Estrogens in Men: Clinical Implications for Sexual Function and the Treatment of Testosterone Deficiency

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ABSTRACT

Introduction. The role of estrogens in male sexual function and the pathogenesis of testosterone deficiency remain controversial and poorly understood.

Aims. To review the distribution of estrogens in normal and testosterone deficient men, their potential role in sexual function, and the clinical implications of elevated estrogens during testosterone therapy.

Methods. A comprehensive, broad-based literature review was conducted on the role of estrogens in male sexual function and testosterone deficiency.

Results. Estrogens elicit a variety of physiological responses in men and may contribute to modulation of sexual function. In the absence of testosterone deficiency, elevations in estrogens do not appear to be harmful and estrogens may help maintain some, but not all, sexual function in castrated men. While the therapeutic use of estrogens at pharmacologic doses has been used to suppress serum testosterone, naturally occurring elevations of estrogens do not appear to be a cause of low testosterone. During testosterone replacement, estrogens may rise and occasionally reach elevated levels. There is a lack of evidence that treatment of elevated estrogen levels during testosterone replacement has benefit in terms of male sexuality.

Conclusion. Further research on the importance of estrogens in male sexual function is needed. Current evidence does not support a role of naturally occurring estrogen elevations in testosterone deficiency or the treatment of elevated estrogens during testosterone therapy. **Kacker R, Traish AM, and Morgentaler A. Estrogens in men: Clinical implications for sexual function and the treatment of testosterone deficiency. J Sex Med **;**:**–**.**

Key Words. Estrogen; Testosterone Deficiency; Testosterone Therapy; Hypogonadism; Aromatase Inhibitors; Estrogen and Male Sexual Function

Introduction

Estrogens have been known to be present in substantial concentrations in men for several decades, yet their role in male physiology remains an area of considerable uncertainty and controversy. As interest in testosterone (T) deficiency and T therapy (TTh) has recently increased, there has been renewed interest in estrogens, particularly their role in sexual function. T and estrogen are inextricably linked, as T is a major source of estradiol (E2) via aromatization (see Figure 1).

Whereas the importance of estrogens in bone health for both men and women is well established, other aspects of normal or abnormal estrogen function are less clear and merit examination. In particular, there is significant inconsistency and confusion over the clinical importance of estrogens with regard to sexual function. Although it is commonly believed that estrogens have a negative impact on male sexual function, in animals E2 appears to be essential for male sexual function. The evidence regarding the contribution of estrogen in human male sexuality is limited and less clear.

For clinicians, the optimal management of high-normal or elevated estrogens remains a point of controversy either for men with symptomatic T deficiency or men with increased estrogen levels after TTh. Through this review, we aim to better

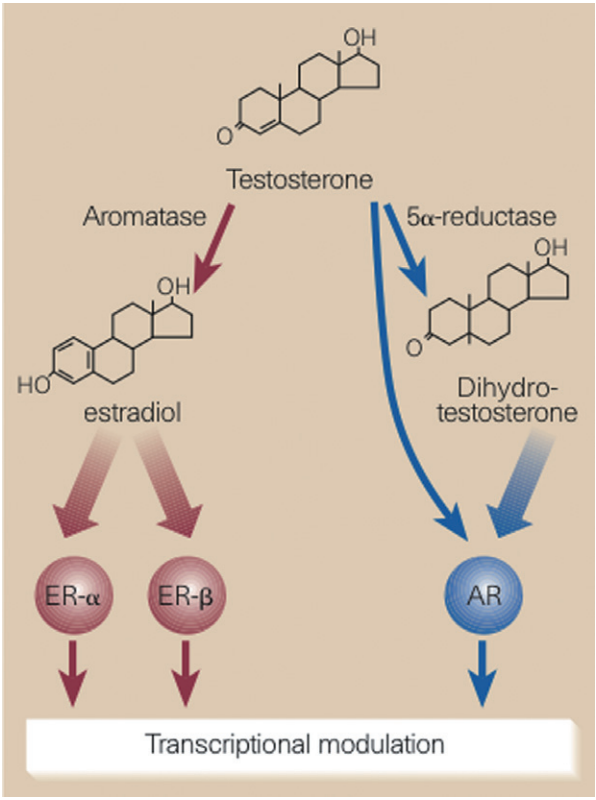

Figure 1 Testosterone and estradiol. Adapted from Sharpe et al. [1]. AR = androgen receptor; ER = estrogen receptor.

understand the clinical implications of estrogens in the treatment of sexual dysfunction and T deficiency in men.

Physiology of Estrogens

The basic steroidal structure of naturally occurring estrogens does not differ between mammals and insects and may have appeared early in evolutionary history [2]. While estrogens are defined by their "estrous," or feminizing, effects, they are found in both genders of most vertebrates [3] and play a role in spermiation and sexual behavior in male rodents [4]. Endogenous estrogens in humans are found as estrone (E1), 17β-estradiol (E2), and estriol (E3). Other variations on the basic steroidal estrogen structure have also been identified in humans, such as estetrol (E4), which is produced only by the fetal liver, and androstane 3β,17β-diol (3βD), which is found in low concentrations in postmenopausal women [5].

Of all known estrogens, E2 has the highest affinity for the estrogen receptors (ERs) and is the most biologically active [6]. In women, over 95% of E2 is produced by the ovaries and E2 levels vary by at least fivefold over a normal ovarian cycle. E1 may account for many of the estrogenic effects after E2 decreases during menopause. E3 is produced by the placenta during pregnancy and in low concentrations by metabolism of E2 in both sexes [7]. In men, E2 is the best studied estrogen and is primarily produced via peripheral aromatization of serum T. However, about 20% of serum E2 in men is produced by Leydig cells. Aromatization of the adrenal androgen androstenedione produces E1, a small portion of which is converted to E2 [8].

