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MEDICAL COMORBIDITIES (J KOVAC AND O RAHEEM, SECTION EDITORS)

The Role of Hormones in Male Sexual Function

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Abstract

Purpose of Review Male sexual dysfunction has many different causes and is often multifactorial in nature. We aim to review the effects that testosterone (T), estrogen, thyroid hormone, prolactin (PRL), and cortisol have on male sexual function.

Recent Findings T deficiency can cause decreased libido and diminished erectile function. Estrogen is necessary for sexual drive but is postulated to inhibit erectile function when elevated. Hyperthyroidism is associated with premature ejaculation (PE), hypothyroidism is associated with delayed ejaculation (DE), and both are associated with erectile dysfunction (ED). Hyperprolactinemia is associated with ED and can cause fertility issues. The role of corticosteroids is largely unknown.

Summary While hormonal disorders can largely influence male sexual health, resolution of sexual dysfunction is achieved in most cases by normalization of hormone levels.

Keywords Hormonal comorbidities · Male sexual health · Testosterone · Estrogen · Thyroid · Prolactin

Introduction

Male sexual dysfunction has many different causes and is often multifactorial in nature. Erectile dysfunction (ED) alone can be caused by vasculogenic or psychiatric disorders, neurogenic conditions, relationship difficulties, medication side effects, and endocrine disorders, which is the focus of this chapter [1]. Endocrine dysfunction can lead to abnormal hormone signaling throughout the body. In regard to male sexual dysfunction, the hormone testosterone (T) receives the most attention; however, other hormonal abnormalities can be associated with male sexual function. This communication will focus specifically on T, estrogen, thyroid hormone, prolactin (PRL), and cortisol and their effects on male sexual function.

This article is part of the Topical Collection on *Medical Comorbidities*

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Testosterone

T is a sex hormone found in both men and women and plays a role in carbohydrate, fat, and protein metabolism, the growth and maintenance of muscle, hair growth, bone metabolism, and male sexual and reproductive function [2, 3]. T deficiency (TD) is a well-established medical condition that presents with both symptoms and documented low levels of circulating plasma T. TD can be due to a primary (testicular) dysfunction, secondary (pituitary or hypothalamic) disorders, mixed (combination of primary and secondary) dysfunction, or caused by the use of certain medications (e.g., gonadotropin-releasing hormone (GnRH) agonists/antagonists) [3, 4]. Generalized symptoms include reduced vitality and motivation, depressed mood, decreased muscle mass and strength, bone loss, and anemia. TD is also reported to be associated with insulin resistance, inflammation, dyslipidemia, vascular risk, ED, and decreased libido [5, 6].

T is involved with many different components of erectile physiology (Fig. 1). Briefly, T is believed to be a factor in regulating (i) nerve structure and function; (ii) the expression and activity of nitric oxide synthase (NOS); (iii) phosphodiesterase type 5 (PDE5) expression in vascular and trabecular

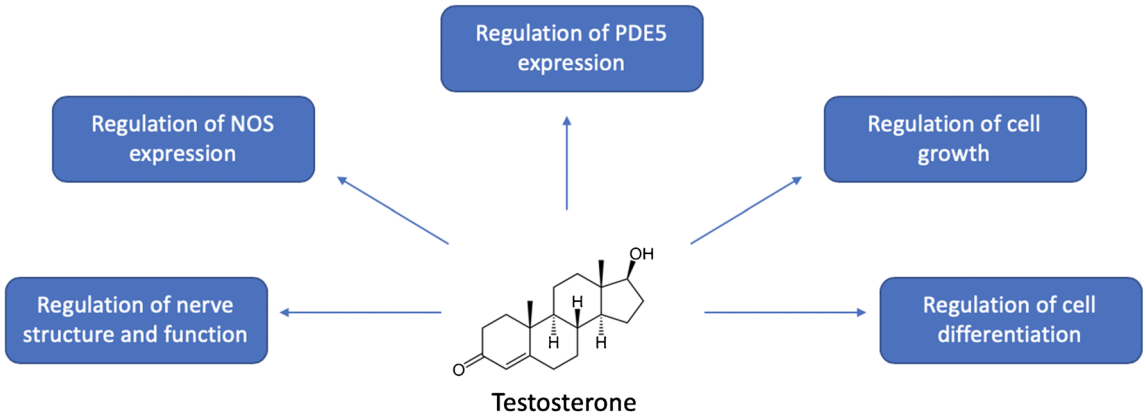

Fig. 1 Hypothesized mechanisms through which T regulates erectile function

smooth muscle; and (iv) cell growth and differentiation [7, 8]. The pathophysiology of TD was delineated, for the most part, through animal castration experiments [7–9].

Clinically, the relationship between T and erectile function is complex and difficult to elucidate, as ED is often multifactorial, making it problematic to determine if TD is a contributing factor. The Massachusetts Male Aging Study (MMAS) obtained ED data from 625 men and did not find a significant association between ED and total T or bioavailable T when controlling for potential confounders [10]. However, the European Male Aging Study (EMAS), a 2010 investigation involving 3300 men, documented a weak relationship between *free* T and erectile function. When these researchers studied only men with low total T (< 8 nmol/L or 231 ng/dL), they also observed a significant relationship between *total* T and erectile function [5]. This finding of a T threshold, beneath which T becomes linearly related to erectile function, has been commented on in other studies [5, 11••]. More recently, the Testosterone Trials surveyed 788 men > 65 years old throughout the USA and noted that at baseline, both total and free T were associated with erectile function as evaluated by the Erectile Function Domain of the International Index of Erectile Function (IIEF) [12].

