Abstract

Androgens are essential for male physical activity and normal erectile function. Moreover, estrogens also influence erectile function, and high estrogen levels are a risk factor for erectile dysfunction (ED). In this review, we summarize relevant research examining the effects of the sex hormone milieu on erectile function. Testosterone affects several organs, particularly erectile tissue. The mechanisms through which testosterone deficiency affects erectile function and the results of testosterone replacement therapy have been extensively studied. Estrogen, the female sexual hormone, also affects erectile function, as demonstrated in both clinical and basic studies. Interestingly, estradiol-testosterone imbalance is considered a risk factor for ED. Furthermore, endocrine-disrupting chemicals have estrogen-like effects and cause ED. Phosphodiesterase-5 (PDE-5) inhibitors, first-line drugs for the treatment of ED, increase the levels of testosterone and estradiol in patients with low testosterone levels. Therefore, estrogen levels should be carefully monitored in patients receiving PDE-5 inhibitors. Future studies are needed to confirm these findings using molecular tools in order to provide insights into the treatment and mechanisms of endocrine-related ED.

Keywords: estrogen, testosterone, endocrine-disrupting chemical, phosphodiesterase-5 inhibitor, erectile dysfunction, endothelial function

1. Introduction

Serum estrogen levels are correlated with symptoms of aging in men, and estrogen may therefore play an important role in aging [1, 2]. Several previous studies have suggested that estrogen levels may also affect erectile function [3–6]. Indeed, older and obese men have been found to have not only low androgen levels but also high estrogen levels. Since testosterone is metabolized to estradiol by aromatase, the particularly high aromatase levels in visceral adipose tissue may explain the elevated estradiol levels among obese men [7]. Visceral adipose tissue often accumulates among men with increasing age. Interestingly, high estrogen levels have been observed in older patients who present with a lack of sexual interest and erectile dysfunction (ED); therefore, these symptoms in the elderly are thought to involve a pathophysiological estrogen-testosterone imbalance [6, 8–10].

Accordingly, in this review, we discuss the effects of sex hormone imbalances on male erectile function.
2. Erectile function and sexual hormones

There are many reports on erectile function and sexual hormones. Erectile function is controlled by complex mechanisms [11], including the vascular and nervous systems [12–16]. One of the most important materials is a nitric oxide (NO). After NO is releasing in the penis, corporal smooth muscle relaxes. However, when NO production is decreased, the erectile function weakened, resulting in ED. The relaxant system is also important for the erectile function. The relaxant system is controlled by both the endothelial and the nervous systems. When the upper stream of smooth muscle relaxant system is weakened, ED is caused; therefore, many studies have focused on smooth muscle relaxation. In contrast, corporal smooth muscle contraction is controlled by constrictors, such as noradrenaline in the flaccid state. However, if the contraction be upregulated in some situations, ED would be caused.

Interestingly, some studies have indicated that smooth muscle relaxation and contraction balance is disturbed by abnormal activation of contractile signaling pathway such as the adrenergic regulation. In some syndromes causing ED, such as diabetes mellitus or metabolic syndrome, the contraction is enhanced [17–19]. One of the important contractile signaling pathways is the RhoA/Rho-kinase signaling pathway. The enhancement is known to occur in aged individuals. The inhibition of RhoA/Rho-kinase signaling pathway by Y-27632 has been shown to improve ED in aged animal models [20, 21]. Interestingly, the contractility of smooth muscle in the corpus cavernosum is regulated by sexual hormones and may play a significant role in erectile function.

