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Multicenter Study on the Prevalence of Sexual Symptoms in Male Hypo- and Hyperthyroid Patients

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Context: Thyroid hormones have a dramatic effect on human behavior. However, their role on sexual behavior and performance has seldom been investigated in men.

Objective: The objective of this study was to evaluate the prevalence of sexual dysfunctions in patients with hyper- and hypothyroidism and their resolution after normalization of thyroid hormone levels.

Design and Setting: We conducted a multicenter prospective study at endocrinology and andrology clinics in university hospitals.

Patients: The study included 48 adult men, 34 with hyperthyroidism and 14 with hypothyroidism.

Main Outcome Measures: Subjects were screened for hypoactive sexual desire (HSD), erectile dysfunction (ED), premature ejaculation (PE), and delayed ejaculation (DE) on presentation and 8–16 wk after recovery from the thyroid hormone disorder.

Results: In hyperthyroid men, HSD, DE, PE, and ED prevalence was 17.6, 2.9, 50, and 14.7%, whereas in hypothyroid men, the prevalence of HSD, DE, and ED was 64.3% and of PE was 7.1%. After thyroid hormone normalization in hyperthyroid subjects, PE prevalence fell from 50 to 15%, whereas DE was improved in half of the treated hypothyroid men. Significant changes were found in the subdomains of the International Index of Erectile Function; ejaculation latency time doubled after treatment of hyperthyroidism (from 2.4 $\pm$ 2.1 to 4.0 $\pm$ 2.0 min), whereas for hypothyroid men it declined significantly, from 21.8 $\pm$ 10.9 to 7.4 $\pm$ 7.2 ($P < 0.01$ for both). TSH and thyroid hormone levels normalized rapidly after treatment, and changes in circulating sex steroids partially reflected the changes in SHBG levels.

Conclusions: In summary, most patients with thyroid hormone disorders experience some sexual dysfunctions, which can be reversed by normalizing thyroid hormone levels. Despite the associated changes in sex hormone levels, the high prevalence of ejaculatory disorders and their prompt reversibility suggest a direct involvement of thyroid hormones in the physiology of ejaculation. **(*J Clin Endocrinol Metab* 90: 6472–6479, 2005)**

HORMONES REGULATE SEVERAL aspects of mammalian sexual behavior. Steroid hormones play a pivotal role in sexual imprinting during fetal development, whereas in adults they directly or indirectly control libido, male erection, and female lubrication. Oxytocin and vasopressin are involved in the regulation of affective behavior, central control of excitation, and ejaculation. Prolactin (PRL) and endogenous opioids inhibit central arousal and mating. Dopaminergic derangement and hyperproduction of GH seriously impair sexuality. Sexual dysfunctions are also common in various adrenal disorders.

Data correlating sexual performance with thyroid hormones are sparse and anecdotal (1). Iodothyronines have dramatic effects on human behavior ranging from severe depression to psychosis. It therefore seems likely that an excess or deficiency of circulating thyroid hormones may affect sexual behavior and performance. However, this aspect has seldom been investigated in men, probably because thyroid hormone disorders are less frequent than in women and physicians often fail to evaluate sexual function (2).

We recently showed that premature ejaculation (PE), a frequent sexual symptom commonly considered psychogenic in nature, had a significant correlation with suppressed TSH values in a selected population of andrological and sexological patients (3). The aim of the current paper is to evaluate prospectively the prevalence of sexual dysfunctions in male patients with hyper- and hypothyroidism before and after recovery from their conditions.

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Abbreviations: DE, Delayed ejaculation; E_2, estradiol; ED, erectile dysfunction; ErF, erectile function; fT, free testosterone; fT_4, free T_4; HSD, hypoactive sexual desire; 5-HT, serotonin; IELT, intravaginal ejaculation latency time; IIEF, International Index of Erectile Function; IntS, intercourse satisfaction; OrF, orgasmic function; OvS, overall satisfaction; PE, premature ejaculation; PRL, prolactin; SxD, sexual desire; tT, total testosterone.

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Subjects and Methods

The study was designed as a multicenter, prospective study of sexual symptoms and dysfunctions, specifically hypoactive sexual desire (HSD), erectile dysfunction (ED), PE, and delayed ejaculation (DE), in adult males during and after recovery from hyper- and hypothyroidism. Subjects included in the study were consecutive, nonselected endocrinology outpatients with clinically symptomatic or mildly symptomatic hyper- and hypothyroidism who met all the following criteria: 1) age between 18 and 70 yr, 2) not investigated or treated for sexual dysfunction before the onset of thyroid symptoms, 3) stable relationship (>1 yr) during the study period, and 4) complete follow-up (defined as at least one visit 2 months after achievement of euthyroidism). The enrollment period lasted 2 yr (2003 and 2004), and the characteristics of the

screened/enrolled subjects reflected the actual distribution of the untreated male population presenting to the recruiting hospitals with altered thyroid hormone levels. All participants gave signed informed consent, and the study was approved by the Local Ethics Committee.