Though the exact neurophysiological mechanism is not fully delineated, libido, or sexual desire, is another aspect of male sexual health that is strongly influenced by T [6]. Hull et al. performed rat experiments to examine the role hormones play in regulating sexual behavior. The researchers observed that stimuli from a receptive female rat towards a male rat leads to the release of dopamine in the nigrostriatal system, mesolimbic area, and medial preoptic area (MPOA). Dopamine release in the nigrostriatal system promotes the somatomotor component of copulation, while dopamine release in the mesolimbic system results in increases in various types of motivation, and dopamine release in the MPOA focuses these motivations towards a sexual target. T is hypothesized to influence the pathway of sexual motivation by (i) permitting increased dopamine release in the MPOA in response to a female and (ii) upregulating NOS activity in the MPOA, which promotes both basal and sexual release of dopamine (Fig. 2) [13]. T likely has other mechanisms of influencing libido that are not yet described.

For the most part, data from human studies has revealed a strong association between T and libido. In the MMAS, both total T and bioavailable T were associated with libido as measured by a 14-point scale assessing self-reported frequency of desire and sexual thoughts [14]. The EMAS obtained similar results and reported that decreased frequency of sexual thoughts was one of the three sexual symptoms associated with TD [5]. The more recent Testosterone Trials used the Sexual Desire Domain of the Derogatis Interview for Sexual Functioning (DISF) and also found a significant association between sexual desire and both total and free T [12]. Lastly, the Concord Health and Aging in Men Project (CHAMP) evaluated over 1200 elderly men (> 70 years) at baseline and at 2-year follow-up to look for a longitudinal association between sexual function and androgen status in those older men. They reported that declines in both free T and total T were significantly associated with decreased sexual desire [15]. Testosterone studies are summarized in Table 1.

There are numerous studies on the efficacy of T replacement therapy (TRT) for treating sexual symptoms of TD, but the results are often contradictory due to, in part, the different etiologies of TD. TRT is effective in treating TD in younger men caused by dysfunction (primary, secondary, mixed, drugs). Brock et al. identified 715 men with a mean age of 55, total T < 10.4 nmol/L or 300 ng/dL, and at least one symptom of androgen deficiency. For 12 weeks, the men were administered either 60 mg of T gel or placebo daily. When compared with the placebo group, the men receiving T had a significantly greater increase in both IIEF score ($p < 0.005$) and Sexual Arousal Interest and Drive (SAID) score ($p < 0.001$) [16].

TRT has less clear benefits in treating age-related TD. In 2007, Boloña et al. released a meta-analysis on randomized placebo-controlled trials for TRT in men with sexual

