REVIEW ARTICLE

Thyroid disorders and male sexual dysfunction

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Though early research suggested that thyroid hormones were not involved with the testes, male spermatogenesis, or erectile function, investigations on this topic over the past few decades have increased and shed new light. A literature review of studies conducted between 1963 and 2022 regarding male sexual dysfunction (SD) and thyroid disorders was performed to define the diagnostic consideration, pathophysiology, and management of SD secondary to thyroid dysregulation. This article provides evidence and interpretation of prior clinical and preclinical studies and contextualizes these studies for clinical practice. Clinical manifestations of SDs included erectile and ejaculatory dysfunction, impaired spermatogenesis, and disruption of the hypothalamic-pituitary-gonadal axis. Our aim of this communication was to perform a literature review detailing the impact of thyroid disorders on male SD. We hope to provide a framework for practicing urologists, endocrinologists, or general practitioners when evaluating patients with concurrent thyroid and male SD. It is important to recognize that thyroid disorders can be an important part of the pathophysiology of male SD in patients. Future research studies are needed to further elucidate the mechanisms involved.

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INTRODUCTION

The link between thyroid disorders and sexual dysfunction (SD) has been well established in females; however, the link between male SD and thyroid disorders has recently garnered interest [1]. The first review on the relationship between thyroid disorders and male SD detailed the paucity of scientific studies on this topic [2]. The incidence of thyroid dysregulation is well documented by sexual medicine physicians treating patients who have this comorbidity [3]. Due to this relationship, it is also important for sexual medicine physicians to recognize the different symptoms of thyroid disorders, which impact multiple systems in the human body (Table 1). This review will investigate the relationship between thyroid disease states and sexual health by examining the impact of thyroid disorders on testicular function and structure, hormonal balance, clinical symptoms of SD, and evaluation and treatment of sexual disorders.

Impacts of hypothyroidism on androgenic hormones

To adequately review the SDs associated with thyroid dysregulation, it is important to briefly discuss the physiologic interactions of the hypothalamus, pituitary gland, and testes. Thyroid hormone (TH) is regulated initially by the hypothalamus [4, 5]. Cell bodies in the periventricular nucleus of the hypothalamus produce and release a peptide hormone, thyrotropin-releasing hormone (TRH), into the hypothalamic-hypophyseal portal system to the anterior pituitary [4]. TRH binds to receptors in the pituitary gland, which induces a signal cascade resulting in transcription and production of thyroid-stimulating hormone (TSH) [4]. TRH also stimulates production of prolactin via action of lactotropic cells in the anterior pituitary [5]. Hypothyroidism results in a reduced production of TH, thyroxine (T4), and triiodothyronine (T3), which leads to upregulation of TSH and TRH (Table 2).

As previously mentioned, TRH can have a nonspecific effect in stimulating production of prolactin [5, 6]. Increased levels of prolactin can result in suppression of gonadotropins [4]. Gonadotropin-releasing hormone (GnRH), which is released from the hypothalamus via the infundibular nucleus, travels to the anterior pituitary gland and binds to gonadotropes to stimulate production of follicular-stimulating hormone (FSH) and luteinizing hormone (LH) [4]. FSH and LH are both glycoproteins with an identical alpha subunit but with a beta subunit unique to each hormone [4]. FSH stimulates proliferation of germ cells (GCs) through stimulation of Sertoli cells (SCs) in the male testes and is vital during the fetal development in secretion of anti-mullerian hormone (AMH), which in turn inhibits formation of female sex organs [7, 8]. SCs, which secrete androgen-binding protein (ABP) to increase the intratesticular concentration of testosterone and to assist with the maturation of spermatogonia, also function in creation of the blood-testis barrier and secretion of inhibin B [9]. LH stimulates Leydig cells (LCs) in the testicle to produce testosterone [4]. Testosterone impacts sexual differentiation, erythropoiesis, muscle content, fat metabolism, and libido [10].

