The Impact of Thyroid Disease on Sexual Dysfunction in Men and Women

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ABSTRACT

Background: Individually, thyroid disease and sexual dysfunction are common conditions that can have a detrimental effect on quality of life. Recent reports have documented an increased prevalence of sexual dysfunction among patients with thyroid disorders. As such, it is important for sexual medicine physicians to be primed on the presentation of patients with overlying sexual and thyroid dysfunction to allow for proper management.

Aim: To review the available literature exploring the relationship between thyroid disease and sexual dysfunction in men and women.

Methods: A PubMed review of existing clinical and pre-clinical studies from 1978 through 2018 was performed.

Main Outcome Measures: The prevalence, symptomatology, pathophysiology, diagnosis and management of patients with sexual dysfunction in the setting of thyroid disease were reviewed.

Results: The prevalence of sexual dysfunction in patients with hypothyroid (59−63% and 22−46% in men and women, respectively) and hyperthyroidism (48−77% and 44−60% in men and women, respectively) has been estimated in select populations. Both hypothyroidism and hyperthyroidism were strongly associated with erectile and ejaculatory dysfunction: hypothyroidism with delayed ejaculation, hyperthyroidism with pre-mature ejaculation. Hypothyroidism and hyperthyroidism have been reported to impair libido in men and women; however, evidence of hypothyroidism's impact on male libido is mixed. Hypothyroid and hyperthyroid women demonstrated impairments in desire, arousal/lubrication, orgasm, satisfaction, and pain during intercourse. Mechanistically, hypothyroidism and hyperthyroidism exert effects on circulating sex hormone levels through peripheral and central pathways and can indirectly provoke psychiatric and autonomic dysregulation that can impair sexual function. Correction to euthyroid state was associated with dramatic resolution of sexual dysfunction in both male and female patients with hypothyroidism or hyperthyroidism.

Conclusion: By improving awareness of the link between thyroid disease and sexual dysfunction, sexual medicine physicians may sooner identify patients whose sexual symptoms may be remedied by treating an underlying thyroid disorder. **Gabrielson AT, Sartor RA, Hellstrom WJG. The Impact of Thyroid Disease on Sexual Dysfunction in Men and Women. Sex Med Rev 2019;7:57−70.**

Key Words: Thyroid Disease; Sexual Dysfunction; Prevalence; Mechanisms

INTRODUCTION

Thyroid disease and its impact on sexual function is a historically under-examined issue; however, the last decade has led to a surge in the number of well-designed population-based and prospective controlled cohort studies exploring this relationship. In 1995, Jannini et al[1] published the first review relating these 2 disease states, and since that time, there have been over a dozen studies investigating the impact of thyroid disease on sexual function. The salience of the current review stems from the fact that thyroid dysfunction is quite common in the general population. Sexual medicine physicians are likely to encounter many patients with concomitant hypothyroidism or hyperthyroidism, and as such, must be cognizant of the role that these disease processes play in sexual health. Furthermore, prompt treatment of a patient's thyroid disease may reduce or eliminate the need for therapies targeting sexual dysfunction. This article will broadly review thyroid disease, sexual dysfunction, the relationship between the 2 conditions, and the role of treatment at their inter-section.

Received March 19, 2018. Accepted May 12, 2018.

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https://doi.org/10.1016/j.sxmr.2018.05.002

Overview of Thyroid Physiology and Disease

The hypo-thalamic-pituitary-thyroid axis is controlled by a series of complex inter-actions that regulate the peptide hormones, thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH), and ultimately the production of thyroxine (T4) and tri-iodothyronine (T3). Hypo-thalamic release of TRH stimulates production of TSH in the pituitary, which is released into systemic circulation and promotes production of T4 and T3 in the thyroid gland. The majority of T4 and T3 are bound to transport proteins in the bloodstream, most notably T4-binding globulin. Additionally, T4 can be further converted to T3, a more potent signaling molecule, by 5'-deiodinase in peripheral target tissues. Free T4 and T3 are unbound and represent the biologically active forms of the hormones, which act to influence numerous essential metabolic activities. These include regulation of protein, fat, and carbohydrate metabolism as well as bone and neural development. End-organ negative and positive feedback dictates production and release levels of TRH and TSH at the hypo-thalamic and pituitary levels[2] (Figure 1).

Hypothyroidism and hyperthyroidism are common medical disorders that manifest themselves in a myriad of ways that have been well described in the medical literature. Primary hypothyroidism is defined by defects within the thyroid gland itself and account for 95% of all forms of hypothyroidism, which can be further separated into sub-clinical and overt disease. In iodine-sufficient populations, the most common cause of hypothyroidism is chronic auto-immune thyroiditis (Hashimoto thyroiditis).[3] In contrast, hyperthyroidism has a broader and larger number of etiologies. The most common cause of hyperthyroidism is Graves' disease, an auto-immune disorder that involves the formation of auto-antibodies that mimic TSH, and can augment TSH receptor downstream signaling.[3]

The prevalence of hypothyroidism estimated by the U.S. National Health and Nutrition Examination Survey III by screening serum TSH, T4, anti-thyroglobulin antibodies, and anti-thyroid peroxidase antibodies, was 4.6%, with 0.3% and 4.3% representing overt and sub-clinical hypothyroidism, respectively. Hypothyroidism was found to affect women 5–8 times more than men.[4] The prevalence of overt hypothyroidism in men, however, is relatively low (0.1%). Nonetheless, clinically silent (sub-clinical) hypothyroidism is not uncommon, even in men (2.8%).[5] The prevalence of hyperthyroidism in the U.S. National Health and Nutrition Examination Survey III was 1.3%, with 0.5% of the population having overt pathology and 0.7% with sub-clinical disease. Hyperthyroidism was also found to be 5 times more common in women[4] (Table 1).

In regard to symptomatology, hypothyroidism presents with some constellation of weight gain, fatigue, constipation, cold intolerance, cognitive slowing, dry skin, edema, myalgia, and/or menstrual irregularities.[6] In contrast, hyperthyroidism presents in both sexes with a combination of increased appetite and weight loss, heat intolerance, tremulousness, palpitations, emotional lability, and anxiety[7] (Table 2). The spectrum of severity ranges from sub-clinical to overt disease, including acute thyrotoxicosis. Menstrual irregularities, infertility, gynecomastia, and/or erectile dysfunction (ED) should also prompt an investigation into thyroid abnormalities.