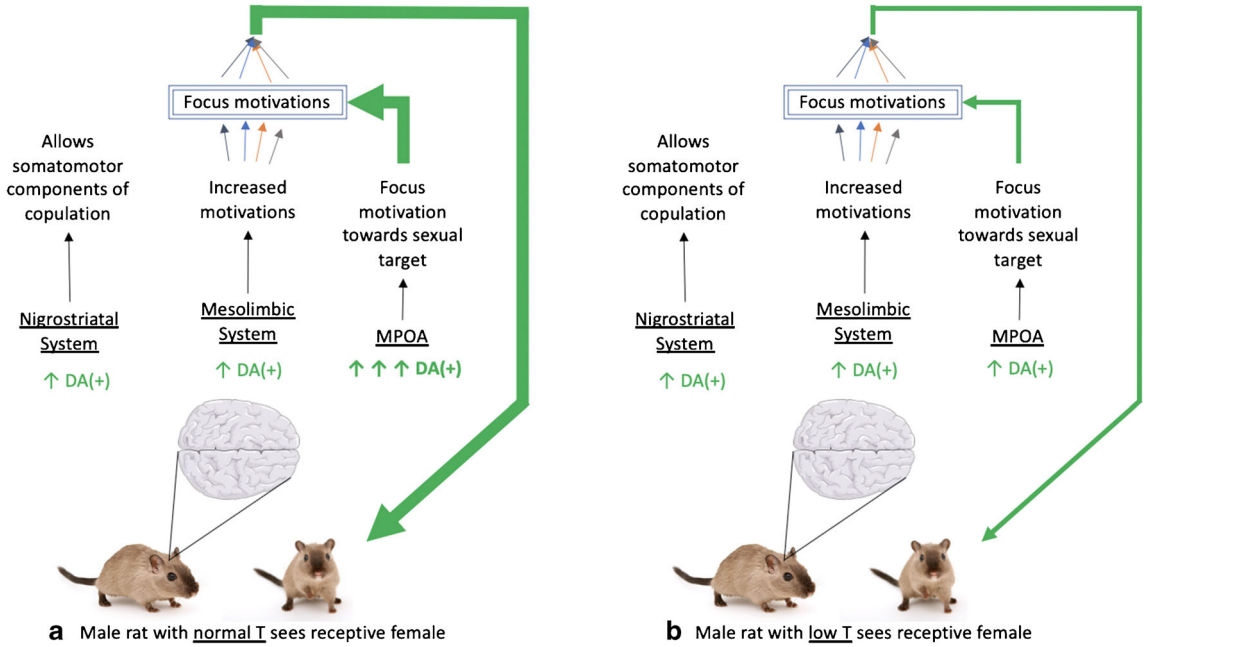

Fig. 2 Physiologic pathway of libido in rats. In a healthy male rat, stimuli from a receptive female lead to increased dopamine (DA) release in the nigrostriatal system, mesolimbic system, and medial preoptic area (MPOA). Respectively, this leads to allowance of the somatomotor components of copulation, increases in various types of motivation (multicolored arrows), and focusing on motivations onto a sexual target (convergence of multicolored arrows). **a** T upregulates basal levels of DA in the MPOA via upregulation of nitric oxide synthase. Additionally, T increases the amount of DA released in the MPOA after stimuli from a receptive female. **b** In a rat with low T, less DA is released in the MPOA resulting in less motivation focused towards a sexual target

dysfunction. They included 17 trials for a total of 863 patients and reported that TRT provided minimal improvements in satisfaction with erections and moderate benefit in libido. However, they admitted that their findings were plagued by inconsistent results across trials, wide confidence intervals, and potential reporting bias [17]. These contradictory results between various T studies led in part to the development of the Testosterone Trials. The Testosterone Trials are a set of seven randomized controlled trials (RCTs) designed to evaluate the benefits of TRT in older men. Researchers identified more than 700 men aged 65 and older who had a total T level below 9.5 nmol/L or 274 ng/dL. For 12 months, they were administered either 50 mg of T gel or placebo daily. When compared with the placebo arm, the group receiving T had a significantly greater improvement in erectile function that was independent of moderating factors including age, body mass index, and diabetes. Additionally, the group receiving T had significantly greater increases in sexual desire than the placebo group, as measured by the DISF [18]. The most recent meta-analysis by Corona et al. attempted to overcome the heterogeneity of human studies evaluating T's effect on sexual function by exclusively including only RCTs that utilized the IIEF to assess the effect of TRT on T-deficient men. The final analysis included a total of 14 studies encompassing nearly

Table 1 Summary of studies on testosterone and male sexual health

Study	*n*	Outcomes	
		Erectile function	Libido
MMAS [10]	625	- No association between erectile function and T	- Total T and bioavailable T are associated with libido
EMAS [5]	3369	- Weak relationship between free T and erectile function - Significant relationship between total T and erectile function in hypogonadal men	- TD is associated with decreased frequency of sexual thought
Testosterone Trials [12]	788	- Total and free T associated with erectile function	- Total and free T are associated with sexual desire
CHAMP [15]	1226	n/a	- Decline in both free and total T is associated with decreased sexual desire

MMAS, Massachusetts Male Aging Study; *EMAS*, European Male Aging Study; *CHAMP*, Concord Health and Aging in Men Project

2300 men. Consistent with the findings of the Testosterone Trial, Corona et al. reported that when compared with men receiving placebo, the men receiving TRT had significantly greater improvements in both erectile function and libido [19]. Of note, patients with more severe TD demonstrated greater improvements in erectile function than those with milder TD. TRT appeared to have less of an effect on patients with metabolic comorbidities, i.e., diabetes and obesity. Overall, TRT appears to be a safe and efficacious treatment for the sexual symptoms of TD and should definitely be considered in men suffering with more severe TD.

Estrogen

17β-Estradiol (E2) and other estrogens regulate many aspects of female reproductive development and function, but they also have a significant impact on male physiology and pathophysiology. Ovaries are the major source of circulating E2 in females, but in males, testes produce approximately 20% of total circulating E2. The remainder derives from the aromatization of T in bone, brain, skin, and adipose tissues [20] (Fig. 3). This is important, as E2 may be produced and metabolized in target tissues, allowing paracrine effects without alteration of overall serum levels [21]. Estrogen receptors (ERs) are abundant in tissues related to sexual function, including the brain, penis, and testis. In the brain, E2 synthesis is increased in areas related to sexual arousal. In the penis, ERs are found throughout the corpus cavernosum with high concentrations localized to the neurovascular bundles [22]. There are a number of causes for elevated E2 levels in men, such as aging, obesity, diabetes, medications, TRT, elevated aromatase activity (i.e., testicular cancer, genetics), and diet. E2 affects libido, erectile function, and spermatogenesis.

Estradiol is measured in the serum by using liquid chromatography-tandem mass spectrometry. Yeap et al. established reference ranges with mass spectrometry by utilizing the population in the health in men study (HIMS) [23]. The patient with below normal estrogen levels might present with libido issues, psychological stress, and/or diseases associated with bone loss. The patient with above normal estrogen levels can present with gynecomastia, ED, and/or psychological stress [24, 25].

E2 is postulated to influence libido through regulation of various receptors and signaling molecules in the brain [22, 26]. The aromatization of T into E2 makes it difficult to differentiate the role of each hormone. Because 80% of E2 is aromatized from T, men with low T will often have low E2. As mentioned previously, men with low T are prone to sexual dysfunctions. How can one determine if this is partially due to concomitant low E2? To answer this question, researchers performed several studies on the effect of E2 supplementation in males with low circulating levels of T. Animal studies show that E2 supplementation increases mating behavior in castrated (low T) male lizards, quail, and hamsters [27–29].