Primary hypothyroidism in multiple studies is associated with hypergonadotropic or hypogonadotropic hypogonadism (Table 2) [11–13]. In a 1998 study, low free testosterone levels were observed in a series of ten patients with primary hypothyroidism [13]. After treatment with levothyroxine, the free testosterone levels of patients improved to normal levels. The LH and FSH levels of patients were inappropriately normal in the setting of hypogonadism, suggesting the defect could be at the hypothalamus-pituitary axis. As mentioned earlier, prolactin is sometimes elevated in patients with primary hypothyroidism due to elevation in TRH and stimulation downstream of lactotropic

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Table 1. Clinical manifestations of disordered thyroid states [52, 55].

	Hyperthyroidism	Hypothyroidism
General	Heat intolerance, excessive sweating, weight loss, weakness, onycholysis, infiltrative dermopathy	Cold intolerance, decreased sweating, hair loss, brittle skin, dry skin, hoarse voice
Ophthalmologic	Exophthalmos, edema, lid lag, lip retraction	Association with diabetic retinopathy
Goiter (thyroid)	Diffuse, smooth, nontender	Either enlarged or atrophic
Cardiovascular	Tachycardia, palpitations, irregular pulse, hypertension with widened pulse pressure	Myopathy, bradycardia, hypertension, metabolic syndrome
Musculoskeletal	Fine tremor, myopathy, osteopathy	Entrapment syndromes, myxedematous heart disease
Endocrinological	Females:	Females:
	Amenorrhea, anovulation, uterine bleeding	Galactorrhea, menorrhagia, infertility
	Males:	Males:
	Gynecomastia, erectile dysfunction, premature ejaculation	Erectile dysfunction, delayed ejaculation, decreased libido, infertility
Neuropsychiatric	Anxiety, depression, insomnia, restlessness, hyperreflexia	Impaired cognition, depression, somnolence, fatigue, delayed relaxation of the deep tendon reflexes.

Table 2. Hormonal changes associated with thyroid disorders [2, 11].

Hormonal changes	Overt primary hypothyroidism	Overt primary hyperthyroidism
Free T3	↓	↑
Free T4	↓	↑
TSH	↑	↓
SHBG	↓	↑
Prolactin	↑, ↔	↔
LH	↓, ↔	↑, ↔
FSH	↓, ↔	↔
Testosterone (free)	↓, ↔	↓, ↔

T3 triiodothyroxine, *T4* thyroxine, *TSH* thyroid-stimulating hormone, *SHBG* sex hormone-binding globulin, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone.

cells. However, even in hypothyroid patients with prolactin levels in the normal range, a decrease in prolactin levels and an increase in free testosterone levels were observed after treatment with levothyroxine [13]. Another known effect of hypothyroidism is the reduction in levels of sex hormone-binding globulin (SHBG), which further results in lower serum total testosterone levels [11, 12].

Impacts of hyperthyroidism on androgenic hormones

In a 1999 study that compared patients with primary hyperthyroidism to healthy controls, serum LH levels were higher in the untreated hyperthyroid group, and LH was more responsive to GnRH stimulation [12]. FSH levels were not significantly different between the two groups, and prolactin levels were not different at baseline (Table 2). Most importantly, levels of free testosterone were significantly lower in the hyperthyroid group compared to the control group, and testosterone was more responsive to GnRH stimulation in the hyperthyroid group (Table 2). This study confirmed previous studies that reported elevated SHBG levels in the hyperthyroid state, which may have contributed to observed lower free testosterone levels (Table 2).

Impact of thyroid hormone on development of Sertoli cells

The impact of TH in the development and function of testicular tissue was largely controversial for many years [2]. It was hypothesized that the testes were unaffected by TH due to their lack of binding sites for TH and their lack of metabolic response to TH, as demonstrated in early animal studies [14, 15]. However, multiple studies over the past two decades have established the role of TH on both the development and maturation of the testes [2, 16, 17].