Diagnostic workup typically involves measurement of serum TSH along with free T4 and/or T3. A suspected diagnosis of hypothyroidism can be confirmed with a high serum TSH (>5.0 mU/L) and low free T4 and/or T3.[6] Hyperthyroidism typically has a suppressed TSH (<0.4 mU/L) and a high free T4 and/or T3.[7] Physical examination findings can also be helpful in delineating the etiology of a patient's thyroid disease (Table 2). It is important to note that thyroid dysfunction may be sub-clinical, in

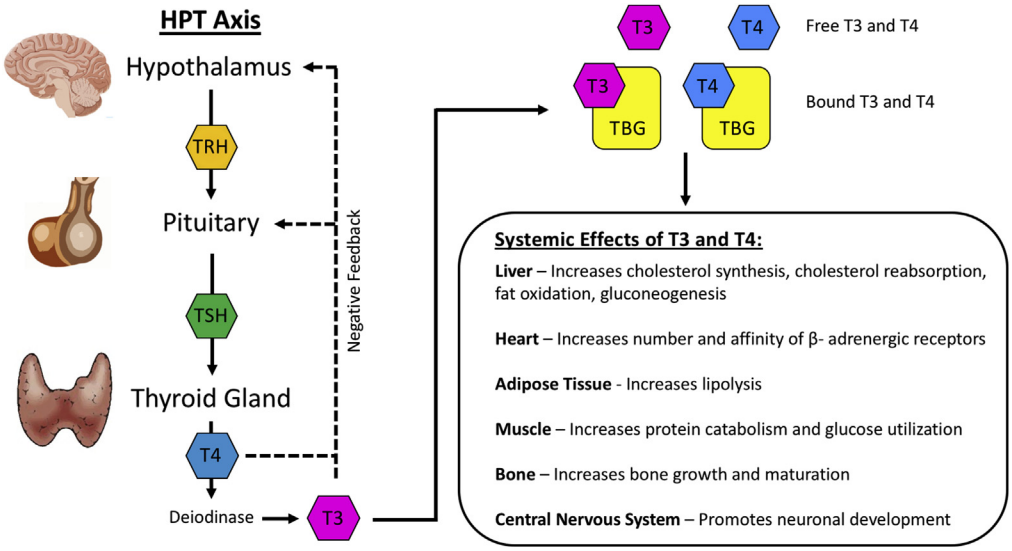

Figure 1. Schematic demonstrating the intact hypo-thalamic-pituitary-thyroid (HPT) axis, as well as the systemic effects that circulating and bound tri-iodothyronine (T3) and thyroxine (T4) exert on the body. TBG = thyroxine-binding globulin; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone. Figure 1 is available in color online at www.smr.jsexmed.org.

Table 1. Highlight of overall prevalence of sub-clinical and overt thyroid disease in the United States as reported in the U.S. National Health and Nutrition Examination Survey III study, as well as overall rates of sexual dysfunction in the setting of hypothyroidism and hyperthyroidism[4]

Thyroid disease category	Prevalence rates
Hypothyroidism	
Overall	4.6%
Sub-clinical (normal free T4 [≥57.9 nmol/L], TSH >4.5 mU/L)	4.3%
Overt (free T4 [<57.9 nmol/L], TSH >4.5 mU/L)	0.3%
Sexual dysfunction in the setting of hypothyroidism	Men 59–63% Women 22–46%
Hyperthyroidism	
Overall	1.3%
Sub-clinical (normal free T4 [<169.9 nmol/L], TSH <0.1 mU/L)	0.7%
Overt (free T4 [≥169.9 nmol/L], TSH <0.1 mU/L)	0.5%
Sexual dysfunction in the setting of hyperthyroidism	Men 48–77% Women 44–60%

T4 = thyroxine; TSH = thyroid-stimulating hormone.

Table 2. Common symptomatology and physical examination findings in patients with hypothyroidism and hyperthyroidism[65,66]

	Hypothyroidism	Hyperthyroidism
Symptomatology	Fatigue	Nervousness
	Dry skin	Diaphoresis
	Depression	Palpitations or tachycardia
	Cold intolerance	Heat intolerance
	Cognitive dysfunction	Fatigue
	Weight gain	Weight loss
	Shortness of breath	Shortness of breath
	Lower extremity edema	Lower extremity edema
	Constipation	Diarrhea
	Muscle or joint pain	Menstrual irregularity
		Emotional lability
	Hypothyroidism	**Hyperthyroidism**
Physical examination findings	Bradycardia	Tachycardia
	Psychomotor retardation (Speech/movement)	Goiter
	Coarse skin	Moist skin
	Delayed deep tendon reflexes	Hand tremor
	Diastolic hyper-tension	Thyroid bruit
	Periorbital edema	Periorbital edema
	Muscle tenderness	Atrial fibrillation
	Macroglossia	Splenomegaly
		Gynecomastia

which there are abnormal increases or decreases in serum TSH without compensatory changes in free T4 or T3 levels.[7] As will be discussed in subsequent sections of this review, sub-clinical thyroid dysfunction can still have a detrimental effect on sexual function in patients, and as such, sexual medicine clinicians may consider screening for thyroid disease in otherwise asymptomatic patients presenting with sexual symptoms.

Treatment for thyroid disease is well defined by guidelines. The primary treatment of hypothyroidism is replacement therapy in the form of synthetic T4 until the patient is euthyroid, which can take up to 4–6 weeks before alterations in hormone levels can be observed. Modalities for treatment of hyperthyroidism include radio-active iodine, various anti-thyroid medications, and thyroidectomy.

Overview of Sexual Dysfunction in Men and Women

Thyroid disorders have been implicated in significant disturbances in both male and female sexual dysfunction (FSD), and these issues will be focused upon herein. Sexual dysfunction, in both men and women, is a highly prevalent and multi-faceted issue, with multiple underlying etiologies. Sexual dysfunction from the man's perspective can be classified into categories of ED, ejaculatory disorders including premature ejaculation (PE) and delayed ejaculation (DE), and decreased libido. PE is the most prevalent male sexual disorder, which occurs in 20–30% of men during their lifetime.[8] ED is another common male sexual dysfunction, which is a highly age-dependent issue, reported to be 18% for the age range of 50–59 years, increasing up to 37% for ages 70–75 years.[9] An estimated 5–15% of men experience diminished libido, many of whom reported concomitant deterioration in other domains of sexual functioning.[9]

From the women's perspective, sexual dysfunction is approached from the domains of sexual desire, arousal/lubrication, orgasm, satisfaction, and pain with sexual activity. According to an international survey of women aged 40–80 years old, 39% of women reported dysfunction in at least 1 of these areas.[10] There is also an element of age–dependent change in FSD, as a genito-urinary syndrome of menopause is reported to cause discomfort, lack of lubrication, or pain in 40% of post-menopausal women.[11] According to the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking study, which surveyed 30,000 women in the United States, 43% of women experienced difficulties with these sexual issues. The most common symptom reported by women in the United States at 39% was reduced desire. Decreased arousal was reported by 26% of women and 21% experienced difficulty with orgasm.[12]

Implicit to this discussion is the inter-connected relationship of sexual and reproductive dysfunction due to overlapping etiologies relevant to alterations in the hypo-thalamic-pituitary-gonadal axis. The most relevant consequence of these hormonal disturbances is

Table 3. Summary of available studies demonstrating an association between hypothyroidism and sexual dysfunction in men and women