Thyroid function and male reproductive hormone axis were investigated using immunoassay commercial kits. The normal reference ranges for thyroid hormones were as follows: TSH, 0.3–5.0 μIU/ml; T_4, 4.5–12.5 μg/dl; free T_4 (fT_4), 0.7–1.7 ng/dl; T_3, 0.8–2.2 ng/ml; fT_3, 1.7–4.8 pg/ml. When appropriate, serum levels of anti-thyroperoxidase, anti-thyroglobulin, and anti-TSH receptor antibodies were titrated and thyroid ultrasound and/or ^{131}I scintigraphy performed. The normal reference ranges for reproductive hormones were as follows: LH, 1.5–10.0 IU/liter; PRL, 2–15 ng/ml (2–15 μg/liter); total testosterone (tT), 2.5–10 ng/ml (8.6–34.6 nmol/liter); free testosterone (fT), 12–40 pg/ml (40–140 pmol/liter); estradiol (E_2), <60 pg/ml (<220 pmol/liter); SHBG, 10–55 nmol/liter.

Sexual performance was assessed by a clinical questionnaire used in our departments since the late 1980s exploring libido, erection, and ejaculation (4), and the International Index of Erectile Function (IIEF) (5). Patients with sexual symptom(s) caused by other conditions known to cause HSD (hypogonadism and hyperprolactinemia), ED (hypogonadism, hyperprolactinemia, and vasculogenic and neurogenic diseases such as diabetes mellitus), PE (prostatitis), or DE (multiple sclerosis) were excluded. From a total of 59 screened subjects, only 48, 34 with hyperthyroidism and 14 with hypothyroidism, were recruited and completed the study. Four subjects were excluded because of concomitant atrial fibrillation (2), congestive heart failure (1), or refusal to sign the informed consent (1). The remaining subjects were excluded because of other concomitant diseases, such as diabetes mellitus (5) and prostatitis (2), known to potentially affect sexual function.

HSD was defined as "persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity" (6). ED was defined as "the chronic impossibility to have or maintain a full erection in the presence of proper erotic stimuli" (7). PE was defined as "an ejaculation occurring with minimal sexual stimulation before, upon, or shortly after penetration and before the person wishes" (6). DE was defined as "slowness to ejaculate" (8). The latter two symptoms were measured as intravaginal ejaculation latency time (IELT), which is the time from the start of vaginal intromission to the start of intravaginal ejaculation (9) measured by a stopwatch (10).

Etiological diagnosis of ED (11) was performed on the basis of laboratory (glycemic, hepatic, lipid, and renal profiles), neurological (bulbocavernous reflex latency time), and vascular (penile-brachial pressure index before and after exercise; color-Doppler ultrasound of the penis before and after prostaglandin E_1 injection) parameters. Organic causes of PE and DE were evaluated by anamnesis, physical examination for neurological diseases, and the Meares and Stamey test, with transrectal ultrasound to exclude prostate inflammation/infection (12). Risk factors (smoke, alcohol, and recreational drugs), iatrogenic causes (medications known to affect desire, erection, or ejaculation), psychorelational events, and any other information possibly correlated with sexual symptoms were recorded. Six patients were taking antihypertensive medications (angiotensin-converting enzyme inhibitors).

All hyperthyroid patients were treated with variable doses of metimazole as needed to achieve rapid normalization of TSH. At the beginning of treatment, in 11 cases it was necessary to add a β-blocker, propranolol, and in four benzodiazepines (for <2 wk). At follow-up, none of the enrolled subjects was on propranolol or benzodiazepines. Hypothyroid subjects received L-thyroxine at various doses, titrated fortnightly to reach a normal TSH values.

Before any therapy, patients were given the Padma-Nathan Sexual Encounter Profile diary, consisting of a series of yes/no questions regarding specific aspects of each sexual encounter (13). Sexual evaluation was carried out at a minimum of 8 wk after complete recovery from thyroid hormone excess or deficiency (median, 10 wk; range, 8–16 wk). At this time, patients underwent a new full sexological interview, IIEF scores were obtained, Sexual Encounter Profile diary cards were reviewed and compared with partner logs obtained in a separate room, and new blood samples were obtained for hormone measurement. All patients with hyperthyroidism were still under metimazole (median dose, 5 mg daily; range, 2.5–15), and all hypothyroid subjects received L-thyroxine (median, 100 μg; range, 50–150).