The effects of alterations in TH levels in SCs have been extensively investigated in rodent studies and in cultures of human SCs. The expression of the α-1 isoform of the nuclear TH receptor in immature SCs has been observed to be the site of binding to TH, with high affinity and specificity [2, 18]. It has further been postulated that the expression of TH receptors within the testes are required during critical periods in the neonatal and prepubertal ages [19]. Studies have consistently demonstrated that congenital hypothyroidism fostered extended proliferation periods of SCs, thus delaying their differentiation [20]. Consistent with these findings, the expression of AMH was prolonged in neonatal hypothyroidism [21]. AMH serves as a surrogate for the division of SCs, and the proposed extended division of SCs, in the setting of congenital hypothyroidism, is augmented by the prolonged expression of AMH [14, 20]. Additionally, ABP and inhibin B, which are markers of SC maturation, are delayed in the setting of congenital hypothyroidism. The demonstrated changes in SC differentiation and division, which were based on TH levels,

indicate the existence of molecular targets of TH [20]. Recent studies have proposed that numerous cell-cycle regulatory pathways are under the modulatory effect of TH, such as the PI3K signaling pathway, p27Kip1 and p21CiP1 cell-cycle inhibitors, as well as JunD and c-Myc oncogenes [22–24].

Moreover, recent studies of SCs in culture have revealed that their maturation is modulated by TH through changes in the cell's physiologic properties. It has been observed that the expressive ratio of androgen and estrogen receptors is increased by rising levels of T3 [25]. Furthermore, the decreased expression of aromatase and ABP has been noted in the presence of increased T3 [26, 27]. Through such mechanisms, the sensitivity of SCs to circulating androgens are increased by the effects of T3, thus propagating the cell maturation.

The size and cellular architecture of testes is dependent on normal TH levels in utero. Studies have observed that TH compels SCs to inhibit proliferation and to stimulate differentiation of cells in rodents and other vertebrates. Animals that were hypothyroid and allowed to become euthyroid were observed to have increased sperm production and larger testicular sizes [28, 29]. It is hypothesized that transient neonatal/prepubertal hypothyroidism results in proliferation and undifferentiation of SCs. Transient hyperthyroidism in juveniles has been demonstrated to cause decreased testicular size and sperm production [29], thereby indicating the role of TH in the development of SCs. Although a similar observation in the setting of hypothyroidism and hyperthyroidism is observed on development of LCs, there is one important difference. Specifically, paracrine factors released from SCs have also been documented to impact the development of LCs [28, 29].

Impact of thyroid hormone on spermatogenesis

GC maturation within the testes has been observed to be affected by changing TH levels [30]. In one rodent study, the initiation of spermatogenesis, with an associated increase in the number of spermatogonia, resulted from the treatment of T3 in neonatal rats [31]. In contrast, a further study indicated a marked arrest in GC maturation and increased apoptosis of GCs when T3 was administered to rats with sexually matured testes [32]. Indeed, spermatogenesis has been demonstrated to be impacted in both hypothyroidism and hyperthyroidism. In one rat model, increased oxidative stress was observed in the testes of hypothyroid rats, with associated increase in apoptotic markers, decreased expression of glucose transporters, and loss of connexin proteins [33]. This could be explained by decreased levels of glutathione, as it has been demonstrated that reduced glutathione synthesis is induced by TH [34]. Recent studies have revealed the clinical implications of such findings. Altered seminal quality was reported in a small series of men with overt hypothyroidism [35, 36]. A further study reported that although subclinical hypothyroidism (SCH) was associated with normozoospermia, sperm samples of men with SCH were burdened by an increased risk for DNA fragmentation [37]. The resulting increased oxidative damage of sperm in the setting of SCH may be responsible for the worse outcomes of assisted reproductive technology in patients with SCH [38, 39]. While a number of such studies revealed differing semen parameters in males with a thyroid disorder, many of these parameters normalize after thyroid disorders are treated in adults, with the exception being in those with these conditions prior to puberty [40, 41].