Aromatization and further modifications of E2 occur in peripheral tissues. Thus, it is important to recognize that estrogen may be produced, metabolized, and have local paracrine effects in target tissues, without necessarily affecting serum estrogen levels. As with T, a substantial fraction of E2 is bound to sex-hormone binding globulin (SHBG) and this fraction is not considered to be biologically active. SHBG binds E2 less avidly than T.

Recently, studies of breast cancer and HeLa cells have revealed that T may induce estrogenic effects independent of aromatase. 3βD, which is produced by an aromatase-independent pathway downstream of dihydrotestosterone (DHT), may mediate these effects [9]. It has been speculated that 3βD or other aromatase-independent estrogens may play a physiologic role in postmenopausal women or in male tissues such as the prostate in the presence of high levels of 5-α reductase. While 3βD is found in postmenopausal women [5], it is not known if it exists in significant concentrations in male serum or tissues.

The two best-characterized ERs are ERα and ERβ. They are found in a variety of tissues in both genders including brain, liver, fat, lung, bladder, and bone marrow [10]. Histologic studies have also found both ERs in corpora cavernosa, neurovascular bundles, urethra, seminal vesicles, and prostate [11], although ERβ generally dominates in urogenital tissues [12]. Steroidal estrogens traverse the cellular lipid membranes and bind ERs in the cytoplasm. The activated complex in turn translocates to the nucleus where it regulates gene expression [13]. There is significant redundancy and interaction between ER subtypes and the individual role of ERα and ERβ are not known. Furthermore, estrogens may also produce rapid and ER independent effects by binding G-protein coupled membrane receptors and activating intracellular signaling mechanisms [14].

Synthetic steroidal estrogens such as diethylstilbestrol (DES) have been developed and bind to the

ER with similar affinity as naturally occurring estrogens. Nonsteroidal compounds such as isoflavones are sometimes classified as "phytoestrogens" as they are found in a variety of plants, notably soy. These compounds have a spatial relationship between hydroxyl groups similar to those found in E2 and can bind ERβ, although only at one-third of the affinity [15]. Equol, a metabolite of soy isoflavones, can also bind ERα. However, the bacteria required to produce equol are not universally present in human flora and circulating serum concentrations are low even when these bacteria are present [16]. Isoflavones may also act as E2 agonists on cell membrane receptors and lead to rapid ER independent effects [17].

Pharmaceuticals such as clomiphene citrate and tamoxifen are classified as selective ER modulators (SERMs). These compounds bind to both ERα and ERβ and have agonist and antagonistic activity specific to target tissues. The SERMs and their metabolites modulate ER activation by inducing conformation changes to the ER and selectively altering signal transduction. Tamoxifen and clomiphene citrate have weak antagonistic effects on hypothalamic ERs. Tamoxifen has peripheral agonist effects on ERs in bone and other tissues [14].

There is substantial evidence that estrogen signaling via the hypothalamic–pituitary–gonadal (HPG) axis plays an important role in controlling gonadotropin-releasing hormone (GnRH) and gonadotropin secretion in men (see Figure 2). Early evidence came from the observation of suppressed gonadotropins and low T in men with rare estrogen-secreting tumors [18]. Similarly, pharmacologic administration of estrogens or industrial exposure to DES profoundly inhibits gonadotropin secretion via decreased pituitary response to GnRH. Compared with T, E2 is an approximately 200-fold more potent inhibitor of gonadotropins [19].

Further insight into the inhibitory effect of estrogens comes from observations in men with low E2 levels who are taking anastrazole, an aromatase inhibitor. For these men, there is a greater pituitary response to GnRH. Interestingly, luteinizing hormone (LH) pulse frequency is also increased suggesting that estrogen has an additional site of action at the level of the hypothalamus [20]. Recent studies have identified ER in both hypothalamic and pituitary tissues [10]. It appears that estrogen acts not only at the pituitary to decrease response to GnRH but also at the hypothalamus to decrease GnRH pulse frequency. Recent studies have also suggested that estrogen signaling interacts with the inhibitory effects of glucocorticoids and opiates on the HPG axis [21].

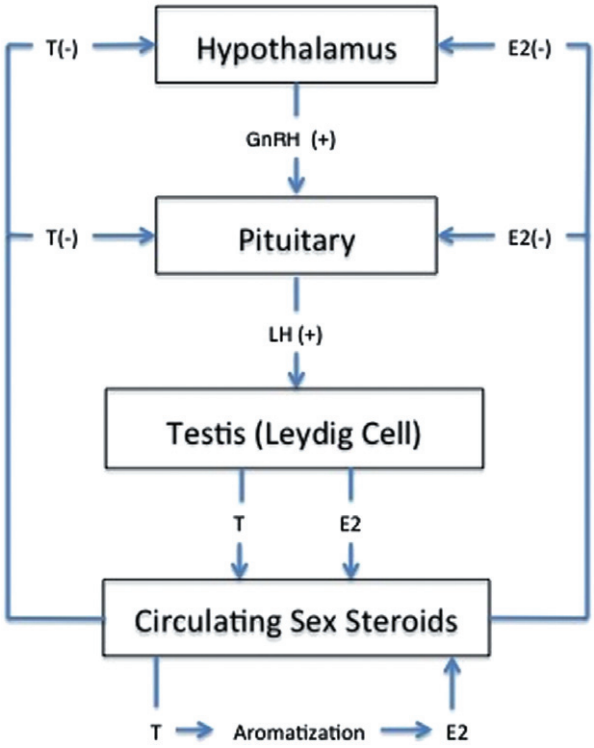

Figure 2 Inhibitory effect of E2 on the hypothalamic–pituitary–gonadal axis. E2 = estradiol; GnRH = Gonadotropin-releasing hormone; T = testosterone.

Epidemiology of Estrogens in Men

Serum estrogen levels in men are mediated by a number of competing influences. As T is the substrate for approximately 80% of serum E2, changes in serum T concentrations will affect E2 levels. Serum E2 levels may also be influenced by changes in aromatase activity [22] and estrogen breakdown and clearance [23]. Population-based cohort studies have found a roughly normal distribution of serum E2 in healthy men, without an obvious group with high or low E2 [24]. Here, we review the existing literature on demographic factors that may influence serum E2. It should be noted that most clinical studies in this review use commercially available unextracted immunoassays, which may have limited precision and accuracy for measurement of lower E2 levels [25].