During the study period, none received other medications for HSD, ED, EP, or DE. However, after the follow-up visit in euthyroidism, specific treatments were prescribed in patients still complaining of sexual dysfunction.

Statistical analysis

Each patient acted as his own control. Results are expressed as mean ± SD. Mean differences in hormone levels were analyzed with the paired and unpaired nonparametric tests as appropriate. The IIEF domain scores were used to compare the effect of treatment on different aspects of sexual function. The domains were calculated using IIEF items 1, 2, 3, 4, 5, and 15 for erectile function (ErF); 9 and 10 for orgasmic function (OrF); 11 and 12 for sexual desire (SxD); 6, 7, and 8 for intercourse satisfaction (IntS); and 13 and 14 for overall satisfaction (OvS). The influences of baseline and posttreatment hormone values on several indices of sexual function and response to treatment were analyzed using bivariate Spearman's correlation and multiple regression analysis. All tests were two-sided, with statistical significance set at 0.05.

Results

Patient characteristics

The mean age of the enrolled subjects was 43.2 ± 12.1 yr (range, 22–62 yr). No significant difference was found in the age at presentation between hyperthyroid (n = 34) and hypothyroid (n = 14) patients. The cause of thyroid hormone excess was Flajani-Basedow-Graves disease in 19 men (55.9%), Plummer disease in six (17.6%), and a toxic multinodular goiter in nine (26.5%). All patients with hypothyroidism were diagnosed having chronic lymphocytic thyroiditis on the basis of positive serum antithyroid autoantibodies. The hormonal characteristics of all patients before and after treatment of their primary conditions are reported in Table 1. In these patients, the pituitary-testicular axis and androgen metabolism were related to the thyroid status. Total T, E_2, and SHBG were higher in untreated hyperthyroid patients than in euthyroidism; the opposite occurred in hypothyroid patients. Hypothyroid patients also showed higher serum PRL levels that, although still within the reference range, correlated with TSH values and dropped significantly during levothyroxine treatment ($P < 0.05$).

Prevalence of sexual disorders

Among 48 men with thyroid hypo- or hyperactivity, only six (12.5%) spontaneously complained about a deterioration in their sexual function and connected its incidence to the concomitant thyroid disease. On direct questioning by a physician and with the use of the IIEF questionnaire, the prevalence of HSD, DE, PE, and ED in the 34 men affected by hyperthyroidism was estimated at 17.6, 2.9, 50, and 14.7%, respectively. In four patients, PE was associated with ED, and in two patients, ED was associated with HSD. In men affected by hypothyroidism, the prevalence of HSD, DE, and ED was 64.3%, whereas the prevalence of PE was 7.1%. In seven of 14 hypothyroid men, HSD was associated with DE, and in six, DE was associated with ED. Only three of 48 patients did not complain of any sexual symptoms.

Evaluation at follow-up

The changes in the prevalence of sexual dysfunctions before and after treatment for thyroid disease are shown in Fig. 1.

In patients with hyperthyroidism (Fig. 1A), the most striking effect of treatment was a drop in the prevalence of PE

TABLE 1. Hormonal characteristics of all subjects before and after achievement of euthyroidism

	Pretreatment		Posttreatment	
	Mean ± SD	Min–Max	Mean ± SD	Min–Max
Hyperthyroidism (n = 34)				
TSH (μU/ml)	Suppressed-0.1		1.6 ± 0.7[b]	0.6–3.3
T_3 (ng/ml)	3.1 ± 0.6	2.1–4.8	1.4 ± 0.4[b]	0.9–2.0
fT_3 (pg/ml)	5.9 ± 1.4	3.9–8.9	3.0 ± 0.6[b]	2.0–4.0
T_4 (μg/dl)	15.6 ± 3.4	8.0–24.0	6.3 ± 1.6[b]	4.5–9.5
fT_4 (ng/dl)	2.9 ± 0.4	1.9–3.1	1.3 ± 0.3[b]	0.7–1.7
tT (ng/ml)	8.0 ± 2.1	4.7–12.0	5.9 ± 1.4[a]	4.0–7.1
fT (pg/ml)	21.3 ± 8.5	12.1–38.0	28.9 ± 4.7[a]	21.0–37.0
SHBG (nmol/liter)	54.5 ± 13.7	34.0–77.0	36.8 ± 11.0[a]	17.0–56.0
LH (IU/liter)	4.1 ± 2.3	1.5–8.4	3.9 ± 1.7	1.9–7.5
PRL (ng/ml)	4.5 ± 2.1	2.0–12.0	4.8 ± 2.2	2.3–12.6
E_2 (pg/ml)	49.9 ± 14.0	27.0–59.0	33.5 ± 11.0[a]	23.0–50.0
Hypothyroidism (n = 14)				
TSH (μU/ml)	18.6 ± 16.0	4.5–49.0	2.4 ± 1.0[b]	1.0–4.0
T_3 (ng/ml)	0.6 ± 0.2	0.3–0.8	1.4 ± 0.4[b]	0.9–2.0
fT_3 (pg/ml)	1.4 ± 0.4	0.6–2.0	3.1 ± 0.7[b]	2.0–4.0
T_4 (μg/dl)	3.1 ± 1.0	1.1–4.5	5.9 ± 1.1[b]	4.0–8.5
fT_4 (ng/dl)	0.5 ± 0.1	0.2–0.7	1.2 ± 0.3[b]	0.9–1.7
tT (ng/ml)	3.2 ± 0.8	2.5–4.5	4.7 ± 1.1[a]	3.6–6.7
fT (pg/ml)	34.2 ± 5.0	28.0–40.0	25.7 ± 4.5[a]	19.0–31.0
SHBG (nmol/liter)	24.3 ± 6.4	15.0–33.0	28.0 ± 6.1	19.0–36.0
LH (IU/liter)	7.0 ± 3.7	2.1–9.6	3.6 ± 0.6[a]	2.8–4.2
PRL (ng/ml)	10.5 ± 3.5	6.0–14.9	6.1 ± 2.8[b]	2.1–11.3
E_2 (pg/ml)	31.3 ± 11.5	16.0–44.0	35.8 ± 11.3	21.0–49.0