Impact of hypothyroidism on erectile dysfunction

Though the exact prevalence of SD in males who present with hypothyroidism is uncertain, small studies have estimated that over 59% of males with hypothyroidism experience some degree of SD [42]. Conversely, it is estimated that 0.2–6% of patients presenting with SD may have underlying hypothyroidism. In one study, 3202 men with signs of SD were evaluated for coexistent hypothyroidism [3]. Approximately, 2.5% of the study population had elevated levels of TSH, which is indicative of either subclinical or overt hypothyroidism [3].

A study in 2005 compared control patients to those with thyroid disorders, diabetes, or obesity, specifically using the International Index of Erectile Function (IIEF) scores to examine any significant difference in ED [42]. The study concluded that patients with thyroid disorders had significantly worse IIEF scores compared to control patients; however, no association was made between ED and treatments, TSH levels, or the presence of thyroid antibodies. A larger study in 2008 confirmed the significant association between ED and thyroid dysfunction (hypo- or hyperthyroid) [43]. In contrast to both these studies, a larger study examining two cohorts, the European Male Ageing Study and the University of Florence (UNIFI) study, observed an association between hyperthyroidism and ED but not between hypothyroidism and ED (Table 1) [3]. Notably, the UNIFI study demonstrated an association between hypothyroidism and ED, but this association was not significant when accounting for other confounding variables [3].

Due to conflicting observations in multiple studies, the link between hypothyroidism and ED remains unclear. Proposed mechanisms center around two phenomena: dysfunction of hormonal axes in hypothyroidism and metabolic syndrome (MetS) as a sequalae of hypothyroidism [3]. Hormonal disruption in hypothyroidism can result in decreased total and free testosterone levels. One study exhibited both a return to baseline of free testosterone levels and an associated resolution of ED in hypothyroid men treated with T4 [44]. An additional proposed mechanism involves the disrupted negative feedback between TH and prolactin. Hyperprolactinemia is induced in the hypothyroid state, and studies have associated increased prolactin levels with ED [45]. Again, the precise mechanism for this is unclear, and the association between hyperprolactinemia and ED is not widely accepted. A further proposed mechanism suggests that hypothyroidism is associated with ED due to underlying MetS. Development of type 2 diabetes mellitus and cardiovascular diseases is enhanced by MetS, both of which are associated with worsening erectile function (EF) [46].

Impact of hyperthyroidism on erectile dysfunction

The estimated prevalence of hyperthyroidism in men seeking treatment for SD is 3.4% [3]. In the previously mentioned study, hyperthyroidism was the only thyroid disorder significantly associated with ED, after confounding variables were accounted. In addition, the study observed an association between low TSH and ED, even when the analysis was adjusted for potential confounders.

While the exact mechanism is still debated, proposed mechanisms for the association between hyperthyroidism and SD have been supported through rodent and human studies. It has been observed that the concentration of beta-adrenergic receptors is upregulated by TH [47]. The resultant increased sensitivity to circulating catecholamines may serve as the catalyst for ED, possibly by impairing relaxation of arterioles in the corpora cavernosa. Additionally, it has been reported that TH receptors are found within the corpus cavernosa of both rodents and humans [48]. In a further animal study of hyperthyroid subjects, induced relaxation of the cavernosa was impaired when induced by both acetylcholine and electric stimulation [49]. However, the sensitivity to nitric oxide (NO) was unchanged. It was thus inferred that the ED associated with hyperthyroidism is mediated by impaired NO synthesis. It is conceivable that this disruption in the synthesis of NO was induced by the direct binding of TH to the corpus cavernosa; however, further studies are needed.

Impact of thyroid disorders on ejaculation

Ejaculatory dysfunction was long thought to be due to psychogenic factors, but studies have revealed an increased prevalence of ejaculatory dysfunction in patients with hyperthyroidism and hypothyroidism [50]. In hyperthyroidism, premature ejaculation (PE) is often present, whereas delayed ejaculation (DE) is often observed in those with hypothyroidism [50].