Hypothyroidism		
Men		
Study	**Patients**	**Results**
Carani et al,[13] 2005	N = 14 Hypothyroid	9 (63.4%) had ED, HSDD, and DE
		1 (7.1%) had PE
		All patients had low total T, estradiol, SHBG*
Krassas et al,[14] 2008	N = 44 Hypothyroid	Higher rates of ED in hypothyroid arm compared to controls (63% vs 34%)*
	N = 71 Controls	SHIM scores inversely correlated with TSH*
Veronelli et al,[15] 2006	N = 55 Hypothyroid	Higher rates of all forms of ED (IIEF-5) in hypothyroid arm compared to controls*
	N = 109 Controls	
Corona et al,[20] 2012 (UNIFI cohort)	N = 3,203 Men presenting to sexual medicine clinic	TSH inversely correlated with ED after adjusting for age, smoking, T level, CDS*
		High TSH correlated with moderate to severe HSDD*
Wortsman et al,[39] 1987	N = 8 Hypothyroid	7 (88%) had Low libido of >1 y duration since diagnosis with hypothyroidism
Jaya Kumar et al,[28] 1990	N = 8 Hypothyroid	3 (38%) had Low libido
Women		
Study	**Patients**	**Results**
Veronelli et al,[40] 2009	N = 24 Hypothyroid	All FSFI domain scores were lower in the hypothyroid arm compared to controls*
	N = 36 Controls	
Atis et al,[41] 2010	N = 25 Hypothyroid	Rates of FSD using FSFI were higher in those with any form of hypothyroidism compared to controls (55% vs 14.6%)*
	N = 25 Sub-clinical hypothyroid	
	N = 20 Controls	
Oppo et al,[29] 2011	N = 17 Hypothyroid	All FSFI domain scores correlated with free T4, inversely correlated with TSH*
	N = 30 Controls	
Pasquali et al,[42] 2013	N = 104 Hypothyroid	FSD associated with any form of hypothyroidism (idiopathic, Hashimoto)*
	N = 53 Controls	Hypothyroidism associated with decreased desire, arousal, lubrication, but not overall FSFI score, orgasmic function, satisfaction, or sexual pain*
Krysiak et al,[22] 2016	N = 50 Hypothyroid	FSFI domain scores were higher in auto-immune hypothyroidism compared to other forms of hypothyroidism*
	N = 18 Controls	
Luo et al,[23] 2018	N = 168 Sub-clinical hypothyroidism	No increased risk of FSD in sub-clinical hypothyroidism
	N = 951 Controls	No difference between groups with respect to FSFI domains

CDS = chronic disease score; DE = delayed ejaculation; ED = erectile dysfunction; FSD = female sexual dysfunction; FSFI = Female Sexual Function Index; HSDD = hypo-active sexual desire disorder; IIEF = International Index of Erectile Function; PE = premature ejaculation; SHBG = sex hormone–binding globulin; SHIM = Sexual Health Inventory for Males; T = testosterone; T4 = thyroxine; TSH = thyroid-stimulating hormone; UNIFI = University of Florence.
*Statistically significant, $P < 0.05$.

hypogonadism. The outcome is dysregulated menses in women and sub-fertility in both men and women. Other issues such as recurrent pregnancy loss are important consequences of thyroid abnormalities, but are outside the scope of this review. Depending on etiology of thyroid hormone deficiency or excess, alterations in sexual function can be distinct.

The goal of this review is to provide an update on available studies that explore the relationship between thyroid disease and sexual dysfunction in men and women. A secondary aim is to help clinicians identify the link between these 2 disease states, and understand the importance of timely screening and management of this patient population.

Table 4. Summary of available studies demonstrating an association between hyperthyroidism and sexual dysfunction in men and women

Hyperthyroidism		
Men		
Study	**Patients**	**Results**
Carani et al,[13] 2005	N = 34 Hyperthyroid	17 (50%) had PE, 6 (17.6%) had HSDD, 5 (14.7%) had ED, 1 (2.9%) had DE
Waldinger et al,[62] 2005	N = 620 Lifelong PE	No association between lifelong PE and hyperthyroidism
Veronelli et al,[15] 2006	N = 13 Hyperthyroid	Hyperthyroid patients had higher rates of all severities of ED as determined by IIEF-5*
	N = 109 Controls	
Corona et al,[35] 2006	N = 755 Men presenting to sexual medicine clinic	PE was higher in patients with low TSH (<0.2 mU/L) compared to the rest of the sample (57.1% vs 26.5%)*
		Patients with ED and TSH <0.2 mU/L had higher rates of PE compared to patients with ED and normal TSH*
Krassas et al[14] 2008	N = 27 Hyperthyroid	ED was higher in hyperthyroid patients compared to controls,* but SHIM scores did not correlate with free T4 or TSH
	N = 24 Controls	
Cihan et al,[44] 2009	N = 49 With untreated hyperthyroidism	Direct correlation between serum TSH and IELT in patients with PE*
Corona et al,[20] 2012 (EMAS cohort)	N = 3,369 Unselected	TSH levels were inversely proportional to ED prevalence*
	N = 38 Hypothyroid	Subjects reporting to never have erections had higher free T4 levels*
Corona et al,[20] 2012 (UNIFI cohort)	N = 3,203 Presenting with sexual dysfunction	Direct correlation between severe ED and overt hyperthyroidism, even after adjustment for age, smoking, T, and PRL*
	N = 108 Hypothyroid	
Women		
Study	**Patients**	**Results**
Oppo et al,[29] 2011	N = 22 Hyperthyroid	All hyperthyroid patients had significant impairment in all FSFI domains
	N = 30 Controls	Direct correlation between TSH and FSFI domains for desire, lubrication or arousal, and orgasm
		Free T4 was inversely correlated with the FSFI desire domain only*
Atis et al,[47] 2011	N = 40 Hyperthyroid	Hyperthyroid patients had lower FSFI scores in all domains compared with age-matched controls*
	N = 40 Controls	FSFI was directly correlated with TSH*
Pasquali et al,[42] 2013	N = 18 Hyperthyroid	Hyperthyroidism was correlated with a decreased desire domain on FSFI only*
	N = 53 Controls	

DE = delayed ejaculation; ED = erectile dysfunction; EMAS = European Male Aging Study; FSFI = Female Sexual Function Index; HSDD = hypo-active sexual desire disorder; IELT = intravaginal ejaculation latency time; IIEF = International Index of Erectile Function; PE = pre-mature ejaculation; PRL = prolactin; SHIM = Sexual Health Inventory for Males; T = testosterone; T4 = thyroxine; TSH = thyroid-stimulating hormone; UNIFI = University of Florence.
*Statistically significant, $P < 0.05$.

METHODS

A literature review was performed in PubMed with the key words "hypothyroidism" and/or "hyperthyroidism" and/or "sexual dysfunction" and/or "thyroid disease" and/or "erectile dysfunction" and/or "hypoactive sexual desire disorder" and/or "ejaculatory dysfunction" and/or "female sexual dysfunction." The articles derived from this search were culled to identify peer-reviewed publications that were relevant to the clinical questions surrounding the relationship between sexual dysfunction and thyroid disease.

RELATIONSHIP BETWEEN THYROID DISEASE AND SEXUAL DYSFUNCTION

Sexual dysfunction in the setting of thyroid endocrinopathy receives little attention in clinical practice. Unfortunately, most reports are based on random, population-based samples derived from select patient populations. Given that the incidence of thyroid disease in men is relatively low, many of the available studies have small sample sizes. Despite these limitations, all studies to date confirm the existence of an association between thyroid disease and sexual dysfunction (Tables 3 and 4).