Age

Multiple large cross-sectional studies have suggested variation in E2 within age groups, but an

overall weak but significant decrease in E2 with age [25–28]. However, this finding is not universal and a few studies have shown no change [29] or an increase in E2 [30] levels with age. Furthermore, some studies have shown an age-related decrease in bioavailable E2 with age, but not total serum E2 [31,32]. For example, among men aged 24–90 in the Rancho Bernardo study, a stronger association was found between age and bioavailable E2 than for total E2, with bioavailable E2 levels decreasing with advancing age [26].

Among 2,623 men over age 65 in the Osteoporotic Fractures in Men (MrOS) study, mean E2 was 65.4 ± 20.9 pmol/L with a decrease of only 9.0 pmol/L between men aged 65–69 and men over 85 years [25]. Although not directly comparable, the mean serum E2 was 70.6 ± 29.2 pmol/L for men aged 18–20 enrolled in the Gothenburg Osteoporosis and Obesity Determinants study [33]. Overall, these data suggest that on a population level, age-related changes in E2 are modest relative to the normal distribution in E2.

Longitudinal data on E2 are lacking, but serum E1 decreased by 3.6% per year over 7–10 years for men enrolled in the Massachusetts Male Aging Study (MMAS). Interestingly, cross-sectional data from the same study were conflicting and showed a minor decrease with age in E1 for the follow-up data, but no significant change for the baseline data. Longitudinal changes in E1 were not affected by obesity, self-reported alcohol consumption, or chronic illness. Further longitudinal studies are needed to better define the extent and significance of age-related changes in serum E2 [34].

A greater decrease in T compared with E2 with age was reported in all cross-sectional studies reviewed, leading to a decreased T : E2 ratio with age. In the longitudinal MMAS study, the age-related decline in E1 was not significantly different from the decline in T.

Body Mass Index (BMI)

Multiple studies have reported higher E2 levels in obese men and a direct relationship between E2 and BMI [29,31]. These findings are not universal, however, and in the MrOS study, BMI did not influence the age-related decrease in E2 although a weak relationship with free E2 was observed [25]. These different results may be due to the fact that BMI reflects both visceral fat, with low aromatase activity, and subcutaneous and gluteal fat with a 10-fold higher aromatase activity. Vermeulen et al. determined that subcutaneous fat as measured by computed tomography in obese men aged 30–60 was significantly and strongly associated with free E2, whereas abdominal fat was not [35].

Race

A large multinational study of sex steroid levels in 5,003 men reported 10–16% higher E2 levels in African and African-American men compared with Asian and Caucasian men independent of age, BMI, and geography. E2 : T ratios were also higher, suggesting that increased aromatase activity may mediate racial differences in sex-hormone levels [36]. Interestingly, African-American men have a lower rate of hip fractures, for which low E2 may be a risk factor [37].

Role of Estrogens in Men

The impact of estrogens on bone health in men is well studied. Longitudinal studies have shown that low total and bioavailable E2 levels are associated with increased rate of bone loss, with increased risk at a threshold of 40 pmol/L [32]. Recent cross-sectional data from the MrOS study revealed a threefold increased risk for osteoporotic fractures in men with a combination of low T, low E2, and high SHBG [38]. Androgen deprivation therapy with GnRH agonists, which leads to dramatic reductions in both T and E2, leads to a decrease in bone mineral density of up to 13% annually and an increased risk of fracture [39].

Males with low E2 levels from congenital aromatase deficiency exhibited tall stature, persistent linear growth, and delayed bone age and osteopenia/osteoporosis. E2 replacement produced skeletal maturation and completed epiphyseal closure. For one man with aromatase deficiency, treatment with T and E2, but not T alone, increased cortical thickness and normalized bone turnover parameters [40]. Estrogen appears to be necessary for normal bone development, but T may also appear to have independent effects through androgen receptors (ARs) on radial bone growth [41].

In addition to bone health, there is growing recognition of the importance of estrogens in cardiovascular health and metabolism. T and E2 together may facilitate endothelial-dependent vasodilation [42] and prevent atherogenesis [43]. Two men with congenital aromatase deficiency exhibited symptoms of the metabolic syndrome including abdominal fat accumulation and impaired insulin sensitivity. Interestingly, for one of these men, a period of treatment with pharma-

cologic doses of T led to acanthosis nigracans, type 2 diabetes, and a sharp increase in insulin resistance. Treatment with E2 improved insulin resistance and liver steatohepatitis, coupled with better glycemic control [44,45]. These cases suggest that a balance between T and E2 may regulate lipid accumulation and glucose homeostasis. Further study is needed, but excess T in the absence of E2 could potentially be harmful.

The importance of estrogens in prostate health is a hotly debated topic, with some studies showing changes in ER distribution in high grade prostate cancer [46]. The relationship between E2 levels and lower urinary tract symptoms (LUTSs) is unclear, with cross-sectional studies alternatively showing a positive, negative, or no association [47,48]. However, longitudinal data from Olmstead Country suggest that rapid decreases in E2 are associated with worsening LUTS [49]. The role of estrogens in prostate pathophysiology has been a subject of ongoing research and has recently been reviewed [50]. It has been postulated that estrogens play a role in prostate carcinogenesis, however this point remains controversial.

The role of estrogens in male fertility remains poorly characterized. Administration of pharmacologic doses of estrogen in men leads to infertility via negative feedback on the hypothalamus and pituitary. Evidence indicates that ERα is necessary for the reabsorption of seminal fluid from the efferent ductules and epididymis, and ERα knockout mice develop testicular swelling and ductal obstruction [51]. Additionally, recent studies have found that estrogen-deprived male baboon fetuses develop germ cell and seminiferous tubule perturbations, similar to rodent models [52].