3. Testosterone deficiency and ED

Testosterone deficiency and ED have been studied extensively [22–25]. Testosterone deficiency causes ED using castrated animal models [26]. Furthermore, the erectile function is discussed by the endothelial NO synthase (eNOS) and neuronal NOS (nNOS) signalings. In some studies, testosterone administration to the castrated animals improved NOS expression in the penis and restored the erectile function [27]. Li et al. showed that testosterone deficiency decreases the upregulating reactive oxygen species production and it decreased eNOS activity (the phospho-eNOS/eNOS ratio) [28]. They also showed the reduction in eNOS activity induced cGMP levels decreased in the penis. Testosterone also alters phosphodiesterase type 5 (PDE-5) expression in the penis. Traish et al. showed that testosterone deficiency decreases PDE-5 activity using the rabbit model [29]. Additionally, Zhang et al. showed that PDE-5 expression was decreased by castration in the rat corpus cavernosum and that testosterone replacement therapy to the rats improved the expression [30]. These results indicate that testosterone is important for regulating PDE-5 expression. Traish et al. also suggested testosterone regulates not only NOS but also PDE-5 [31].

Testosterone also affects the smooth muscle of the corpus cavernosum. Reilly et al. reported that testosterone deficiency reduces the number of α-adrenergic-1 receptors in the castrated rats’ smooth fascia [32]. Moreover, testosterone modulates the adrenergic response of the corpus cavernosum vascular smooth muscle [33]. These results indicate that when testosterone levels decrease, smooth muscle contractility also decreases. On the other hand, Sopko et al. showed that the levels of RhoA and Rho-kinase proteins are increased in the castrated rats’ corpus cavernosum [34]. Their results indicated that testosterone deficiency increased smooth muscle contractility, leading to the decreasing erectile function and
hypertension. Thus, although testosterone deficiency may increase contraction, additional research is required to more fully elucidate its impact on smooth muscle contraction.

Interestingly, testosterone also directly affects smooth muscle relaxation. Using isometric tension analysis, Yue et al. showed that the smooth muscle of rabbit coronary arteries and aortas are relaxed by testosterone [35]. Others have also reported that testosterone activates smooth muscle ATP-sensitive K+ channels and regulates the relax response of the smooth muscles [36]. These findings indicate that testosterone may regulate erectile function locally by acting on corpus cavernosum smooth muscle. These results indicate that testosterone may affect both genomic and nongenomic mechanisms of erectile function.

Testosterone also affects the structure of the penis. For example, castrated rats exhibit smooth muscle loss and fibrosis [37], and testosterone deficiency increases the volume of collagen in the internal pudendal arteries [38]. These effects of testosterone indicate that testosterone deficiency causes programmed trabecular smooth muscle cell death (apoptosis) [29]. Traish et al. also indicated that testosterone deficiency is related to the accumulation of fat-containing cells (fibroblasts or preadipocyte-like cells), particularly in the penis [39]. Interestingly, Wang et al. showed that testosterone deficiency decreases erectile function and increases collagen in the corporeal cavernosum by inhibiting autophagy and promoting apoptosis of the smooth muscle cells in rats’ penis [40]. Although their report had several limitations, they discussed the important role of testosterone in regulating the structural integrity of the corpus cavernosum and erectile function. This resulted from testosterone regulating the counterregulation of autophagy and apoptosis by modulating the interactions between BECN1 and Bcl-2 (key dual regulators of autophagy and apoptosis) [41, 42].

4. Estrogen and ED in clinical studies

Estrogen, the female sex hormone, also affects erectile function. Interestingly, Tivesten et al. reported that circulating free testosterone is positively associated with the ankle-brachial index (ABI) in a large population-based cohort of elderly males. They show that testosterone has a negative association with the degree of atherosclerotic disease in the lower extremities [43]. On the other hand, estrogen also has association with ABI negatively in the males, leading to higher estradiol levels associated with increased atherosclerosis. Besides, when lower extremity peripheral arterial disease (PAD) was defined as an ABI of less than 0.90, they showed that low serum testosterone and high serum estradiol are associated with lower extremity PAD. Moreover, both low testosterone levels and elevated estradiol levels affect erectile function and are associated with increased ED severity when present individually or concomitantly [44]. Low testosterone levels were thought to be the main effector; however, the presence of concomitantly elevated estradiol levels increased the severity of ED in patients with low testosterone levels. These reports indicated that female sex hormones also affect male health. Srilatha and Adaikan demonstrated that estradiol-testosterone imbalance is a risk factor for ED [8, 45, 46]. They showed that higher levels of estradiol were present in older patients experiencing with lack of sexual interest and ED, after adjustment for age [8]. Additionally, they concluded that the estradiol-testosterone hormonal balance may be a determinant of successful management outcomes for ED. Wu et al. also reported an association between sexual dysfunction and changes in estradiol and testosterone levels in Chinese men [47], and O’Connor et al. reported that estradiol
was associated with sexual function-related distress; higher levels were related to
greater distress in 2838 men, ages 40–79 years, who completed the European Male
Aging Study-Sexual Function Questionnaire [48]. These reports specifically dem-
onstrated the relationship between high estrogen milieu and male erectile function.