HYPOTHYROIDISM AND SEXUAL DYSFUNCTION

Prevalence

The true prevalence of sexual dysfunction in men and women with hypothyroidism is unknown, and has been difficult to measure given the limited number of available studies. 1 Small study involving men presenting with hypothyroidism found that 9 of the 14 (63.4%) patients had sexual dysfunction in the form of hypoactive sexual desire, PE and DE, and ED.[13] Another small study (n = 44) demonstrated that 63% of hypothyroid subjects had some form of ED, which was significantly higher than the rate in healthy controls (34%).[14] Another similar study conducted by Veronelli et al[15] showed that 59% of men with hypothyroidism had ED. Anecdotal evidence has also demonstrated that over 60% of men with hypothyroidism experience ED.[16]

On the other hand, the prevalence of hypothyroidism in patients presenting to clinic with sexual symptoms has been estimated to be between 0.2–6% in select populations. Slag et al[17] reported outcomes of 401 men diagnosed with ED and found that 20 (5%) of these men also had co-existing sub-clinical hypothyroidism as measured by TSH, T3, and T4. A second study, which surveyed 600 men with ED, detected unsuspected hypothyroidism in 36 (6%) patients.[18] Another study involving 305 men with idiopathic infertility found that over 3% of subjects had sub-clinical hypothyroidism and 7.5% of subjects had positive thyroid autoantibody titers.[19] A study conducted at the Sexual Medicine and Andrology Unit at the University of Florence (UNIFI) analyzed a consecutive series of 3,203 heterosexual men presenting for sexual dysfunction. This study found that 79 (2.5%) men presenting for signs and symptoms of sexual dysfunction had high TSH levels indicative of sub-clinical or overt hypothyroidism (>4.5 mU/L).[20] Studies have demonstrated a much lower prevalence of co-existing hypothyroidism and reproductive dysfunction. A study conducted by Kolettis et al[21] involving 536 men being evaluated for primary or secondary infertility found that only 1 (0.2%) patient had concomitant hypothyroidism.

Despite the relatively higher incidence of hypothyroidism in women, few studies have formally evaluated the prevalence of FSD in the setting of hypothyroidism. In a study involving 50 women with hypothyroidism, 23 (46%) were found to have FSD as determined by the validated Female Sexual Function Index (FSFI) score.[22] In another study that enrolled 168 Chinese women with sub-clinical hypothyroidism, 36 (21.4%) were found to have FSD as measured by the Chinese version of the FSFI (score <23.45). In this study, the incidence of decreased desire was 14.3%, decreased arousal was 17.9%, decreased lubrication was 21.4%, decreased orgasms was 21.4%, low sexual satisfaction was 23.2%, and sexual pain was 23.2%.[23] The prevalence of menstrual disturbances in women with hypothyroidism has been estimated to be between 25–70%.[24] There are many studies that demonstrate a high prevalence of reproductive dysfunction (ovulatory dysfunction and infertility) in women with thyroid disease; however, this is outside of the scope of this review.[25,26]

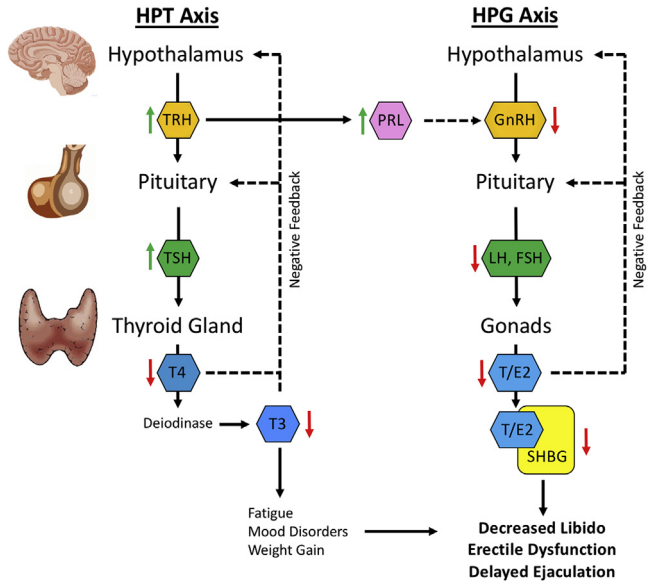

Figure 2. Schematic demonstrating the hormonal effects of hypothyroidism on sexual dysfunction via inter-actions between the hypo-thalamic-pituitary-thyroid (HPT) and hypo-thalamic-pituitary-gonadal (HPG) axes. Sequela of hypothyroidism include: (1) decreased free and total testosterone, and sex hormone–binding globulin (SHBG); (2) disinhibition of prolactin (PRL) via increased thyrotropin-releasing hormone (TRH), promoting hypo-gonadal hypo-gonadism; and (3) fatigue, mood disorders, and weight gain due to reduced levels of circulating thyroid hormones. E2 = estriadol; FSH = follicle stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; T3 = tri-iodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone. Figure 2 is available in color online at www.smr.jsexmed.org.

Proposed Mechanisms

The precise mechanism by which hypothyroidism causes sexual dysfunction is not well characterized; however, several associated hormonal axes have been implicated. Studies have demonstrated that thyroid deficiency can exert both direct and indirect effects on sexual function (Figure 2).

In men, hypothyroidism may cause sexual dysfunction by disrupting regulation of the hypo-thalamic-pituitary-gonadal axis at the level of the hypo-thalamus and pituitary, leading to reduced circulating sex hormone levels. Studies have shown that hypothyroidism is associated with decreased concentration of total and free serum testosterone, as well as sex hormone–binding globulin (SHBG) when compared to euthyroid counterparts.[15] Levels of dehydroepiandrosterone (DHEA), DHEA sulfate, and estrogenic metabolites of DHEA have also been shown to be decreased in patients with hypothyroidism compared to healthy controls.[27] Gonadotropin levels in hypothyroid patients are typically not elevated, and hypothyroidism has been shown to attenuate luteinizing hormone release in response to exogenous gonadotropin-releasing hormone.[28] This supports the notion that deficiencies in thyroid hormone cause a hypo-gonadotropic hypo-gonadal state, which can ultimately drive sexual dysfunction. This mechanism is supported by the study conducted by Carani et al,[13] which

showed that T4 treatment in hypothyroid men caused serum free testosterone, SHBG, and prolactin (PRL) levels to return to baseline, along with resolution of sexual dysfunction symptoms within clinically relevant time frames. In women, studies have demonstrated that low circulating thyroid hormone concentration is the most important factor driving FSD in hypothyroidism. This is supported by a study conducted by Oppo et al,[29] which demonstrated a strong correlation among circulating free T4 levels, TSH, and degree of FSD in hypothyroid women. Interestingly, this correlation was not present in women with hyperthyroidism.[29]

Studies have also revealed that prolonged primary hypothyroidism can lead to hyper-prolactinemia, which is another potential mechanism for sexual dysfunction that applies to both men and women. Hypothyroidism-mediated elevations in TRH increases the production of PRL by the anterior pituitary. Consequent hyper-prolactinemia exerts inhibitory effects on the pulsatile release of gonadotropin-releasing hormone, leading to reduced testosterone, DHEA, and estrogen production. PRL is also released following orgasm in both men and women, and is thought to contribute to post-orgasmic refractory period.[30] Hyper-prolactinemia is strongly associated with hypo-active sexual desire disorder (HSDD) in both men and women. Interestingly, hyper-prolactinemic men with hypo-active sexual desire treated with testosterone had no resolution of sexual symptoms. However, when these patients were treated with PRL-lowering agents (dopamine agonists, ie, cabergoline, bromocriptine), over 90% of men experienced improvements in sexual desire.[31] High levels of PRL have been shown to both directly and indirectly promote menstrual dysregulation including anovulation.[32] Hyper-prolactinemia has also been associated with ED and DE; however, the relationship is still a topic of debate. 1 Study involving 102 patients (51 with hyper-prolactinemia, 51 healthy controls) found statistically significant decreases in nocturnal erections in patients with hyper-prolactinemia (96.7%) compared with controls (13.7%).[33] However, another large study involving 2,146 men demonstrated no association between hyper-prolactinemia and ED, even after adjusting for testosterone status.[34] Hyper-prolactinemia and DE have also been reported, though they are mostly associated with concomitant ED; associations between hyper-prolactinemia and DE are weak.[35]