Estrogens and Male Sexual Function

The role of estrogens in male sexual function remains poorly understood. In some animals, estrogens appear to potentiate or maintain mating behavior and erections while other studies suggest that estrogen administration may lead to erectile dysfunction (ED). As estrogen administration affects T levels through gonadotropin suppression, the independent effects of estrogen levels on male sexual function are difficult to ascertain. In humans, population-based and cohort studies have not shown a relationship between estrogen levels and sexual function. It is possible that estrogenic sexual effects are different for eugonadal, hypogonadal, and castrated men. For castrated men, there is some evidence that estrogens may maintain some sexual function in the absence of T. In this section, we review the existing studies on the role of estrogens in male animal and human sexual function and development.

Estrogens in Male Animals

In several higher vertebrate species, estrogens have a role in male sexual function and behavior. Intracranial E2 administration into known sexual centers of the brain restores mating behavior in castrated male lizards [53] and systemic administration increases mating behavior in quail [54]. In castrated rats and hamsters, E2 restores mating behavior [55], preserves the excitation of the bulbocavernosus muscle [56], and maintains erections during copulation [57]. Male knockout mice for ERα and ERβ lack typical male mating and aggressive behavior [58]. At birth, ERs are highly expressed whereas ARs are sparsely expressed in limbic neurons controlling these sexually dimorphic behaviors. During development, stimulation of ERs is necessary and sufficient for the expression of ARs and aromatase found in mature adult male neural pathways. After masculinization, execution of male behavior appears to be influenced by both ERs and ARs although the mechanisms and relative contributions of each are unknown [59].

In rodent studies, administration of exogenous estrogens leads to histologic changes associated with ED. Administration of oral E2 valerate or a phytoestrogen diadzein to rabbits reduced smooth muscle and decreased response to erectile neurotransmitters in corpora cavernosa organ bath studies [60]. Treatment of male rabbits with bisphenol-A, a xenoestrogen produced thickening of the tunica albuginea, subtunical deposition of fat, and decreased sinusoidal space [61]. It should be noted that T levels were dramatically reduced in these studies following estrogen administration, confounding simple conclusions. Similarly, in rats treated with diadzein, T and LH levels were reduced in parallel with reductions in apomorphine-induced erections [62]. While administration of estrogens appears to have antierectile effects, it is not clear what, if any, effect is independent of reductions in T.

The relevance of these animal studies to human sexuality is unclear. The distribution of ERs is known to vary between male mammals, including humans. In general, ERα dominates in rodent testicular tissue, whereas in human testis ERβ is dominant with two variants, ERβ1 and ERβ2, which have different patterns of expression. ERβ2 is also present in primates but has not been iden-

tified in rodents [63]. It was previously believed that ERα is absent from human testicular tissue, although it has recently been identified in small amounts [64]. Serum estrogen levels also vary between the males of mammalian species and are markedly higher in some nonprimate mammals, such as horses [65]. It is possible that the importance of estrogen in male sexual function is preserved despite evolutionary changes in ER expression and function, and animal studies may have some relevance to human sexual function.

Estrogens and Human Sexual Development

Little is known about estrogen in the sexual development of young men. A 28-year-old male with loss-of-function mutation in the ERα, normal total T, and elevated E2 reported strong heterosexual interest and normal erectile and ejaculatory function [66]. This is in contrast to the mouse model, where ERα knockouts do not exhibit mating behavior toward females. However, the patient had intact ERβ, which may be more important to human sexual function. In another case, a 27-year-old male with congenital aromatase deficiency leading to undetectable E2 and low but detectable E1 also had normal pubertal development and erections sufficient for penetration. The patient had severe osteoporosis and was treated with transdermal E2 for 6 months in order to bring E2 into the normal range. Interestingly, estrogen therapy led to a decrease in total serum T from 899 to 106 ng/dL along with a decrease in testicular volume and worsened sperm motility and morphology. The patient denied sexual dysfunction with estrogen therapy [67].

Estrogens and Human Sexual Function

A few studies have examined the importance of serum estrogen levels to human male sexuality, but no clear relationship has yet been demonstrated. A large-scale observational study from Olmstead County examined the relationship between total E2 and male sexuality in a population with a regular sexual partner. Libido and erectile function were assessed by the Brief Male Sexual Function Inventory and no correlation with serum E2 was found [68]. Similarly, a cohort study of 348 men hospitalized with urologic or musculoskeletal problems found no relationship between E2 levels and International Index of Erectile Function (IIEF) scores. However, increased E2, but not decreased T, was associated with nonsexual symptoms on the Aging Male Symptom (AMS) scale [69]. Another cohort study of 375 healthy men aged 45–85 years found that E2 levels correlated with T but not with sexual or nonsexual AMS scores [70].

While cohort and population-based studies have not demonstrated a relationship between ED and E2, E2 may be implicated in the subset of men with ED secondary to venous leakage. A comparison of men with cavernosal veno-occlusive dysfunction had significantly higher E2 levels compared with patients with ED due to other causes [71]. E2 has been found to accelerate repair of arterial injury through induction of nitric oxide and vascular endothelial growth factor (VEGF) expression [72], and one may speculate that a related vascular mechanism may play a role in men with ED.

Several investigators and clinicians have hypothesized that the interactions between androgens and estrogens, possibly reflected in the T : E2 ratio, may be important to sexual function. However, direct evidence of the importance of this ratio is limited. A study of men with ED showed an increase in the T : E2 ratio after 12 months of successful treatment with tadalafil. This was primarily driven by decreases in E2 and was observed in nonobese patients only [73].

Estrogens in Castrated Men

Studies of castrated men suggest that E2 may play a role with respect to erectile function but may be less important for libido. Some data come from men undergoing hormonal therapy with estrogen for prostate cancer and from individuals undergoing male-to-female (MtF) gender reassignment. Men undergoing castration surgically or using a GnRH analog may also yield insight into the role of estrogens. Castration produces profound decreases in both T and E2, but E2 decreases by a smaller amount. E1 may still be produced through aromatization of adrenally produced androstenedione, and some E1 may ultimately be converted to E2 [31].