Human men with low T also require E2 to increase libido; however, it usually does not need to be supplemented, as most patients treated with TRT will aromatize some T into the needed E2. Carani et al. reported on an interesting case of a hypogonadal man with a disabling mutation in his aromatase gene. Individual TRT did not improve the patient's libido, as there was no way to convert the supplemented T into E2. This subject required supplementation with both T and E2 concurrently to regain his full sex drive, suggesting that both of these hormones are required for proper sexual functioning [30]. In a similar study, Finkelstein et al. administered TRT to two groups of men, one of which received concurrent treatment with an aromatase inhibitor. The group receiving the aromatase inhibitor were unable to convert the supplemented T into E2, allowing the researchers to evaluate if E2, generated via aromatization, was required for the full benefit of TRT. They observed significantly decreased libido in the group that had been administered the aromatase inhibitor, suggesting again that E2 is crucial for sexual desire [31]. Tan et al. analyzed hypogonadal men and the association of libido with estrogen levels in a multi-institutional retrospective cohort and also reported an association between low estradiol levels and decreased libido [32]. A final piece of evidence supporting E2 as an influencer of libido comes from studies on prostate cancer patients. Prostate cancer patients treated with androgen receptor (AR) blockers had better outcomes in maintaining sexual activity when compared with patients treated with androgen deprivation therapy (ADT) who were at castrate T levels (T < 50 ng/dl). The authors hypothesized that this was due to higher E2 levels in the group treated with AR blockers (patients treated with ADT have decreased levels of T which

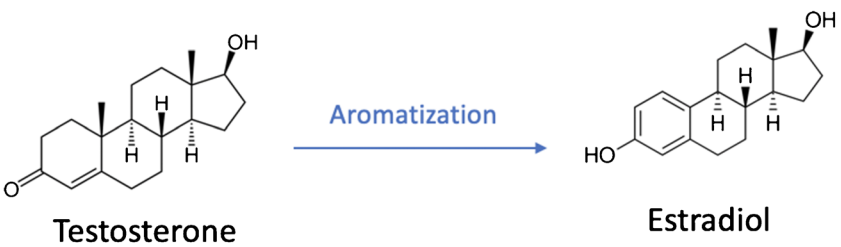

Fig. 3 Testosterone is converted to estradiol by aromatase

Table 2 Important studies on estrogen and male sexual health

Study	*n*	Outcomes	
		Erectile function	Libido
Tan et al. [32]	24,503	n/a	- Low estradiol is associated with decreased libido
O'Connor et al. [33]	2963	- Higher estradiol levels were not significantly associated with ED	- Higher estradiol levels were associated with sexual function distress
Finkelstein et al. [31]	198	- The addition of aromatase inhibitors in men taking T replacement therapy is associated with decreased erectile function	- The addition of aromatase inhibitors in men taking T replacement therapy is associated with decreased sexual desire
Zuniga et al. [34]	256	- Estrogen levels > 32 pg/mL were strongly associated with an increased likelihood of erectile dysfunction	n/a

results in decreased aromatization to E2; patients treated with AR blockers have normal levels of T with normal aromatization to E2) [22, 24]. These studies are summarized in Table 2.

While E2 appears to have a positive effect on libido, it may inhibit erectile function. E2 in animal models impedes normal penile development, including diminished bulk of the bulbospongiosus muscle, reduction of the corpus cavernosum, and an accumulation of fat cells within the cavernosal tissues that lead to venous leakage ED in adult life. In addition to influences on structure, E2 has a significant effect on penile vasculature [22]. Mancini et al. observed that low serum E2 levels in men were associated with a greater degree of ED secondary to venous leakage [35]. O'Connor et al. similarly investigated the effect of serum E2 in European men, and although they found that serum E2 had an association with sexual function distress, it was concentrated in the psychological domains rather than the physiologic domains [33]. Lastly, Zuniga et al. measured serum E2 in 256 men and noted an association with clinically significant ED after controlling for T, age, body mass index, and smoking status [34].

There is also evidence that E2 influences male fertility. Spermatogenesis requires E2 at every level, including (i) modulation of GnRH in the hypothalamic-pituitary-gonadal axis; (ii) regulation of Leydig cells by local LH inhibition; (iii) influencing tight junction formation in Sertoli cells; and (iv) stimulation and support of germ cells [22]. Interestingly, severely decreased sperm motility has been noted in men with mutated estrogen receptor subtype α (ERα) and in ERα genetically deleted male mice. It is hypothesized that the lack of ERα results in excessive fluid accumulation in the epididymis, which may contribute to abnormal sperm morphology and function [36].