Serum estrogen levels are controlled by aromatase but can be altered under some
conditions. Lamba et al. reported that antiretroviral therapy is associated with
sexual dysfunction and increased serum estradiol levels in men [49]. Moreover, they
found that total estradiol levels may be increased based on sex hormone-binding
globulin (SHBG) levels. Drugs such as phenytoin are known to cause elevations
in serum estradiol and SHBG [50]. Increased levels of SHBG, for example, due to
induction of aromatase or SHBG synthetase, lead to a decrease in the free androgen
index. Additionally, increased levels of SHBG and/or a low free androgen index
have been associated with hypertension, osteoporosis, varicose veins, sexual dys-
function, and adverse serum lipids [51–56]. All these side effects have been reported
in association with antiretroviral therapy as well. SHBG, similar to other globulins,
is upregulated in patients with acquired immunodeficiency syndrome and human
immunodeficiency virus infection [57, 58]. Hassan et al. have also reported the
association of overhydration with male sexual dysfunction and depression in hemo-
dialysis patients [59]. They showed that overhydration in hemodialysis patients was
associated with a higher prevalence of sexual dysfunction and depression, lower
serum levels of total testosterone and dehydroepiandrosterone, and higher levels
of serum estradiol. Intriguingly, Tivesten et al. reported that circulating estradiol is
a predictor of the progression of carotid artery intima-media thickness in middle-
aged men [60]. They also reported that elderly men with low serum testosterone
and estradiol have increased risk of mortality and that patients with low testos-
terone and estradiol levels have the highest risk of mortality [61]. Serum estrogen
levels can be altered by some drugs and sex hormones. Therefore, ED induced by
high estrogen may be related to mortality.

5. Estrogen and ED in basic research

Interestingly, estrogen administration decreases erectile function in animal
models [62, 63]. Researchers administered estradiol orally to rats, resulting in high
estradiol levels and low testosterone levels. Moreover, the intracavernous pressure
(ICP) response to nerve stimulation was also impaired in all treated groups, and
trichrome staining demonstrated the presence of cavernosal connective tissue
hyperplasia in long-term study groups [62]. Oral administration of estradiol to rab-
bits resulted in high estradiol levels and low testosterone levels, similar to the effects
in rats. Additionally, acetylcholine induced endothelium-mediated relaxation in
normal animals, but this effect was significantly attenuated in treated groups, and
NO-mediated nonadrenergic, noncholinergic neurotransmission was decreased in
the treatment groups [63].