A relative increase in bioactive estrogen is suggested by the finding of gynecomastia in some castrated men. Gynecomastia is the enlargement of glandular breast tissue that may occur in response to medications, estrogen-secreting tumors, or prior to a T surge in mid-to-late puberty [74]. Rigorous study of gynecomastia is difficult as some men diagnosed as having gynecomastia may actually have pseudogynecomastia or fatty prominence of the breasts without glandular tissue. However, it is commonly believed that gynecomastia results from a relative excess of estrogenic activity over androgenic activity. Up to

10% of men with prostate cancer treated with orchiectomy and an even higher proportion treated with a GnRH analog may develop gynecomastia. Tamoxifen, a SERM with antagonistic effects to breast tissue, is effective in reversing gynecomastia, providing further evidence for estrogenic activity in castrated men [75].

Interestingly, castration may be associated with preservation of sexually stimulated erectile function, even in the absence of sexual interest. Historians have reported "elevated" libido or erectile function sufficient for penetration for eunuchs across multiple cultures [76]. A review of castration of European sex offenders in the early 20th century found that some men retained a capacity for sexual intercourse. A more modern German study of sex offenders in the 1970s used a control group of noncastrated sex offenders but still relied on self-reported sexual symptoms. One-third of men reported erections sufficient for penetration, but all men reported a decrease in libido. Only 5% reported a "less than profound" decrease in sexual interest [77]. The question arises whether variation in nonandrogenic hormones, especially estrogens, may account for the persistence of sexual function and desire in some of these men.

Greenstein et al. reported that four of 16 castrated patients with prostate cancer developed erections in response to erotic visual stimuli documented by plethysmography and judged by both patient and investigator to be sufficient for penetrative intercourse [78]. Bergman et al. reported a higher rate of sexual activity among men with prostate cancer treated with DES (8 of 10) compared with orchiectomy, although sexual activity was self-reported and not necessarily synonymous with functional erection or orgasm [79]. Pooled data by Wibowo et al. demonstrated a similar nonsignificant trend toward increased self-reported potency in prostate cancer patients treated with DES vs. orchiectomy [50]. These data on castrated men come from small studies or historical anecdotes but suggest that estrogens may contribute to maintenance of sexual function in men in the absence of T.

Men with prostate cancer treated with an AR antagonist such as bicalutamide are likely to have higher E2 levels through aromatization of T. Patients treated with an antiandrogen alone have a higher rate of gynecomastia compared with men treated with surgical castration [39]. Bales and Chodak [80] and Tyrrell et al. [81] found greater quality of life secondary to sexual function and interest in prostate cancer patients randomized to bicalutamide compared with castration. These findings may result from the preservation of normal estrogen levels in men treated with an AR antagonist compared with the profoundly decreased estrogen levels seen in men who undergo castration.

Studies of sexual function in MtFs are limited by self-selection of estrogen supplementation and timing of gender reassignment surgery. However, this unique group provides some data on estrogen use in castrated genetic males. One study involved 25 presurgical MtFs receiving transdermal estrogen in addition to androgen suppression with an androgen antagonist, GnRH analogs, or both. All men reported no change in erectile function after hormonal therapy as assessed by the IIEF-15 questionnaire, although these data were not gathered prospectively. All men had normal penile color-coded Doppler ultrasonography (CDU) during pharmacologic and self-stimulated erection and 12 of the 25 men had normal nocturnal penile tumescence (NPT) tests. Interestingly, NPT results were highly correlated with T levels, whereas there was no relationship between T and CDU measures. These data suggest that T may be required for nocturnal erections, but nonandrogen pathways, possibly mediated by E2, may maintain sexually stimulated erection in the absence of T [82]. At our center, one MtF sought care for painful erections adequate for vaginal intercourse despite being on high-dose estrogens with presumably suppressed T.

These historical accounts and studies of castrated men suggest that in the absence of T, E2 may be sufficient for sexually stimulated erections but may not be sufficient for maintaining sexual interest and nocturnal erections. Similar results have been reported for young hypogonadal men, in whom erectile function in response to sexual stimuli was normal despite decreased sexual interest and nocturnal erections [83]. However, it is possible that prolonged lack of sexual interest and nocturnal erections may ultimately compromise erectile function in older hypogonadal men [84]. In contrast to animal studies suggesting a role for estrogen in facilitating mating behavior, there is a lack of data on the influence of E2 on libido and sexual interest in men with low T.

Further prospective research utilizing validated instruments and plethysmography is needed to further define the sexual role of estrogen in humans in the absence of T. Hopefully, motivation for this research may be found in a growing recognition of the possible benefits of estrogen

supplementation in androgen deprivation therapy in terms of bone health and also possibly cardiovascular function and mental acuity [50]. Additionally, it would be interesting to measure changes in the distribution of ERs in men after castration.

Estrogens in Eugonadal Men

Two studies have examined the role of estrogens in eugonadal men and suggest that aromatization of T is not required for normal sexual function. In a double-blinded randomized controlled trial, young healthy volunteers were administered a GnRH antagonist and then were randomized to receive T replacement with or without testolactone, an aromatase inhibitor. Men who received T replacement and testolactone had profoundly decreased E2 levels compared with men who did not receive testolactone. However, there was no difference in the frequency of sexual fantasies, masturbation, and intercourse between men who had T replacement with and without testolactone [85]. Similarly, Gooren did not find any change in sexual function after administering testolactone or tamoxifen to healthy, eugonadal men [86]. While these studies show that sexual function is not affected by acute withdrawal of estrogen in young, eugonadal men, the effect of chronic inhibition of estrogenic activity is not known.