Thyroid

In a healthy adult, thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the pituitary to release thyroid-stimulating hormone (TSH), which ultimately results in the production of thyroxine (T4) and triiodothyronine (T3) in

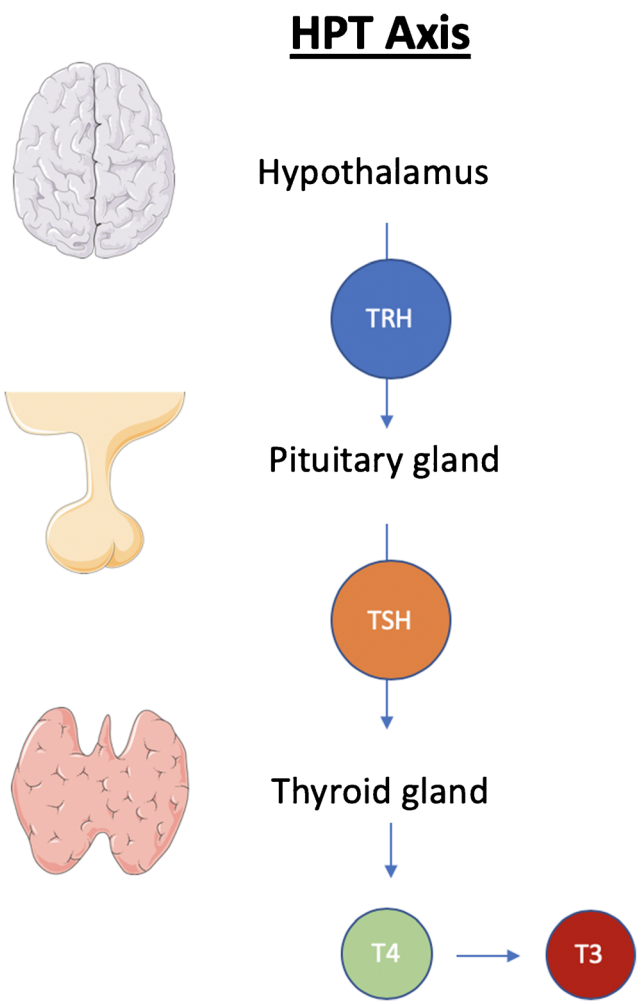

Fig. 4 Hypothalamic-pituitary-thyroid axis

the thyroid gland (Fig. 4). Free, or unbound, T3 and T4 (fT3 and fT4) are the bioactive forms of these thyroid hormones. They have a range of effects, including regulation of basal metabolic rate, lipolysis/lipogenesis, bone and neural development, and metabolism of fats, carbohydrates, and proteins [37]. Hyperthyroidism and hypothyroidism are common medical disorders and diagnosis typically involves measurement of serum TSH and fT4 and/or fT3. A low TSH (< 0.4 mU/L) and a high fT4 and/or fT3 suggest a diagnosis of hyperthyroidism. A high TSH (> 5.0 mU/L) and low fT4 and/or fT3 suggest a diagnosis of hypothyroidism [38]. Hypo/hyperthyroidism can be further classified as "subclinical" or "overt" depending on the degree to which fT3, fT4, and TSH are disordered. Both hyperthyroidism and hypothyroidism are associated with male sexual dysfunction, specifically, ED, premature ejaculation (PE), delayed ejaculation (DE), and low libido.

Hyperthyroidism

Hyperthyroid men may present to the physician with symptoms of nervousness, diaphoresis, weight loss, heat intolerance, diarrhea, and lower extremity edema. On physical exam, the physician may find tachycardia, moist skin, tremors, periorbital edema, or a goiter [38]. The prevalence of sexual dysfunction in men presenting with hyperthyroidism ranges from 48–77%. The pathophysiology of hyperthyroidism and sexual dysfunction is not yet fully understood. One theory is that hyperthyroidism causes increased levels of sex hormone-binding globulin (SHBG), which binds T and dihydrotestosterone (DHT) with a greater affinity than it binds estrogen. This results in a functional decrease in circulating androgens and induces an altered sexual response [39]. Another theory is that hyperthyroid patients often present with anxiety, emotional lability, fatigue, and myalgias—all of which may contribute to sexual dysfunction [40]. Elevated thyroid hormone is also believed to target more specific pathways related to ED and PE. It is suggested to impair erectile function by hindering NO-dependent relaxation in the corpora cavernosa and to contribute to PE by enhancing seminal vesicle contraction and increasing activity of the bulbospongiosus muscle [40, 41].

The most common sexual sequelae of hyperthyroidism are ED and PE. The previously mentioned EMAS measured participants' levels of fT4 and TSH and identified 108 patients with hyperthyroidism. They observed that these hyperthyroid men were more likely to have impaired erectile function than euthyroid participants in their study (hazard ratio HR = 2.31, $p = 0.005$, and HR = 14.18, $p = 0.019$; for subclinical and overt hyperthyroidism, respectively) [42]. This finding was replicated by researchers at the Andrology and Sexual Medicine Outpatient Clinic at the University of Florence (UNIFI). The UNIFI study consisted of 3203 men, of which 103 had hyperthyroidism. After controlling for confounding variables, researchers noted that hyperthyroid men were at increased risk for severe ED when compared with euthyroid men in this study (HR = 11.67, $p = 0.023$) [42]. Veronelli et al. and Krassas et al. also reported higher rates of ED in hyperthyroid men when compared with euthyroid controls as measured by IIEF-5 and Sexual Health Inventory for Males (SHIM-5) respectively [43, 44].

The studies on the association between hyperthyroidism and PE are less conclusive. Cihan et al. identified 43 patients with hyperthyroidism and noted that 72% exhibited PE. Carani et al. reported on 34 men with hyperthyroidism and found the prevalence of PE to be 50% [45]. However, Waldinger et al. performed a larger study including more than 600 men with lifelong PE and reported no relationship between TSH and PE [46]. This implies that hyperthyroidism is only associated with the acquired type of PE. A summary of these studies is provided in Table 3.