In our previous studies, subcutaneous administration (s.c.) of estradiol to rats
resulted in high estradiol levels and low testosterone levels, thereby decreasing
erectile function [64]. Moreover, we administered testosterone to rats with high
estrogen-induced testosterone deficiency; however, erectile function did not
improve. Interestingly, estrogen administration increases the contraction of smooth
muscle in the corpus cavernosum, upregulating the RhoA/Rho-kinase signaling
pathway, which is involved in ED [18]. Vignozzi et al. demonstrated that high-fat
diet-induced ED is associated with high estradiol levels, rather than low testoster-
one levels [65].
We also investigated the influence of estradiol-testosterone imbalance on erectile function in rats (Figures 1–6; Table 1). Male Wistar ST rats (11 weeks old, Japan SLC Inc., Hamamatsu, Japan) were separated into five groups. In the low testosterone (Low-T) group (n = 11), rats were injected with goserelin (LH-RH agonist, 0.9 mg/kg, s.c.). In the low testosterone and high estrogen (Low-T/High-E) group (n = 11), rats were injected with goserelin and estradiol (3 μg/kg/day, s.c.) daily from weeks 2 to 4. In the high estrogen (High-E) group (n = 11), rats were injected with estradiol daily from weeks 2 to 4. In the high estrogen and testosterone (High-E/High-T) group (n = 11), rats were injected with estradiol and testosterone (3 mg/kg/day, s.c.) daily from weeks 2 to 4. In the control group (n = 11), rats were not injected with any hormone. Table 1 shows the sex hormone concentrations in rats. Goserelin injection significantly decreased serum bioavailable testosterone (control: 1.20 ± 0.13 ng/mL, Low-T: 0.55 ± 0.04 ng/mL, P < 0.01 versus the control; Low-T/High-E: 0.73 ± 0.06 ng/mL, P < 0.05 versus the control). Testosterone injection significantly increased serum bioavailable testosterone (control: 1.20 ± 0.13 ng/mL, High-E/High-T: 2.58 ± 0.31 ng/mL, P < 0.001 versus the control). Estradiol injection significantly increased serum estrogen (control: 102.5 ± 8.7 pg./mL, Low-T/High-E: 275.4 ± 34.4 pg./mL, P < 0.01 versus the control; High-E: 332.3 ± 17.4 pg./mL, P < 0.001 versus the control; High-E/High-T: 401.5 ± 51.6 pg./mL, P < 0.001 versus the control).

Figure 2 shows the erectile response to electrical field stimulation of the cavernous nerve in the different experimental groups. Analysis of the ICP/MAP ratio revealed that the ratios in the Low-T (0.52 ± 0.03), Low-T/High-E (0.46 ± 0.03), High-E (0.44 ± 0.03), and High-E/High-T (0.44 ± 0.02) groups, which represented

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**Figure 1.**
Experimental design. In the control group, rats were injected with vehicle for 2 weeks. In the Low-T and High-E groups, rats were injected with goserelin acetate (LH-RH agonist, 0.9 mg/kg subcutaneously) at day 0. In the estrogen-treated (High-E) group, rats were injected with estradiol (3 mg/kg/day subcutaneously) for 2 weeks. In the estrogen- and testosterone-treated (High-E/High-T) group, rats were injected with estradiol (3 mg/kg/day subcutaneously) and testosterone (3 mg/kg/day subcutaneously) for 2 weeks. At the end of the period, rats were underwent erectile function testing in vivo or in vitro.
all treated rats, were significantly lower than in the control group (0.70 ± 0.04, 
\( P < 0.01 \)). These data suggested that erectile responses were decreased in rats with a
sex hormone imbalance.

**Figure 3** shows the contractile response of rat corpora cavernosa strips to
increasing concentrations of noradrenaline (NA). Increasing concentrations of
NA were found to contract rat corpora cavernosa strips in all groups. In particular,
10 μM NA resulted in statistically significant differences in the in vitro penile
contractile response among the experimental groups (control: 154.5 ± 14.1%, Low-T:
169.8 ± 14.8%, Low-T/High-E: 200.2 ± 21.1%, High-E: 198.9 ± 15.3%, High-E/High-T:
249.7 ± 13.5%). Although the contractile response did not differ between the control
group and the Low-T group \((P > 0.05)\), the contractile responses in the Low-T/High-E, High-E, and High-E/High-T groups were higher than the response in the control group \((P < 0.05)\).