Indirect effects of hypothyroidism on sexual dysfunction can be attributed to the systemic impact of low circulating T3 and T4. Hypothyroidism is associated with fatigue, somnolence, depressed mood, and mood disorders (refractory depression, anxiety), which all undoubtedly contribute to sexual dysfunction in both men and women. Long-standing hypothyroidism can also contribute to the development of mental dysfunction mimicking that of psychiatric disorders. Hypothyroidism has also been associated with metabolic syndrome in both men and women.[36] Metabolic syndrome potentiates the development of cardio-vascular disease and type 2 diabetes, which both independently drive the development of sexual dysfunction.[37]

Male Sexual Dysfunction in Hypothyroidism

There are several reports demonstrating an association between sexual dysfunction in male hypothyroid patients, most notably in the form of ED, ejaculatory dysfunction, HSDD, and alterations in sperm characteristics and fertility (Table 3).

ED, which is defined as the inability to achieve or sustain an erection satisfactory to engage in sexual intercourse, is probably the most studied of the sexual dysfunctions that occur in men with hypothyroidism. In a small study involving 14 Italian men with hypothyroidism, it was found that 9 patients (63.4%) had concurrent ED. In this same cohort, it was noted that total testosterone, estradiol, and SHBG levels were significantly decreased compared to healthy euthyroid controls.[13] Krassas et al[14] conducted a more robust study of 44 hypothyroid men as well as 71 healthy controls. This study found that 63% of hypothyroid patients reported some form of ED compared to 34% in the control group ($P < .0001$). Furthermore, patients with hypothyroidism in this study had Sexual Health Inventory for Men (SHIM) scores that correlated positively with free T4 levels ($P = .005$) and negatively with TSH levels ($P < .001$).[14] Another study conducted by Veronelli et al[15] compared International Index of Erectile Function (IIEF)-5 scores for 55 hypothyroid patients and 109 healthy controls. Of the 55 hypothyroid patients included in the study, 30 (55%) had some form of ED. It was also observed that hypothyroidism was significantly associated with higher incidences of all forms of ED as determined by IIEF-5 score (mild, moderate, and severe) when compared to healthy controls. Interestingly, this finding remained significant after adjusting for age, suggesting that thyroid hormones were more important than age as a risk factor for ED.[15] In another study, TSH levels were inversely associated with the ability to achieve an erection sufficient for intercourse. This finding was also confirmed by multi-variate analysis after adjusting for confounding variables such as age, smoking status, testosterone level, and chronic disease score. In this cohort, patients with sub-clinical hypothyroidism had statistically significant increased prevalence of severe ED compared to euthyroid counterparts. Interestingly, patients with overt hypothyroidism had no significant increased risk of severe ED compared to controls.[20]

There have also been several reports that suggest a relationship between hypothyroidism and ejaculatory dysfunction, which includes PE and DE. Among the 14 hypothyroid men included in the study conducted by Carani et al,[13] 9 (64.3%) had concomitant DE, and 1 (7.1%) had PE. It was also shown that exogenous administration of levothyroxine resulted in a 2-fold decrease in ejaculatory latency and a reduction in DE. These findings support the notion that thyroid hormones not only play a role in ankle reflexes (as has been previously reported), but in the ejaculatory reflex as well.[38]

Limited reports have demonstrated an association between hypothyroidism and decreased libido. In the study of Carani et al,[13] 63.4% of the hypothyroid patients had HSDD, 7 of

whom also had concomitant ED. The UNIFI study also found that moderate or severe HSDD was significantly associated with higher TSH levels when compared to those with mild or no HSDD. However, this association was not observed in multivariate analysis after adjusting for testosterone level, chronic disease score, and general psychology score.[20] In a study involving 8 consecutive patients with hypothyroidism, 7 (88%) endorsed markedly decreased sexual drive of greater than 1-year duration.[39] Another study involving 8 men with primary hypothyroidism found that 3 (38%) had subjective loss of libido, 1 of which was associated with hyper-prolactinemia.[28]

FSD in Hypothyroidism

The association between hypothyroidism and FSD has been documented; however, fewer studies are available when compared to men. Particular focus has been placed on the link between hypothyroidism and changes in libido, arousal/vaginal lubrication, and orgasm (Table 3).

The first notable study was conducted in 24 pre-menopausal women with hypothyroidism who were administered the FSFI during routine outpatient follow-up at a single institution. Results from this study found statistically significant reductions in all domains of the FSFI in women with clinical hypothyroidism compared to healthy controls.[40] Another study involving 25 women with overt hypothyroidism, 25 women with sub-clinical hypothyroidism, and 20 healthy age-matched controls, demonstrated that the rates of FSD were significantly higher in those with any form of hypothyroidism as measured by the validated FSFI. 56% of the women with clinical hypothyroidism had FSD and 54.6% of women with sub-clinical hypothyroidism had FSD, compared to only 14.6% of women experiencing FSD in the control group.[41] In 1 study conducted by Oppo et al,[29] 17 patients with hypothyroidism with age-matched controls were assessed for sexual function parameters using the validated FSFI before and after treatment. In these patients, all FSFI domains (desire, arousal/lubrication, orgasm, satisfaction, and pain) were directly correlated with free T4 and inversely related to serum TSH ($P < .0001$).[29] A recent prospective study involving 104 women with thyroid disease found that women with clinical hypothyroidism experienced higher prevalence of FSD, with significant decreases in desire, arousal, and lubrication compared to controls. Additionally, FSD was significantly associated with any hypothyroid disease (idiopathic hypothyroidism, Hashimoto thyroiditis, nodular goiter) compared to controls: 46.1% vs 20.7%, respectively. On FSFI domain sub-group analysis, it was found that hypothyroidism was also significantly associated with decreased desire, arousal, and lubrication, but not overall FSFI score, orgasmic function, satisfaction, or sexual pain.[42]

In the study conducted by Krysiak et al[22] involving 50 women with hypothyroidism, it was noted that 23 (46%) had FSD. When stratified by etiology of hypothyroidism, the mean total FSFI score was found to be higher in women with auto-immune hypothyroidism than those with Hashimoto thyroiditis or non-immune sub-clinical hypothyroidism. Findings from this study suggest that FSD was lower in patients for whom hypothyroidism resulted from inflammatory infiltration of the thyroid gland rather than thyroid failure as a consequence of previous thyroidectomy, radioiodine treatment, external beam radiotherapy, iodine deficiency, or thyroid hypoplasia.[22]

A survey-based study conducted by Luo et al[23] involving 1,119 Chinese women (168 with sub-clinical hypothyroidism, 951 healthy controls) demonstrated results that conflict with the aforementioned studies. With respect to FSFI score, a total of 297 participants (26.5%) were at risk for FSD (FSFI score $\leq$23.45), including 36 (21.4%) in the sub-clinical hypothyroidism arm and 261 (27.4%) in the control group. There was no significant difference in the rates of FSD between the 2 groups. Furthermore, sub-group analysis revealed no significant difference between the 2 groups with respect to the incidence of low desire, low arousal, poor lubrication, decreased orgasms, low satisfaction, and sexual pain.[23]

Since the incidence of hypothyroidism also peaks at the age of menopause, perimenopausal symptoms may overlap with symptoms of hypothyroidism and independently contribute to FSD. As such, screening for hypothyroidism in women within this age range is generally recommended.[43] Given the somewhat mixed results from the aforementioned studies, future well-designed prospective controlled studies are warranted.