The treatment of hyperthyroidism appears to resolve any associated sexual dysfunctions. Carani et al. reported that men treated for hyperthyroidism saw the rate of PE rate drop from 50 to 15%, with improved IIEF scores and libido [45]. Similarly, the UNIFI study documented that normalization of thyroid hormone through medical therapy decreased the prevalence of severe ED [42].

Hypothyroidism

Hypothyroid men may present to the physician with symptoms of fatigue, dry skin, depression, weight gain, and cold intolerance. On physical exam, the physician may find bradycardia, coarse skin, delayed deep tendon reflexes, and psychomotor retardation [38]. The prevalence of sexual dysfunction in men presenting with hypothyroidism is difficult to measure due to limited studies, but anecdotal evidence suggests it is around 60%. The pathophysiology of hypothyroidism and sexual dysfunction is not yet fully understood. One theory is that hypothyroidism disrupts the hypothalamic-pituitary-gonadal axis causing decreased serum testosterone, dehydroepiandrosterone (DHEA), DHEA sulfate, and estrogen metabolites [38, 47]. Another theory is that prolonged hypothyroidism leads to hyperprolactinemia which in turn causes sexual dysfunction [38]. Lastly, sexual dysfunction may be related to the systemic effects of hypothyroidism, i.e., fatigue, somnolence, and depressed mood.

The most common sexual sequelae of hypothyroidism are ED and DE. In a study of 14 hypothyroid patients, 9 (64%) reported having ED. These men also had significantly decreased T and E2 when compared with euthyroid controls [45]. Veronelli et al. identified 55 hypothyroid patients and observed a significantly higher rate of ED when compared with euthyroid controls [43]. Krassas et al. identified 44 hypothyroid patients and also noted significantly elevated rates of ED when compared with euthyroid controls [44]. Unlike

Table 3 Summary of studies on hyperthyroidism and male sexual health

Study	*N* (hyperthyroid)	Outcomes	
		Erectile function	Premature ejaculation
Wu et al. (EMAS) [5]	108	- More likely to have impaired erectile function	n/a
Corona et al. (UNIFI) [42]	103	- Hyperthyroid men are at increased risk of severe ED	n/a
Veronelli et al. [43]	13	- Higher rates of ED	n/a
Krassas et al. [44]	27	- Higher rates of ED	n/a
Cihan et al. [41]	49	- Prevalence of ED is 56%	- Prevalence of PE is 72%
Carani et al. [45]	34	- Prevalence of ED is 15%	- Prevalence of PE is 50%

EMAS, European Male Aging Study; *UNIFI*, Andrology and Sexual Medicine Outpatient Clinic at the University of Florence; *ED*, erectile dysfunction

hyperthyroidism, not all studies agreed on the relationship between hypothyroidism and ED. The EMAS identified 38 men with hypothyroidism and found no difference in erectile function when compared with euthyroid participants in this study [42]. The UNIFI study identified 79 hypothyroid patients and also reported no association between severe ED and hypothyroidism when controlling for confounding variables [42].

While hyperthyroidism is associated with PE, hypothyroidism may be associated with DE. Carani et al. identified 14 hypothyroid men and reported the rate of DE to be 64%, over 10 times the rate of DE seen in the general population [45]. A summary of these studies is provided in Table 4.

Similar to hyperthyroidism, medical treatment of hypothyroidism is an effective way to manage DE patients. Almost half of the patients with DE in the Carani et al. study had resolution of symptoms after thyroid hormone normalization. Additionally, successfully treated patients reported increased sexual desire and improved erectile function as measured by the IIEF-5 [45].

Prolactin

Prolactin (PRL) was first isolated in 1933. Its role in milk production was well recognized, but further experimentation revealed that it was also involved in regulating metabolism and the immune system [48–50]. PRL is produced in the anterior pituitary gland by lactotroph cells and subsequently enters the bloodstream (Fig. 5). Regulation of PRL is multifocal, with dopamine acting as an inhibitor and estrogen promoting secretion [51]. Hyperprolactinemia in men is characterized by a blood serum PRL level > 20 ng/mL; less than 1% of the general population is affected [52, 53]. The most common cause of hyperprolactinemia is the presence of a prolactinoma [54, 55]. Prolactinomas should be suspected in men with serum PRL levels > 250 ng/mL, while serum PRL levels > 500 ng/mL are more suggestive of a macroprolactinoma [56]. Other common causes of hyperprolactinemia in men include stress, pathological dysfunction of dopamine receptors, and pharmacologic interference with the dopamine pathway (i.e., antipsychotics, antiemetics) [57–61]. Men with hyperprolactinemia commonly have diminished energy, reduced muscle mass, and increased risk of osteopenia [62]. Additionally, hyperprolactinemia is associated with ED, gynecomastia, and infertility [53, 63].