A prospective study was conducted on 34 patients with hyperthyroidism and 14 with hypothyroidism to compare the pretreatment and posttreatment rates of ED, PE, and DE [44]. A significant proportion of hypothyroid men had ED and DE. DE was noted to improve in more than half of the men after treatment. In addition, the intravaginal ejaculation latency time (IELT), defined as time from vaginal intromission to intravaginal ejaculation, in hypothyroid men improved significantly after treatment, including those with DE, thus suggesting a direct involvement of TH in ejaculation.

The link between hyperthyroidism and PE is well established in animal and human studies (Table 1) [44]. In the previously mentioned study, 17 (50%) of 34 hyperthyroid patients were observed to have PE, and this number dropped to 5 (15%) patients once TSH levels were normalized (hyperthyroid disorder was treated) [44]. Also, the IELT in hyperthyroid patients doubled on average after treatment of hyperthyroidism. Furthermore, a positive correlation in this study was observed between TSH and IELT.

Larger studies have also observed the association between PE and hyperthyroidism. A study that examined patients with hyperthyroidism reported that 31 (72%) of 43 patients had PE, with 30 (70%) of 43 patients having definite PE (defined as IELT less than 60 s) [51]. Although only 24 (56%) of the 43 patients followed up in this study, the IELT scores of those 24 patients significantly increased when euthyroid status was achieved, especially in those with definite PE (IELT improved from 36.5 s to 104.8 s in this group) [51]. This study also revealed that hyperthyroid patients with definite PE had an increased incidence of anxiety, which decreased with the treatment of underlying thyroid disorder, thereby suggesting that anxiety and PE could be sequalae from the hyperthyroid state [51]. The association between hyperthyroidism and PE was further documented in a cohort study that recruited 53 patients with self-reported PE between May and July of 2016. Of the 53 patients, 8 (15%) had hyperthyroidism, and those with hyperthyroidism had the longest duration of PE (57.75 ± 42.30 months) and the shortest IELT duration (27.25 ± 22.34 s) [52]. A Brazilian study, which evaluated 63 patients with PE and 39 controls, noted that TSH levels were significantly lower in the PE group compared to the control group ($p = 0.017$) [53]. Additionally, the LH and prolactin levels were significantly different between the two groups ($p = 0.007$ for both LH and prolactin), which suggests the possibility of confounding variables contributing to PE [53]. It should be noted that this study performed a multivariate analysis and that LH was documented to be an independent risk factor for PE [53].

In contrast to the aforementioned evidence, a Dutch cohort study, which recruited 620 male patients with life-long PE without ED, showed no association between thyroid dysfunction and EF [54]. Of the 620 patients, only 14 (2%) had TSH < 0.3, and no patients had elevated thyroxine levels [54]. The low number of hyperthyroid patients in this cohort study may have made it difficult to observe a significant association.

Prior to understanding how TH impacts ejaculatory function, it is essential to review how ejaculatory mechanisms work. Ejaculation or the expulsion of seminal fluid is defined as a spinal reflex triggered by genital and/or brain stimulation that occurs in three phases: emission, expulsion, and orgasm [50]. The spinal ejaculation generator (SEG) is located at spinal levels T12-L2 and is responsible for coordinating this reflex [50]. Initially, afferent signals, either from genital nerves or supraspinal (brain) neurons, cause excitation of the SEG and activation of sympathetic and parasympathetic nerves. Parasympathetic nerves stimulate production of seminal fluid, and sympathetic nerves induce spermatozoal transport through the contraction of the vas deferens and seminal vesicles. Next, adrenergic neurons in the pelvis stimulate contraction of the seminal vesicles and prostate, causing seminal and spermatic fluid to pool in the prostatic urethra, which eventually stimulates the urethral-muscular reflex. Final ejaculation is stimulated by somatic nerves from S2-S4 (pudendal), which activate the levator ani, bulbocavernosus, and bulbospongiosus muscles to rhythmically contract [50].