HYPERTHYROIDISM AND SEXUAL DYSFUNCTION

Prevalence

Prevalence estimates of sexual dysfunction in the setting of hyperthyroidism have been mixed, given the differences in collection methodologies (ie, cut-off values for TSH that constitute hyperthyroidism) and the dearth of robust studies.

In men, the prevalence of thyroid dysfunction in patients presenting for sexual dysfunction has been estimated to be between 3.4–57.1% based on 2 studies with different cut-off values for TSH. In the study conducted at the UNIFI, of the 3,203 men presenting for symptoms of sexual dysfunction, 108 (3.4%) had hyperthyroidism based on TSH levels <0.4 mU/L. On further testing, only 7 patients had overt hyperthyroidism and the remaining 101 patients had sub-clinical hyperthyroidism.[20] In a consecutive series of 755 men presenting with sexual dysfunction as determined by the validated Structured Interview on Erectile Dysfunction, it was found that 57.1% of men with pre-existing hyperthyroidism had PE. However, the TSH cut-off for this study was stricter than the UNIFI study (TSH <0.2 mU/L).[35] On the contrary, estimates of sexual dysfunction in patients presenting with hyperthyroidism were more consistent, and ranged from 48–77%. In a study conducted by Veronelli et al[15] involving 13 men with overt hyperthyroidism, 10 (77%) patients had some form of ED. The European Male Aging Study, which involved an un-selected cohort of 3,369 men in Florence, demonstrated that the 108 men with biochemical evidence of

hyperthyroidism (TSH < 0.35 mU/L) had higher rates of severe ED compared to euthyroid controls. In this study, 62% of men with overt hyperthyroidism and 25% of men with sub-clinical hyperthyroidism had severe ED, as evidenced by never having spontaneous organic erections.[20] In a study conducted by Cihan et al[44] involving 43 patients with un-treated hyperthyroidism, it was observed that 31 (72.1%) patients met diagnostic criteria for PE and 24 (55.8%) had ED based on IIEF-5 score. Carani et al[13] also included 34 patients with hyperthyroidism in their multi-center prospective study evaluating the prevalence of sexual symptoms in men with thyroid dysfunction. 22 (65%) of the 34 hyperthyroid men experienced some form of sexual dysfunction, and the prevalence of HSDD, DE, PE, and ED were 17.6%, 2.9%, 50%, and 14.7%, respectively.[13] Abalovich et al[45] studied 25 men experiencing active Graves' disease, and found the prevalence of impaired sexual function, gynecomastia, and low testicular volume to be 48%, 24%, and 12%, respectively. The study of Krassas et al[14] involving 27 hyperthyroid men found that 19 (70%) men had SHIM scores consistent with ED (SHIM score ≤21). A similar study performed by the same group prospectively analyzed the impact of hyperthyroidism on reproductive function in men. Of the 23 hyperthyroid men included in the study, 13 (57%) reported some form of sexual dysfunction. 9 (39%) Patients associated the onset of symptoms with the onset of their hyperthyroidism, and 6 (26%) patients endorsed ED.[46]

Hyperthyroidism as a driver of sexual dysfunction in women has also been documented in several studies; with prevalence estimates ranging from 44–60%. Atis and colleagues[47] administered the FSFI survey to 40 women with clinical hyperthyroidism and 40 age-matched controls. Using the proposed FSFI full-scale cut-off of 26.55, 24 (60%) of the women with hyperthyroidism had FSD, compared to only 13 (33%) of the healthy controls.[47] In a study conducted by Pasquali et al[42] including 18 hyperthyroid women, FSD was noted in 8 (44.1%) patients, compared to 11 out of the 53 (21%) healthy controls. Lastly, a study conducted by Oppo et al[29] included 22 hyperthyroid women, and found that all patients had significant impairment in all FSFI domains, with a mean total FSFI score significantly below the full-scale cut-off of 26.55 for FSD (mean of 24.1).[29]

Proposed Mechanisms

Similar to the mechanisms noted in patients with hypothyroidism, studies have demonstrated that hyperthyroidism can both directly and indirectly modulate sexual function. Although the exact mechanism is still a topic of debate, 3 pathways have been implicated: sympathetic, endocrine, and psychiatric (Figure 3).

There is considerable overlap between the manifestations of thyrotoxicosis and sympathetic nervous system activation (tachycardia, anxiety, emotional lability). Furthermore, it has been shown that thyroid hormones augment sensitivity to adrenergic agonists via up-regulation of β-adrenergic receptor density.[48] Although

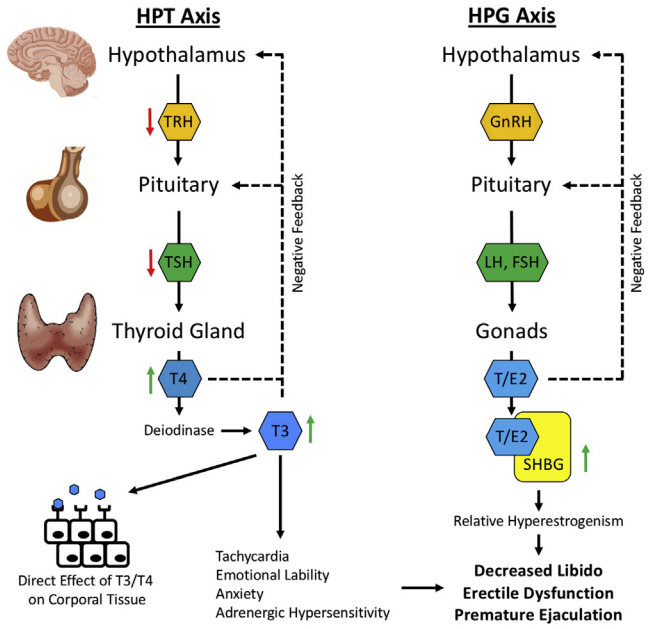

Figure 3. Schematic demonstrating the hormonal effects of hyperthyroidism on sexual dysfunction via inter-actions between the hypo-thalamic-pituitary-thyroid (HPT) and hypo-thalamic-pituitary-gonadal (HPG) axes. Sequela of hyperthyroidism include: (1) direct binding of tri-iodothyronine (T3)/thyroxine (T4) to cognate receptors within the corpora cavernosa endothelial and smooth muscle cells; (2) direct impairment of the nitric oxide pathway; (3) alterations in circulating estrogen levels; and (4) sympathetic nervous system activation (tachycardia, anxiety, emotional lability, increased sensitivity to adrenergic agonists). GnRH = gonadotropin-releasing hormone; SHBG = sex hormone–binding globulin; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone. Figure 3 is available in color online at www.smr.jsexmed.org.