The mechanism through which PRL influences erectile function is not fully understood. One theory is that PRL causes ED through its inhibitory effect on luteinizing hormone (LH). A rat study by Smith and Bartke compared LH levels in control rats with LH levels in rats with artificially elevated levels of PRL. They found that the rats with elevated PRL had significantly less serum LH than controls (23.8 ± 2.5 vs

Table 4 Summary of studies on hypothyroidism and male sexual health

Study	*N* (hypothyroid)	Outcomes	
		Erectile function	Delayed ejaculation
Carani et al. [45]	14	- Prevalence of ED is 64%	- Prevalence of DE is 64%
Veronelli et al. [43]	55	- Significantly higher rate of ED	n/a
Krassas et al. [44]	44	- Significantly higher rate of ED	n/a
Wu et al. (EMAS) [5]	38	- No difference in erectile function	n/a
Corona et al. (UNIFI) [42]	79	- No association between severe ED and hypothyroidism	n/a

EMAS, European Male Aging Study; *UNIFI*, Andrology and Sexual Medicine Outpatient Clinic at the University of Florence; *ED*, erectile dysfunction

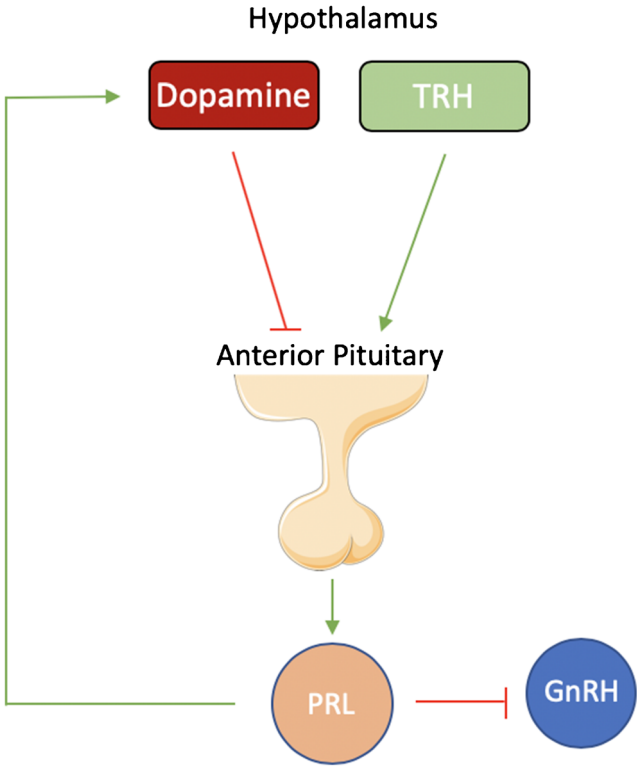

Fig. 5 Prolactin production

40.4 ± 9.5; $p < 0.05$) [64]. Decreased serum LH results in decreased serum T, which diminishes erectile function as previously described. Badal et al. argue against this mechanism of action, citing evidence that hyperprolactinemia patients do not regain erectile function with T supplementation. They suggest instead that chronically elevated levels of PRL lead to the downregulation of dopamine receptors in regions of the hypothalamus associated with sexual and erectile function [65]. Regardless of the mechanism, studies have long associated hyperprolactinemia with sexual dysfunction.

In 1978, Carter et al. studied 22 men diagnosed with PRL-secreting tumors and identified impotence in 20 of them [66]. Johri et al. used the IIEF to measure erectile function in 138 ED patients. They identified three patients (2.2%) with hyperprolactinemia, which is higher than expected based on the prevalence in the general population. Additionally, these patients with hyperprolactinemia were reported to have severe ED as defined by IIEF < 10 [67]. While this study had a small sample size, Johnson et al. had similar findings. They measured PRL levels in 330 men with ED and noted the prevalence of hyperprolactinemia to be ~2% [68]. Corona et al. also identified an association between sexual dysfunction and hyperprolactinemia in a study of 2146 subjects. These investigators categorized patients into three groups: no hyperprolactinemia, mild hyperprolactinemia (PRL > 420–735 mU/L), and severe hyperprolactinemia (PRL levels > 735 mU/L). They then assessed the sexual dysfunction and hypogonadism status using the Structured Interview on Erectile Dysfunction (SIEDY) and ANDROTEST Structured Interview questionnaires, with higher scores indicating more severe sexual dysfunction. The group with severe hyperprolactinemia was found to have significantly higher SIEDY and ANDROTEST scores ($p < 0.005$ and $p < 0.05$ respectively) than the group with normal PRL levels. In addition to higher questionnaire scores, the group with severe hyperprolactinemia had a hazard ratio of 8.60 (3.85–19.23) for the diagnosis of sexual dysfunction after adjusting for T and TSH levels [69]. These studies are summarized in Table 5.

Hyperprolactinemia also causes reduction in spermatogenesis. To understand the role of PRL on sperm production, it is important to highlight normal spermatogenesis. The hypothalamus produces GnRH which stimulates the production of LH and follicle-stimulating hormone (FSH) in the pituitary gland. LH and FSH are then secreted in the blood and travel to the testis where FSH initiates spermatogenesis via its influence on Sertoli cells and LH activates T production in Leydig cells. It is hypothesized that PRL disrupts this process by (i) inhibiting GnRH secretion and (ii) directly affecting spermatogenesis by binding to receptors on the Leydig and Sertoli cells [70].