The influence of increased estrogenic activity on sexual function in eugonadal men is unknown. A man who received ethinyl E2 25 μg once daily for 6 weeks for stuttering priapism maintained T within the normal range and reported adequate erections and sexual function [87,88]. With regard to endogenous estrogenic activity, a subset of men in the European Male Aging study with increased CAG repeat length in the AR gene was noted to have increased T and E2 levels. For these men, estrogenic activity as measured by calcaneal bone density was increased without any signs of androgen deficiency or impairment of sexual function [89].

Causes of Elevated Estrogens in Men

The upper limit of normal for E2 in men is not clinically defined. Laboratory reference ranges are assay dependent, but the upper bound is often stated as approximately 50 pg/mL or 160 pmol/L. We have previously discussed epidemiologic associations with E2, noting that BMI and African descent may be correlated with higher levels of E2. Here, we further examine factors and conditions that may lead to elevated estrogens in men.

Obesity is associated with an increase in E2 [31], likely secondary to increased aromatase activity in subcutaneous and gluteal fat [35]. Interestingly, E2 was reduced in obese men 2 years after gastric bypass surgery, and SHBG was increased, resulting in an even greater decrease in bioavailable E2 [90].

Genetic differences in aromatase may account for some of the difference in E2 levels in men. Homozygosity for a mutation in the CYP19 gene that codes for aromatase in young Swedish men results in 13% higher E2 compared with the normal genotype. This difference was also found in older men, although to a slightly lesser degree. Heterozygosity for the gene was associated with intermediate levels of E2 [91]. Polymorphisms in the aromatase gene may also be associated with an increased incidence of gynecomastia [92]. A rare gain-of-function mutation leading to increased aromatase activity by 11–24 times and markedly elevated E2 levels has also been identified. At least one man with this mutation presented with gynecomastia and hypogonadotropic hypogonadism [93]. It is conceivable that other gain-of-function mutations exist and may not be rare in some populations.

Animal and laboratory studies suggest that alcohol may suppress gonadotropins levels or directly impair Leydig cell function. However, baseline T levels are no different between alcoholics and controls [94]. Population-based studies have not found a conclusive relationship between alcohol consumption and T or E2 levels [26,30] While the influence of alcohol abuse on sex steroids remains unclear, E2 levels may also be affected by drugs or alcohol through potentiation of aromatase activity or inhibition of hepatic metabolism of E2.

Antiepileptic drugs, such as phenytoin and carbemazapime, are associated with high E2 levels in men with sexual dysfunction [95]. It has been suggested that this is secondary to increased aromatase activity. In many cases, the belief that increased E2 may be present is due to observations of gynecomastia related to a drug or condition. In most such cases, the relationship with estrogens is not known.

Clinical Implications of Elevated Estrogens

Elevated Estrogens and T Deficiency

Administration of exogenous estrogen at pharmacologic doses and, in rare cases, estrogen hypersecretion from adrenal tumors are known to

down-regulate T through gonadotropin suppression [96]. For this reason, it has been postulated that relatively high levels of endogenous serum estrogen may be responsible for T deficiency in some men. A frequently cited study of the inhibitory effect of E2 on LH production used a continuous infusion of 90 μg/day of E2 [19], which is considerably higher than the 25–40 μg/day naturally produced [8].

However, low T is most often associated with reduced concentrations of E2, not elevated E2. In population-based studies, total T parallels total E2, even at lower T levels [24]. TTh studies in otherwise healthy men with low or low normal T revealed E2 levels within the normal range, with most at the lower end of this range (Table 1). A study of men undergoing TTh at our institution suggested a limited relationship between T and E2 levels in men. No difference in E2 was found between men with very low (<200 ng/dL), low (200–300 ng/dL), or "normal" (>300 ng/dL) serum T [100].

Men with moderately increased E2 secondary to a nonrare polymorphism in the aromatase gene did not have lower gonadotropins or serum T compared with men without the mutation [91]. In another study, three men with rare gain-of-function mutation in aromatase had E2 levels many times the upper limit of normal (up to 1,439 pmol/L for one patient). For these men, T levels were low, but LH was within age-adjusted normal limits, suggesting that T was lowered by increased conversion to E2 rather than via feedback inhibition of gonadotropins. It appears that physiologic increases of E2 are different from pharmacologic increases, even at very high E2 levels. This difference may be mediated by changes in ER concentrations, by interaction with other inhibitory or excitatory signaling pathways on the HPG axis, or by the physiology of exogenously administered vs. endogenously produced estrogens [93].

Although the data indicate that the majority of T-deficient men have low or normal levels of E2, some of these men will have elevated E2. It remains to be determined whether these men respond differently to TTh compared with men without elevated E2. In addition, it appears to be unknown whether reducing serum E2 provides additional benefits to these men. While E2 is measured in many studies of TTh (Table 1), we did not identify any studies that examined the relationship between E2 and response to TTh. This is a topic that merits investigation.

Aromatase Inhibitors in T Deficient Men

Men with normal T have increases in LH and T in response to anastrazole [20]. Similarly, aromatase inhibitors increase T levels and decrease E2 levels in men with low T. E2 is known to suppress gonadotropins and some of the increase in T is likely due to reduced negative feedback from E2. T may also rise from decreased peripheral conversion to E2.

Only two studies of aromatase inhibitors in men with low T were identified in this review. A study of letrozole in severely obese men with hypogonadism demonstrated a significant increase in LH and T and decrease in E2 from baseline. T levels increased by 6 weeks and were sustained after 6 months of treatment. The presence of symptoms of low T at baseline and the response to letrozole was not reported [102].

In another study, 88 men with low T over 60 years were randomized to anastrazole or placebo. At baseline, all men reported symptoms of low T as determined by the Androgen Deficiency in Aging Males (ADAM) questionnaire. For men treated with anastrazole, T levels peaked after 3 months and were still significantly increased over baseline and placebo at 12 months. After 12 months of treatment, 11 of 44 patients receiving a placebo reported resolution of symptoms of low T, compared with only seven of 44 patients receiving anastrazole. Furthermore, patients treated with anastrazole did not have changes in body composition or muscle strength, or an increase in hematocrit, as would normally be seen in TTh studies [103]. It is worth noting that in this one study sexual symptoms were not improved despite normalization of serum T. This may have been due to inadequate improvement in serum T concentrations or perhaps a central effect of aromatase inhibition.

