozole. Prostate Cancer Prostatic Dis 2005;8:75–83.
65 Tunio MA, Al-Asiri M, Al-Amro A, Bayoumi Y, Fareed M. Optimal prophylactic and definitive therapy for bicalutamide-induced gynecomastia: Results of a meta-analysis. Curr Oncol 2012;19:e280–8.
66 Rhoden EL, Morgentaler A. Treatment of testosterone-induced gynecomastia with the aromatase inhibitor, anastrozole. Int J Impot Res 2004;16:95–7.
67 Zondek B. Mass excretion of oestrogenic hormone in the urine of the stallion. Nature 1934;193:209–10.
68 Jayle MF, Scholler R, Sfikakis A, Heron M. [Excretion of phenol steroids and 17-ketosteroids after the administration of chorionic gonadotropins to men]. Clin Chim Acta 1962;7:212–20.
69 Rochira V, Granata AR, Madeo B, Zirilli L, Rossi G, Carani C. Estrogens in males: What have we learned in the last 10 years? Asian J Androl 2005;7:3–20.
70 Rochira V, Carani C. Aromatase deficiency in men: A clinical perspective. Nat Rev Endocrinol 2009;5:559–68.
71 Schlegel PN. Aromatase inhibitors for male infertility. Fertil Steril 2012;98:1359–62.
72 Pavlovich CP, King P, Goldstein M, Schlegel PN. Evidence of a treatable endocrinopathy in infertile men. J Urol 2001;165:837–41.
73 Carreau S, Bouraima-Lelong H, Delalande C. Estrogen, a female hormone involved in spermatogenesis. Adv Med Sci 2012;57:31–6.
74 Bharti S, Misro MM, Rai U. Clomiphene citrate potentiates the adverse effects of estrogen on rat testis and down-regulates the expression of steroidogenic enzyme genes. Fertil Steril 2013;99:140–8.
75 Clark RV, Sherins RJ. Treatment of men with idiopathic oligozoospermic infertility using the aromatase inhibitor, testolactone. Results of a double-blinded, randomized, placebo-controlled trial with crossover. J Androl 1989;10:240–7.
76 Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. J Urol 2002;167(2 Pt 1):624–9.
77 Patry G, Jarvi K, Grober ED, Lo KC. Use of the aromatase inhibitor letrozole to treat male infertility. Fertil Steril 2009;92:829 e1–2.
78 Cavallini G, Beretta G, Biagiotti G. Preliminary study of letrozole use for improving spermatogenesis in non-obstructive azoospermia patients with normal serum FSH. Asian J Androl 2011;13:895–7.
79 Saylam B, Efesoy O, Cayan S. The effect of aromatase inhibitor letrozole on body mass index, serum hormones, and sperm parameters in infertile men. Fertil Steril 2011;95:809–11.
80 Finkelstein JS, Klibanski A, Neer RM, Greenspan SL, Rosenthal DI, Crowley WF, Jr. Osteoporosis in men with idiopathic hypogonadotropic hypogonadism. Ann Intern Med 1987;106:354–61.
81 Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. J Clin Invest 2000;106:1553–60.
82 Leder BZ, LeBlanc KM, Schoenfeld DA, Eastell R, Finkelstein JS. Differential effects of androgens and estrogens on bone turnover in normal men. J Clin Endocrinol Metab 2003;88:204–10.
83 Lee H, Finkelstein JS, Miller M, Comeaux SJ, Cohen RI, Leder BZ. Effects of selective testosterone and estradiol withdrawal on skeletal sensitivity to parathyroid hormone in men. J Clin Endocrinol Metab 2006;91:1069–75.
84 Greendale GA, Edelstein S, Barrett-Connor E. Endogenous sex steroids and bone mineral density in older women and

men: The Rancho Bernardo Study. J Bone Miner Res 1997;12:1833–43.
85 Slemenda CW, Longcope C, Zhou L, Hui SL, Peacock M, Johnston CC. Sex steroids and bone mass in older men. Positive associations with serum estrogens and negative associations with androgens. J Clin Invest 1997;100:1755–9.
86 Khosla S, Melton LJ, 3rd, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: A key role for bioavailable estrogen. J Clin Endocrinol Metab 1998;83:2266–74.
87 Murphy S, Khaw KT, Cassidy A, Compston JE. Sex hormones and bone mineral density in elderly men. Bone Miner 1993;20:133–40.
88 Rudman D, Drinka PJ, Wilson CR, Mattson DE, Scherman F, Cuisinier MC. Relations of endogenous anabolic hormones and physical activity to bone mineral density and lean body mass in elderly men. Clin Endocrinol (Oxf) 1994;40:653–61.
89 Boonen S, Vanderschueren D, Cheng XG, Verbeke G, Dequeker J, Geusens P. Age-related (type II) femoral neck osteoporosis in men: Biochemical evidence for both hypovitaminosis D- and androgen deficiency-induced bone resorption. J Bone Miner Res 1997;12:2119–26.
90 Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson MK. Bone loss and bone size after menopause. N Engl J Med 2003;349:327–34.
91 Travison TG, Araujo AB, Beck TJ, Williams RE, Clark RV, Leder BZ. Relation between serum testosterone, serum estradiol, sex hormone-binding globulin, and geometrical measures of adult male proximal femur strength. J Clin Endocrinol Metab 2009;94:853–60.