circulating catecholamines are typically normal in hyperthyroid patients, the increased sensitivity to adrenergic agonists increases sympathetic tone and may serve as the nidus for ED and PE. There may also be a direct action of thyroid hormones on the control of erection and ejaculation, in addition to an effect mediated by hyperthyroidism-induced anxiety. Both α and β thyroid hormone receptors have been detected in human corpora cavernosa endothelial and smooth muscle cells.[49] Furthermore, animal studies of hyperthyroidism have demonstrated impairment in nitric oxide (NO)-dependent relaxation of the corpora cavernosa tissue.[50] In rabbit corpora cavernosa, both acetylcholine- and electrical stimulation–induced relaxations were impaired, whereas sensitivity to a sodium nitroprusside (NO donor) was unchanged.[51] These findings suggest an effect of thyroid hormones in penile NO formation that is a crucial mediator of the erectile mechanism in both animals and human beings. When taken together, ED in the setting of hyperthyroidism may be a consequence of direct binding of thyroid hormone to its associated receptors in the genitourinary tract. An experimental model of induced hyperthyroidism in male rats also demonstrated enhanced seminal vesicle contraction and activity of bulbo-spongiosus muscle compared to controls.[52] These findings support the observation that elevated

circulating thyroid hormone decreases ejaculation latency and erectile function, and notions that this phenomenon may be independent from hyperthyroidism-induced anxiety. It has also been hypothesized that thyroxin specifically alters the activity of serotoninergic pathways by binding receptors within the brain leading to a diminished control of ejaculation.[53] In animals with experimentally induced hypothyroid states, increased serotonin turnover in the brain stem has been observed.[54] Furthermore, DE is a common and therapeutically useful side effect of serotoninergic drugs, indicating that this pathway is involved in the ejaculatory control mechanism.[55]

Another potential mechanism by which excess thyroid hormone may affect sexual function could be through alterations in circulating estrogen levels. Hyperthyroidism has been shown to increase SHBG, which binds androgens with higher affinity than estrogens, leading to a relative hyper-estrogenism. Additionally, although circulating free testosterone levels are often normal in hyperthyroid patients, the elevation in SHBG causes bioavailable testosterone to be decreased.[45] Androgens play an important role in male and female sexual function including libido and sexual desire.[56] This phenomenon may be attributed to the presence of androgen receptors in human vulvar epithelium, vaginal mucosa, sub-mucosa, and smooth muscle.[57] Additionally, it has been hypothesized that NO synthase activity in the clitoris may also be under testosterone regulation.[56] A study conducted in hypogonadal rabbits revealed that estrogens modulate oxytocin-induced epididymis contractility, which plays a central and peripheral role in the ejaculatory mechanism.[58]

Hyperthyroidism-associated psychiatric disturbances such as irritability and depression contribute to sexual dysfunction as well. The prevalence of depression and anxiety in patients with hyperthyroidism has been estimated to be 31−69% and 33−61%, respectively.[59] Depression and anxiety have been shown to both independently increase sexual dysfunction.[60,61]

Male Sexual Dysfunction in Hyperthyroidism

The most common sexual sequela of hyperthyroidism is ED and ejaculatory dysfunction (Table 4). The European Male Aging Study was a prospective, non-interventional cohort study that included 3,369 healthy men aged 40−79 years, 38 (1.1%) of whom had biochemical evidence of hypothyroidism (TSH >5.5 mU/L). This study found that logarithmically transformed TSH levels were inversely proportional to ED prevalence and subjects reporting to never have erections showed concomitant higher free T4 levels. These associations were confirmed in multi-variate analysis after adjusting for confounding variables such as body mass index, Beck Depression Inventory score, Short Form 36 health survey score (physical component), use of antidepressants, smoking habit, and testosterone level.[20] In the UNIFI study, which included 108 men with biochemical evidence of hyperthyroidism, there was a statistically significant association between severe ED and overt hyperthyroidism. This finding remained significant even after adjusting for age, smoking habit, testosterone, PRL levels, and presence of PE.[20] Furthermore, the study of Krassas et al[14] demonstrated a statistically significant greater proportion of hyperthyroid patients with ED compared to controls (70% vs 34%). Interestingly, however, SHIM scores did not correlate with either free T4 or TSH levels in these patients. The study of Veronelli et al[15] also demonstrated a statistically significant association between hyperthyroidism and all forms of ED as determined by IIEF-5 questionnaire.

Several reports have drawn a link between hyperthyroidism and ejaculatory dysfunction. In the study conducted by Corona et al[35] that included 755 men, logarithmically transformed TSH was significantly lower in patients with PE compared to patients without PE, even after adjustment for age. The prevalence of PE was also significantly higher in patients with abnormally low TSH (<0.2 mU/L) compared to the rest of the sample (57.1% vs 26.5%). Interestingly, patients with ED and TSH <0.2 mU/L had significantly higher rates of PE compared to patients with ED and normal TSH, suggesting that hyperthyroidism is associated with PE independent of whether the patient has concomitant ED.[35] The study of Cihan et al[44] involving 43 men with untreated hyperthyroidism also confirms the association between hyperthyroid state and PE. In this study there was a statistically significant direct correlation between serum TSH and intravaginal ejaculation latency time (IELT) in patients with PE. Additionally, half of the hyperthyroid patients included in the Carani et al[13] study had PE. It is important to note that in a study of 620 men with lifelong PE, there was no association between PE and hyperthyroidism. Results from this study suggest that hyperthyroidism may only increase the risk of developing the acquired type of PE.[62]

There have been reports of decreases in libido associated with hyperthyroidism, however no studies have established a significant association between the 2. Carani et al[13] noted that 17.6% of hyperthyroid men had HSDD, which is higher than what has been reported in the general population (15%), however, the lack of control group in this study prohibits an association from being drawn.[63] Additionally, the UNIFI study demonstrated no significant difference in the rates of hypo-active sexual desire in hyperthyroid patients compared to healthy controls.[20]

FSD in Hyperthyroidism

The best data regarding FSD in the setting of hyperthyroidism are derived from 3 studies (Table 4). The first study to investigate this relationship was conducted by Oppo et al.[29] As mentioned in earlier sections, all 22 hyperthyroid patients had significant impairments in all FSFI domains, with a mean total FSFI score significantly below the full-scale cut-off for FSD. However, contrary to the findings observed in the hypothyroid patients in this study, in hyperthyroid patients, the correlations between FSFI domains and TSH were less evident and reached the level of statistical significance only for desire, arousal/lubrication, and orgasm, while free T4 displayed a significant inverse correlation

only with the desire domain. Thus, when compared to hypothyroidism, hyperthyroid-induced FSD may be less directly related to the concentration of circulating thyroid hormones.[29] The next reported study conducted by Atis et al[47] found that women with clinical hyperthyroidism had significantly lower FSFI scores in all domains (desire, arousal, lubrication, orgasm, satisfaction, pain) compared with age-matched controls. On the contrary, the last and most recent study conducted by Pasquali et al[42] involving 18 patients found that hyperthyroidism was significantly associated with a decreased desire domain on FSFI only. Although results from the aforementioned studies demonstrate differences in the extent to which hyperthyroidism causes FSD, the preponderance of evidence supports that it negatively impacts female sexual function.