In a study conducted on rats exposed to L-thyroxine, an increase in the contractility of the seminal vesicle and the bulbospongiosus muscle was observed but resolved spontaneously after a 28-day washout period, after which rats were euthyroid, and normal contractility of the seminal vesicle and the bulbospongiosus muscle was recorded [55]. This indicates that TH may have a direct impact on pelvic floor musculature and accessory sex organs involved in the ejaculatory reflex. Similar to how the ankle reflex is depressed in hypothyroid patients, the ejaculatory reflex also becomes delayed, which explains the DE and increased IELT observed in hypothyroid patients [50].

Evaluation and treatment of sexual dysfunction secondary to thyroid disorders

The diagnostic workup for both hypothyroidism and hyperthyroidism consists of an initial screening of TSH levels, with subsequent evaluations of free T3 and T4 levels [56]. This initial screening should be performed if patients exhibit symptoms of thyroid dysfunction (Table 1). Further diagnostic protocol may involve screening with a thyroid antibody panel to delineate the true etiology of the disordered thyroid state [56]. A positive benefit lies within such a screening workup, as SD has been documented to improve after treatment for an underlying thyroid dysfunction.

Levothyroxine, a synthetic formulation of T4, therapy remains the standard of care for the treatment of hypothyroidism [57]. A study evaluated EF in 44 patients with hypothyroidism and observed an increase in the Sexual Health Inventory for Men (SHIM) scores after treatment with levothyroxine [43]. Furthermore, a strong positive correlation was found between SHIM scores and free T4 levels. In 2020, a randomized controlled trial was conducted on 40 males with subclinical hypothyroidism [58]. Subjects in the trial were delegated into either an untreated control group or a treatment group, which was administered levothyroxine. EF was measured with the IIEF-5 score and peak systolic velocity (PSV) of the cavernous artery, using a penile duplex Doppler ultrasound following an intracavernosal injection of alprostadil. Significant increases in the IIEF-5 score and PSV were recorded in the treatment group once euthyroid status was achieved. No increase in such measures was noted in the control group. Studies have also revealed clinical improvement in DE in hypothyroid patients after appropriate thyroid treatment. In one study, the resolution of DE was reported in half of the hypothyroid patients after treatment with levothyroxine. In such patients treated with levothyroxine, the IELT decreased significantly from a mean of 21.8–7.4 min [44].

The achievement of euthyroid status in hyperthyroid patients can involve medical treatment with antithyroid drugs, such as propylthiouracil and methimazole; surgical thyroidectomy; or radioactive iodine therapy [59]. Increases in SHIM scores were observed in a study evaluating 27 hyperthyroid males who achieved euthyroid status following treatment [38]. In a further study, 49 treatment-naïve males with active hyperthyroidism were treated with medical therapy, radioactive iodine therapy, or surgical thyroidectomy until euthyroidism was achieved [51]. It was found that the mean IELT significantly increased from 2.4 min pretreatment to 4.0 min posttreatment. The prevalence of PE decreased from 50 to 15% after thyroid status was normalized [51].

CONCLUSION

Male SD is impacted significantly by thyroid disorders. Dysregulation of the hypothalamic-pituitary-gonadal axis is one of the major contributing factors that facilitates changes in libido, ED, and ejaculatory dysfunction in patients with thyroid disorders. Research reveals that thyroid dysfunction impacts the development and function of testicular tissue, action of accessory sex organs, and responsiveness of structures involved in the neuromuscular pathways essential to erectile and ejaculatory function. More studies in animals and human subjects are needed to further elucidate the impact of TH on male sexual function.

DATA AVAILABILITY

The data in this paper can be found by searching the listed references on PubMed.

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AUTHOR CONTRIBUTIONS

Conceived and/or designed the work that led to the submission, acquired data, and/or played an important role in interpreting the results: RM, DS, and WJGH. Drafted or revised the manuscript: RM, DS, and WJGH. Approved the final version: WJGH. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: WJGH.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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