Interestingly, in the letrozole study, only one of 12 severely obese patients had elevated E2 prior to treatment. Individual data were not reported in the anastrazole study, but baseline E2 levels were on the low end of normal, with a mean of 55.8 pmol/L, several standard deviations below the upper limit of normal. These results should be interpreted with caution given concerns regarding accuracy of the assays used [25]. However, elevated E2 does not appear to be common in these men with low T.

In these two studies, aromatase inhibitors alone did not relieve symptoms of low T despite normalizing T levels. It is possible that this is due to insufficient T levels attained with aromatase

Table 1 Estrogen response in T therapy trials

Trial	Subjects	Intervention	Baseline E2	Impact on E2	Comment
Allan et al. [97]	60 men aged > 55 with T < 15 nmol/L and BMI < 30	RCT (52 weeks) 1) Androderm 5 mg daily 2) Placebo	 1) 50.9 ± 4.1 pmol/L 2) 53.6 ± 5.0	↔	No significant change in E2. Specific values not reported.
Amory et al. [98]	75 men aged > 65 with T < 12.1 nmol/L	RCT (36 months) 1) T enanthate 200 mg IM q 2 week 2) T + finasteride 3) Placebo	 1) 83.3 ± 44.4 2) 71.5 ± 33.7 3) 84.0 ± 33.3 pmol/L	↑	Significant increase in E2 for all men receiving T. Greater increase in E2 for men receiving both T and finasteride. Specific values not reported.
Chiang et al. [99]	38 men aged 20–75 with T < 300 ng/dL or FT < 8.7 pg/mL	RCT (3 months) 1) Daily androgel 5 g 2) Placebo	 1) 46.1 ± 23.7 2) 52.1 ± 16.0 pg/mL	↔	1) 54.5 ± 24.7 2) 47.3 ± 21.8 Nonsignificant increase in E2
Reyes-Vallejo et al. [100]	211 men, mean age 55.2 ± 9.7, with T < 300 ng/dL or FT < 1.5 ng/dL	Retrospective study: gel (137 points), T enanthate (65), patch (8), buccal (1) 1) T levels: 0–200 2) 201–300 3) 300+	All: 26.0 ± 9.93 pg/mL 1) 21.3 ± 12.9 2) 28.3 ± 10.8 3) 26.7 ± 7.85	↑	Specific values for each group not provided. Mean increase of 2.37 pg/mL in E2 for all subjects.
Schubert et al. [101]	40 men aged 18–64 with T < 5 nmol/L	RCT (30 weeks) 1) T ethanate 250 mg q 3 weeks 2) T undecanoate 1,000 mg q 6–9 weeks Prolonged TTh (N = 32): T undecanoate 1,000 mg q 8–12 weeks	 1) 23.1 ± 4.96 2) 21.6 ± 6.91	↑	1) 27.5 ± 9.33 2) 29.6 ± 8.02 E2 rose in parallel with T. Decline in E2 over time with prolonged TTh.

BMI = body mass index; E2 = estradiol; FT = free testosterone; IM = intramuscular; RCT = randomized controlled trial; T = testosterone; TTh = testosterone therapy

inhibitors compared with TTh. However, it is also possible that aromatization of T to E2 is partially responsible for some of the symptomatic and body composition response. Further research on the use of aromatase inhibitors in men with low T is needed.

Estrogen Modulators in T Deficient Men

Clomiphene citrate is a SERM sometimes used in the treatment of T deficiency, particularly when maintenance of fertility is desired, as treatment does not reduce gonadotropins or sperm concentration. Clomiphene acts as a weak estrogen antagonist at the level of the hypothalamus [104], increasing GnRH pulse frequency and both LH and follicle-stimulating hormone [105]. Shabsigh et al. treated 36 men with T deficiency with clomiphene citrate for 4–6 weeks and observed increases of nearly 150% in serum T [106]. Other studies have shown improvement in erectile function with clomiphene citrate in men with secondary T deficiency [107] and a recent nonrandomized study showed similar improvement in ADAM scores with clomiphene citrate compared with topical TTh [108].

While clomiphene citrate likely works by decreasing negative estrogenic feedback on the HPG axis, symptomatic benefit may be primarily due to increases in T alone. In the study by Shabsigh et al., T : E2 ratios increased, but this was driven by increases in T. Average E2 was not elevated at baseline and there was a nonsignificant increase from 32.3 to 46.3 pg/mL after treatment with clomiphene. The significance of these estrogen levels on overall estrogenic activity is unclear, particularly in the setting of a SERM. Tamoxifen not only has antagonistic effects on hypothalamic ERs but also has peripheral agonist effects that can decrease bone turnover and increase bone mineral density [109]. Tamoxifen has also been shown to raise T levels and may be effective in the treatment of male infertility [110] but does not seem to affect sexual function in healthy young men [86]. Further research is needed to determine how peripheral estrogenic effects of SERMs relate to male sexual function in the setting of T deficiency.

Estrogen Response to TTh

The response of estrogen to T administration was studied by Lakshman et al. In a group of young men and another group of older men, T enanthate was administered after pharmacologic gonadotropin suppression with leuprolide. Both total and free E2 levels increased with T administration in a dose-dependent fashion that was consistent with saturable Michaelis-Menten kinetics. There was a higher rate of aromatization in the group of older men that was partially but not completely explained by greater fat mass [111].

These results suggest that in T-deficient men, TTh should result in an increase in serum E2, possibly with greater increases in older or obese men. A PubMed review was performed to identify studies of TTh in which changes in E2 were reported. We limited our review to studies in T-deficient older men, without obvious chronic physical or mental illness or debilitation. Six studies were identified and are described in Table 1. There is substantial intra-assay variation and E2 levels are not directly comparable between studies. Additionally, interassay variation may be higher for low E2 levels [25].