**Figures 4 and 5** show the relaxant response of NA-precontracted rat corpora cavernosa strips to increasing concentrations of sodium nitroprusside (SNP) and Y-27632. In all groups, increasing concentrations of the NO donor SNP relaxed rat corpora cavernosa strips (control: Emax = 16.8 ± 10.3%, Low-T: Emax = 59.7 ± 7.6%, Low-T/High-E: Emax = 53.4 ± 5.0%, High-E: Emax = 55.2 ± 6.8%, High-E/High-T: Emax = 61.1 ± 1.5%). In the treated groups, the sensitivities to SNP were significantly lower than in the control group \((P < 0.01)\). Increasing concentrations of
Rho kinase inhibitor Y-27632 completely relaxed rat corpora cavernosa strips in all groups (control: half-maximal inhibitory concentration \( [IC_{50}] = 1.22 \times 10^{-6} \) M, Low-T: \( IC_{50} = 2.43 \times 10^{-7} \) M, Low-T/High-E: \( IC_{50} = 1.31 \times 10^{-7} \) M, High-E: \( IC_{50} = 2.26 \times 10^{-7} \) M, High-E/High-T: \( IC_{50} = 1.25 \times 10^{-7} \) M). When using \( 10^{-6} \) M and \( 10^{-5} \) M Y-27632, the sensitivities to Y-27632 in the treated groups were significantly lower than in the control group (\( P < 0.01 \)); thus, the graphs for the treated groups were shifted to the left.

**Figure 6** shows the histological analysis of the rats’ corpora cavernosa. The area ratio of the cavernous smooth muscle was analyzed (control: 10.5 ± 1.4%, Low-T: 7.4 ± 1.1%, Low-T/High-E: 13.2 ± 0.4%, High-E: 11.6 ± 0.1%, High-E/High-T: 19.4 ± 1.1%). Similarly, the area ratio of the collagen fiber was analyzed (control: 58.4 ± 2.5%, Low-T: 63.2 ± 3.0%, Low-T/High-E: 66.5 ± 2.3%, High-E: 58.8 ± 2.2%, High-E/High-T: 58.7 ± 1.4%). No statistically significant differences between the experimental groups were observed in the overall area ratios of smooth muscle, collagen fiber, and other parameters according to \( \chi^2 \) tests for independence (\( P > 0.05 \)).
Overall, we demonstrated that changes in the sex hormone milieu affected erectile function in rats, and our hypothesis that the sex hormone imbalance associated with ED was supported by both in vivo and in vitro experiments using pharmacological tools.

6. Estrogen receptors (ERs) in erectile function

Several reports have suggested an association between ERs and ED. Schultheiss et al. have shown the ER distribution in the corpus cavernosum penis of adult humans [66]. Additionally, Dietrich et al. have demonstrated that the corpus cavernosum and corpus spongiosum smooth muscles were immunoreactive for the androgen receptor (AR), ER-α, and ER-β and that endothelial cells were negative for AR, sporadically positive for ER-α, and positive for ER-β [67]. Jesmin et al. have demonstrated that ER-α was predominantly localized in the sensory corpuscle of the glans penis [68]. On the other hands, they also reported that the ER-β was localized around the neurovascular bundle, artery, and nerve [68]. Spyridopoulos et al. have shown that the potential antiapoptotic effects of estrogen were impaired by reduced ER-β expression, and loss of antiapoptotic genes in the rat corpus cavernosum was associated with the pathogenesis of ED [69]. These reports indicate that the ER exists in the corpus cavernosum and has various functions. Moreover, the ER has been reported to be altered under some conditions. Shirai et al. have demonstrated that vascular endothelial growth factor treatment restores erectile function through stimulation of the insulin-like growth factor system and ER-β gene at the mRNA and protein levels in the corpus cavernosum of diabetic rats [70–72]. They had shown the expression of ER-β mRNA in male rat aortas before and after balloon denudation injury. Interestingly, the expression of ER-α mRNA in vascular endothelial and smooth muscle cells was very low levels after injury; however, the expression of ER-β mRNA in vascular endothelial cells was high after injury. Thus, the vascular protective effects of estrogen on endothelial and smooth muscle cells were exclusively mediated by ER-β, not ER-α [73]. Shirai et al. also demonstrated that the functionally predominant form of ER in the rat corpus cavernosum was ER-β and that age-related alterations in ER-β expression were likely related to the pathogenesis of ED in older rats. Thus, they concluded that downregulation of sex hormone receptors in the corpus cavernosum of aging rats is associated with ED [74]. Goyal et al. demonstrated the influence of estrogen on the structure of the corpus cavernosum [75–79] and showed that exposure to antiandrogens induces permanent structural abnormalities, including accumulation of fat cells, loss of smooth muscle cells and sinusoids, and reduced thickness of connective tissue trabeculae and tunica albuginea in the corpora cavernosa [76]. They also demonstrated that the ER and AR mediate cavernous smooth muscle cell differentiation, as shown by downregulation of MYH11 expression at the mRNA and protein levels and by reduced immunohistochemical staining of smooth muscle alpha actin using rats [79]. Therefore, a high estrogen milieu and alterations in ER expression may affect erectile function.