The goal of PRL reduction therapy is to reduce serum PRL levels, diminish associated prolactinoma size, and treat sexual dysfunction symptoms [71]. To date, there are two recognized medications that can reduce serum prolactin levels, no matter the given adenoma status. The first line of treatment for patients with any type of hyperprolactinemia is cabergoline. Cabergoline is a dopamine agonist that works to inhibit PRL production in the pituitary [72]. Patients who are not responsive to cabergoline are commonly treated with bromocriptine, another dopamine agonist [73]. Typically, resolution of hyperprolactinemia leads to resolution of sexual dysfunction. In the previously mentioned study of 20 impotent men with hyperprolactinemia, 13 were given bromocriptine and all 13 showed major clinical improvement [66]. If men do not fully respond to a dopamine agonist, they can attempt TRT for the management of sexual symptoms. Patients who have hyperprolactinemia refractory to all medical therapy may elect surgical treatment. This is only suggested to patients who are unresponsive to dopamine agonists, have persistent symptoms, and have unchanging or enlarging adenomas. In severe cases, postoperative radiation therapy may be used for aggressively growing adenomas [74].

Corticosteroids

Corticosteroids are hormones in males and females that aid in the regulation of a variety of metabolic processes ranging from protein catabolism and carbohydrate metabolism to augmenting the immune system. They are synthesized and excreted via the adrenal gland. Corticosteroids are separated into two distinct classes, mineralocorticoids, which influence salt and

Table 5 Summary of studies on hyperprolactinemia and sexual function

Study	*n*	Outcome
Carter et al. [66]	22 men with hyperprolactinemia	- 91% of men with high PRL tumors presented with impotence
Johri et al. [67]	138 men with ED	- Prevalence of hyperprolactinemia in men with ED is 2.2% - Patients with hyperprolactinemia had more severe ED, as defined by IIEF scores < 10
Johnson et al. [68]	330 men with ED	- Prevalence of hyperprolactinemia in men with ED is ~2%
Corona et al. [69]	2146 men	- Using the SIEDY and ANDROTEST scores, hyperprolactinemia was found to be a predictor of ED with a hazard ratio of 8.60 [3.85–19.23].

ED, erectile dysfunction

water homeostasis, and glucocorticoid, which will be the focus of this section [75]. Deficiencies in corticosteroids are rare; Addison's disease or primary adrenal insufficiency occurs in roughly 1 per 10,000 men in the USA [76]. Iatrogenic deficiency can develop with prolonged steroid supplementation and subsequent discontinuation [77].

The role of glucocorticoids, namely cortisol, in sexual function is not yet fully understood. Animal studies in bulls and boars revealed an association between serum cortisol levels and mating activities (mounting, intromission, and ejaculation) [78]. A rat study reported normal levels of penile neuronal NOS (nNOS) in rats that had undergone castration, but decreased penile nNOS in rats that had undergone adrenalectomy and castration, suggesting one pathway in which glucocorticoids may affect erectile function [79]. Granata et al. found an association between corticosteroids and sexual function in humans. They identified 12 men with a recent diagnosis of autoimmune corticosteroid deficiency and measured sexual function using the IIEF-15 at baseline and again after steroid replacement therapy. Erectile function, libido, and orgasmic function all improved with treatment [80]. However, not all human studies point to a positive association between cortisol and sexual function. In 2003, 54 men had systemic and cavernosal cortisol measurements taken while exhibiting different penile states (flaccid, tumescent, rigid, detumescent). Penile tumescence and rigidity were achieved with the use of sexually explicit movies and self-stimulation. As penile erection progressed into the rigid state, cortisol levels significantly dropped in both systemic and cavernosal blood suggesting that decreased cortisol levels facilitate sexual activity [77]. Similar results were observed in a study of 105 men who had measurements obtained of their bioavailable cortisol. When sexual dysfunction was determined with the IIEF, a statistically significant negative association was discerned between bioavailable cortisol and IIEF scores [81].

Primary adrenal insufficiency rarely presents as primary infertility, but this has been described in the literature. Causes of infertility are broad; the differential includes genetic abnormalities, congenital anomalies, acquired disorder of the testes, and hormonal dysfunction. As part of the hormonal workup for infertility, infrequent signs of Addison's disease may be identified allowing diagnosis [82]. Infertility from Addison's disease is due to hypocortisolism. The exact mechanism of how decreased cortisol causes infertility is poorly understood. Semen analyses of patients with Addison's disease have been shown to be significant for oligoteratospermia [83].

Conclusion

Hormones regulate many processes throughout the body, including sexual function. The pathophysiology of how these hormones affect tissue has not yet been fully elucidated, and more animal studies are needed to determine the exact mechanisms through which they act. T deficiency can present with decreased libido and diminished erectile function. Estrogen plays a role in sexual drive but is postulated to inhibit erectile function if too high. Hyperthyroidism is associated with PE, hypothyroidism is associated with DE, and both are associated with ED. Men with ED are more likely to have hyperprolactinemia than those in the general populace. Additionally, elevated PRL levels can cause fertility issues by disrupting spermatogenesis. The role of corticosteroids is the least clear, with reports of both positive and negative effects on sexual function. Resolution of sexual dysfunction is achieved in most cases by normalization of hormone levels.

Compliance with Ethical Standards

Conflict of Interest Dr. Hellstrom reports serving as consultant/advisor for Abbvie and on the speaker's bureau for Endo. Dr. Greenberg, Dr. Koller, Dr. Herzog, and Dr. Dick each declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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