In five of the six studies, mean baseline E2 was near the lower limit of normal. Only Chiang et al. reported levels that are generally considered toward the upper limit of normal although an assay reference range was not reported [99]. In five studies, E2 increased relative to baseline or placebo, but this only reached significance in three of the four largest studies. The increases in E2 paralleled increases in T, which is in accordance with the results shown by Lakshman et al. Additionally, there was an overall trend to greater increases with T injections, compared with topical therapies, although this was not rigorously evaluated. This may be due to higher peak serum T concentrations. Intramuscular T undecanoate may lead to greater increase in E2 over T enanthate [101].

In these studies, the number of patients who developed E2 levels above the normal range was not reported, however mean values were all well within normal limits. Interestingly, in some cases, an initial elevation in E2 was followed by decreased E2 after prolonged TTh [98]. This may be due to reduced adipose mass or decreased T concentrations. This observation was also seen in the study by Schubert et al. in which 14 of 32 patients treated for 28 months with intramuscular T undecanoate demonstrated an initial increase in E2 followed by a subsequent decline [101]. The influence of fat mass on E2 was not explored, but average BMI was 29.1 ± 5.1 kg/m^2, near the threshold for obesity, and it is known that fat mass reliably decreases with TTh.

Amory et al. studied patients receiving T enanthate with or without finasteride. The authors found that E2 increased after therapy in both groups, with greater E2 increases for patients

receiving finasteride. The authors commented on E2 results without providing actual data [112]. Inhibition of the conversion of T to DHT may result in increased availability of T as a substrate for aromatization to E2. DHT is not aromatizable but may be converted to an estrogen, 3βD, though aromatase-independent pathways. Compared with E2, 3βD is a weak binder of the ER and its clinical relevance is unknown [9]. It is possible that five alpha reductase inhibitors may increase estrogenic activity in men, as suggested by the occasional development of gynecomastia in men receiving these medications.

Elevated E2 During TTh: To Treat or Not To Treat?

TTh may lead to elevations in serum E2 and in some cases to levels above the upper limit of normal. The development of nipple or breast tenderness or frank gynecomastia has been reported in association with TTh, and in these cases there is a clear indication for the use of aromatase inhibitors to reduce E2. Some authors recommend withdrawal first of TTh with subsequent resolution of symptoms, followed by the use of aromatase inhibitors together with reinitiation of TTh [113]. Some clinicians, particularly in the antiaging community, advocate the routine use of aromatase inhibitors with TTh even in the absence of symptoms of estrogen excess. These clinicians believe that maintaining a relatively low estrogen concentration improves male health and the efficacy of TTh.

However, the basis for this belief is uncertain. In one randomized controlled trial, treatment of men with low T with anastrazole normalized T levels, but there was no improvement in symptoms of low T or changes in body composition, muscle strength, or hematocrit [103]. Further studies of this nature are needed. Furthermore, E2 levels in some men treated with aromatase inhibitors decreased below 40 pmol/L, considered the threshold at which there is increased risk of developing osteoporotic changes. Additionally, case reports of men with congenital aromatase deficiency suggest that aromatase inhibition may risk decreasing insulin sensitivity, potentially worsened by TTh [44,45].

The only trials identified in this review that compared the use of TTh with and without an aromatase inhibitor were conducted in men with hyposexuality and seizure disorders. One trial showed a significant benefit in sexual interest from the addition of testolactone therapy [114]. A second trial involving 40 men reported a trend toward improved libido in men treated with T and anastrazole over T alone, although this did not reach statistical significance. Some men in the T-only group reported improvement in libido despite increases in E2 with TTh [115].

The results of these studies should be interpreted with caution as it is not clear how this group compares with the larger group of T-deficient men. These men were all treated with antiepileptic drugs such as phenytoin and carbemazapime, which increase SHBG, likely through induction of hepatic synthesis, and may therefore impact androgen and estrogen concentrations and metabolism. Impotence, decreased libido, and infertility are common and associated with a deficiency in free T despite normal total T levels [116]. E2 levels are increased in hyposexual men with epilepsy compared with men with normal sexual function and with healthy controls [95].

We therefore find no evidence to support the contention that relative reductions in E2 via the use of aromatase inhibitors or other agents in conjunction with TTh offer benefits beyond that offered by TTh alone. Anecdotally, in our practice, there have been rare cases of men who failed to experience symptomatic benefits from TTh and were found to have elevated E2 concentrations. Some of these men have responded to steps to lower E2 concentrations, either by reduction in T dosage or by addition of aromatase. However, these cases are anecdotal, and even if treatment was beneficial, the rarity of such occurrences does not justify the routine use of aromatase inhibitors together with TTh. Moreover, aromatase inhibitors may reduce E2 levels below a crucial threshold for bone health, and dual-energy X-ray absorptiometry (DXA) monitoring should therefore be considered for individuals receiving such therapy.

Conclusions

E2 is essential to normal male sexual function in animals, however the data are inconclusive as to its effect in humans. There is some evidence that estrogens may contribute to the persistence of sexually stimulated erectile function when serum T is severely depressed, such as in men who have undergone castration for advanced prostate cancer men. It does not appear that naturally occurring elevations in E2 are harmful with respect to T levels or sexual function. E2 may increase during TTh, but elevations above the normal range are uncommon. Elevations in E2 may resolve with prolonged TTh. Symptoms of estrogen excess,

such as gynecomastia or nipple tenderness, are rare. Men who experience such symptoms should consider temporary or permanent discontinuation of TTh, or the addition of an aromatase inhibitor. We do not recommend the routine use of aromatase inhibitors with TTh. In the absence of signs of estrogen excess, we also find no reason to recommend the use of aromatase inhibitors in men who experience positive benefits from TTh despite elevated or high-normal E2 concentrations. When an aromatase inhibitor is used, it should be titrated so that E2 levels remain above 40 pmol/L to preserve bone health, and monitoring of bone mineral density with DXA is recommended.

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