7. Endocrine-disrupting chemicals and ED

Some endocrine-disrupting chemicals have physiological effects similar to those of estrogen. Bisphenol A (BPA) is a widely used endocrine-disrupting chemical that is thought to have adverse health effects [80]. BPA has been widely produced and used as a common ingredient in the manufacture of plastics. Humans are mainly
exposed to BPA through ingestion of foods containing BPA, and increasing evidence supports its association with impaired male reproductive function [81]. Manfo et al. reported that BPA also decreases erectile function [82], and Li et al. showed that BPA-exposed workers had significantly increased risk of ED (odds ratio = 4.5, 95% confidence interval: 2.1–9.8) [83, 84]. Moon et al. were the first to report the influence of BPA on erectile function using animal model [85]. They observed thickening of tunica albuginea, sub tunical deposition of fat, and decreased sinusoidal space with subsequent increases in trabecular smooth muscle content by histological analysis in BPA-treated animals and demonstrated endothelial dysfunction in BPA-treated rabbits. Kovanecz et al. also reported that BPA decreases nNOS and vascular endothelial growth factor expression in rats [86, 87]. In these reports, BPA-induced ED was similar to high estrogen-induced ED. Thus, the relationship between endocrine-disrupting chemicals and ED should be carefully considered.

8. ED treatment and estrogen

PDE-5 inhibitors are the first choice for patients with ED. Recently, some interesting papers on PDE-5 inhibitors and estrogen have been published. Greco et al. reported a reduction in estrogen levels in patients with ED after chronic exposure to tadalafil, a PDE-5 inhibitor, and a concomitant increase in the testosterone-estrogen ratio [88]. They also showed that increased testosterone-estrogen ratios were not related to increases in testosterone serum levels, but rather to the possible effects of tadalafil on aromatase activity. Aversa et al. also demonstrated that daily tadalafil decreases serum estradiol levels [9]. In contrast, Spitzer et al. have reported that the PDE-5 inhibitor sildenafil increased estradiol levels in 40 men (ages 40–70 years) with ED, despite increasing testosterone levels [89]. Additionally, several reports have demonstrated that PDE-5 inhibitors increase testosterone levels [90–96]. When testosterone is low, estradiol levels may also be low because testosterone is metabolized to estradiol by aromatase. PDE-5 inhibitors can increase not only testosterone but also estradiol in patients with low testosterone levels. Therefore, estrogen levels should be carefully monitored in patients receiving PDE-5 inhibitors.

9. Conclusions

The sex hormone milieu affects erectile function, and sex hormone imbalances, particularly low testosterone levels combined with high estrogen levels, cause ED. Interestingly, estradiol has protective effects on female health, but harmful effects on male erectile function. Overall, these results provide insights into the possible treatments of endocrine-related ED. Future research should confirm these findings in more specific experiments using molecular tools.

Conflict of interest

The authors declare no conflicts of interest.
Estrogen for Male Function: Effect of Changes in the Sex Hormone Milieu on Erectile Function

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