MANAGEMENT CONSIDERATIONS

The burden of sexual dysfunction in patients with thyroid dysfunction is significant; however, several of the above-mentioned studies revealed that treating a patient's thyroid disease had the potential to ameliorate their sexual dysfunction as well.

Hypothyroidism

Krassas et al[14] treated 44 men with biochemical evidence of hypothyroidism with L-T4 and administrated the validated SHIM questionnaire before treatment and 1 year after initiation of treatment when all patients were euthyroid. 37 of the 44 Men (84.1%) had SHIM scores of 21 or less (indicating some degree of ED) prior to treatment; only 13 (29.5%) men had SHIM scores of 21 or less after treatment. This study found that treated patients had statistically significant increases in SHIM score compared to before treatment (mean SHIM of 17.0 pre-treatment vs 24.0 post-treatment, P value $< .0001$). There was also no difference in SHIM scores between treated patients and healthy controls at 1-year follow-up.[14] In a similar study conducted by Carani et al,[13] 14 men with hypothyroidism were treated with L-T4 to achieve a euthyroid state. Correction of hypothyroidism led to a resolution of DE in half of the subjects, and this was associated with significant decreases in IELT. Notably, hypothyroid patients receiving treatment had decreases in IELT regardless of whether or not they had DE at baseline. ED burden was also reduced from 64.3% (9/14) to 21.4% (3/14) when returned to a euthyroid state. There were significant increases in patient's IIEF scores following treatment; however, the only individual domain that reached significance was intercourse satisfaction. Furthermore, patients with HSDD found a significant improvement of symptoms following initiation of treatment.[13]

Correction of hypothyroidism in women also yielded positive effects on sexual function, as evidenced by the study conducted by Oppo et al.[29] Oppo et al[29] demonstrated complete normalization of desire, satisfaction, and pain domains of the FSFI in treated hypothyroid patients, while arousal and orgasm domains were largely unchanged.[29]

Hyperthyroidism

Krassas et al[14] also demonstrated significant improvement in sexual function in 27 hyperthyroid patients treated with anti-thyroid medication (ie, methimazole). 19 of the 27 (70.4%) patients had SHIM scores consistent with ED (less than or equal to 21) prior to treatment compared to only 7 (25.9%) after correction to euthyroid state. There was also a significant increase in SHIM scores in treated hyperthyroid patients compared to pre-treatment baseline (mean SHIM of 14.5 pre-treatment vs 23.0 post-treatment, P value $< .0001$).[14] In another study involving 34 hyperthyroid patients, correction to euthyroid state yielded significant improvements in IIEF score, particularly in the erectile function and intercourse satisfaction domains. Furthermore, treatment reduced the prevalence of PE from 50% to that of the general population (15%). This study also observed resolution of both DE and HSDD in most patients.[13] The study of Corona et al[20] also demonstrated that normalization of thyroid hormone levels significantly decreased the prevalence of severe ED from 28.6−0% of patients. In the study of Cihan et al,[44] 24 hyperthyroid patients were treated with either radio-active iodine ($n = 7$), total thyroidectomy ($n = 7$), or anti-thyroid medication only ($n = 10$). The rate of definitive PE in this group (based on IELT measurements) decreased from 66% (16 of 24 patients) before treatment to 25% (6 of 24 patients) after treatment. Additionally, correction from hyperthyroid to euthyroid state significantly prolonged IELT from 75.8 ± 99.3 seconds to 123 ± 96.4 seconds, as well as produced significant improvements in all IIEF domains except for intercourse satisfaction.[44]

Similar to the results of hypothyroidism, correction of hyperthyroidism in women improved sexual function parameters. Restoration of euthyroidism in a study involving 22 hyperthyroid women yielded significant improvements in all FSFI domains (desire, arousal, lubrication, satisfaction, and pain); however, there was no significant change in the orgasm domain. It is noted that, although there was significant improvement in the pain domain, the pain scores were still higher than healthy euthyroid controls.[29]

CONCLUSION

Male and female sexual function require normal libido, an intact hypo-thalamic-pituitary-gonadal axis, neurovascular integrity to the genitalia, as well as physiologic levels of sex hormones. However, recent evidence presented in this review and others suggests that thyroid axis dysregulation also plays a major role in sexual dysfunction that cannot be overlooked.[64] Unfortunately, well-designed studies that describe the prevalence, pathophysiology, and outcomes of patients with sexual dysfunction in the setting of thyroid disease are severely lacking. This may be attributed to the fact that sexual symptoms are often not a priority when dealing with the systemic effects of thyroid hormone deficiency or excess. Additionally, patients may be reticent to discuss sexual dysfunction during visits to their primary physician or endocrine specialist due to embarrassment or

shame. Despite the limitations on available studies, several reports in select patient populations have allowed researchers to estimate the prevalence and suggest potential mechanisms for how thyroid disease causes sexual dysfunction.

Recent studies have demonstrated that the prevalence of sexual dysfunction in patients with hypothyroidism is as high as 59–63% and 22–46% in men and women, respectively. The rates of sexual dysfunction in patients with hyperthyroidism are similarly striking: 48–77% and 44–60% in men and women, respectively. Interestingly, many of the men and women included in the aforementioned studies were below the age of 40 years, suggesting that thyroid disease may be a particularly relevant etiology of sexual health problems in young adults.[13,22] A previous review has also drawn attention to thyroid disease as an important potential cause of ED in young men.[65] The mechanism by which thyroid disease drives sexual dysfunction remains unknown, however, studies have demonstrated that hypothyroidism and hyperthyroidism exert effects on circulating sex hormone levels through peripheral and central pathways as well as indirectly provoke psychiatric and autonomic dysregulation that can impair sexual function. Hypothyroid patients have been found to have decreased concentrations of total and free serum testosterone, SHBG, DHEA, and metabolites of DHEA, as well as increased concentrations of PRL, which promotes a hypo-gonadotropic hypo-gonadal state. Hypothyroidism is also classically associated with symptoms of fatigue, weight gain, and depressed mood, which contribute to diminished interest in sexual activity in both men and women. In contrast, hyperthyroidism enhances sensitivity to circulating catecholamines, alters serotonin turnover, exerts direct effects on thyroid hormone receptors found in human cavernosal tissue, and impairs NO-dependent corporal vasodilation. Hyperthyroidism also increases SHBG, leading to a relative hyperestrogenism and reduces bioavailable testosterone.

Both hypothyroidism and hyperthyroidism were strongly associated with ED and ejaculatory dysfunction. Hypothyroidism was associated with DE whereas hyperthyroidism was associated with PE. Both forms of thyroid disease impaired libido in men and women. Hypothyroid and hyperthyroid women demonstrated impairments in desire, arousal/lubrication, orgasm, satisfaction, and pain during intercourse. Interestingly, correction of the thyroid deficiency or excess was associated with dramatic resolution of sexual dysfunction in men and women patients with hypothyroidism or hyperthyroidism. By improving awareness of the link between thyroid disease and sexual dysfunction, sexual medicine physicians may sooner identify patients whose sexual symptoms can be remedied by treating an underlying thyroid disorder.

ACKNOWLEDGMENTS

Special thanks to Jessica Daigle for her assistance in the preparation and submission of this article.

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Conflict of Interest: The authors report no conflicts of interest.

Funding: None.

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