Min, Minimum; Max, maximum.
[a] $P < 0.05$; [b] $P < 0.001$, pretreatment *vs.* posttreatment.

from 50 to 15%, a figure similar to that found in the general population (14%) (see Ref. 14). Moreover, HSD and DE resolved in most of these patients. The effects of treatment were also reflected by changes in the IIEF domain scores; a significant improvement was found in the ErF and IntS domains (Fig. 2A, *left*). In treated hyperthyroid patients, self-reported IELT doubled from 2.4 ± 2.1 to 4.0 ± 2.0 min (Fig. 2B, *left*).

In patients with hypothyroidism (Fig. 1B), among which PE was nearly absent, a resolution of DE was obtained in half of the subjects after thyroid hormone normalization. ED almost disappeared, and patients with HSD found a significant improvement of symptoms while on treatment. These effects were also reflected by changes in the IIEF domains' score (Fig. 2B). Although a tendency toward improvement was found in every domain, a significant change was found only in the IntS domain ($P < 0.05$). The variation of total IIEF score was also statistically significant. In men with hypothyroidism, IELT decreased significantly from 21.8 ± 10.9 to 7.4 ± 7.2 min ($P < 0.01$). Interestingly, such reduction was found either in hypothyroid patients that were complaining of DE at baseline or in those who were not. However, when comparing hypothyroid patient with and without DE, a borderline difference in ejaculation latency was still found (when both in euthyroidism, $P = 0.048$). This finding suggests that either a carried over effect was present or other underlying factors (*i.e.* psychological) were involved.

Comparing the response to treatment in hyperthyroid and hypothyroid patients, it was noted that the overall change in total IIEF score was higher in the hypothyroid patients than in hyperthyroid patients, whereas the variation of IELTs were more consistent in thyrotoxic men. This suggests that in hyperthyroid patients the major dysfunction lies in control of ejaculation timing, whereas in hypothyroid patients a wider involvement of sexual function may occur.

Hormonal influences on sexual function and response to treatment

Table 2 shows the correlation matrix between hormones at baseline and several indices of sexual function before and after resolution of the underlying thyroid disorder. TSH, thyroid hormones, and SHBG were significantly correlated with IELT and its variation during treatment. Thyroid hormone excess and defect were inversely associated with both disorders of ejaculation, PE and DE. PRL was positively associated with the presence of HSD and negatively with the IIEF SxD score. PRL was also correlated with PE and DE; however, this correlation was lost when adjusted for TSH levels. Neither the presence of ED nor the IIEF ErF domain correlated with baseline hormone values, with the exception of a weak association with reduced fT_4 levels. tT was negatively correlated with indices of SxD and positively with PE. These correlations were lost when tT was adjusted for SHBG levels, suggesting that it was a spurious result caused by SHBG elevation. Analysis on the influence of posttreatment hormone values on various parameters of sexual function at follow-up revealed only three significant association: 1) a positive correlation of posttreatment TSH values with the IIEF domain of SxD, 2) a negative correlation between posttreatment PRL values and change in IELT, and 3) a positive association between posttreatment E_2 and the OrF domain of the IIEF.

To explore whether baseline or posttreatment hormone values had a predictive effect on restoration of sexual performance and satisfaction, three multiple-regression models

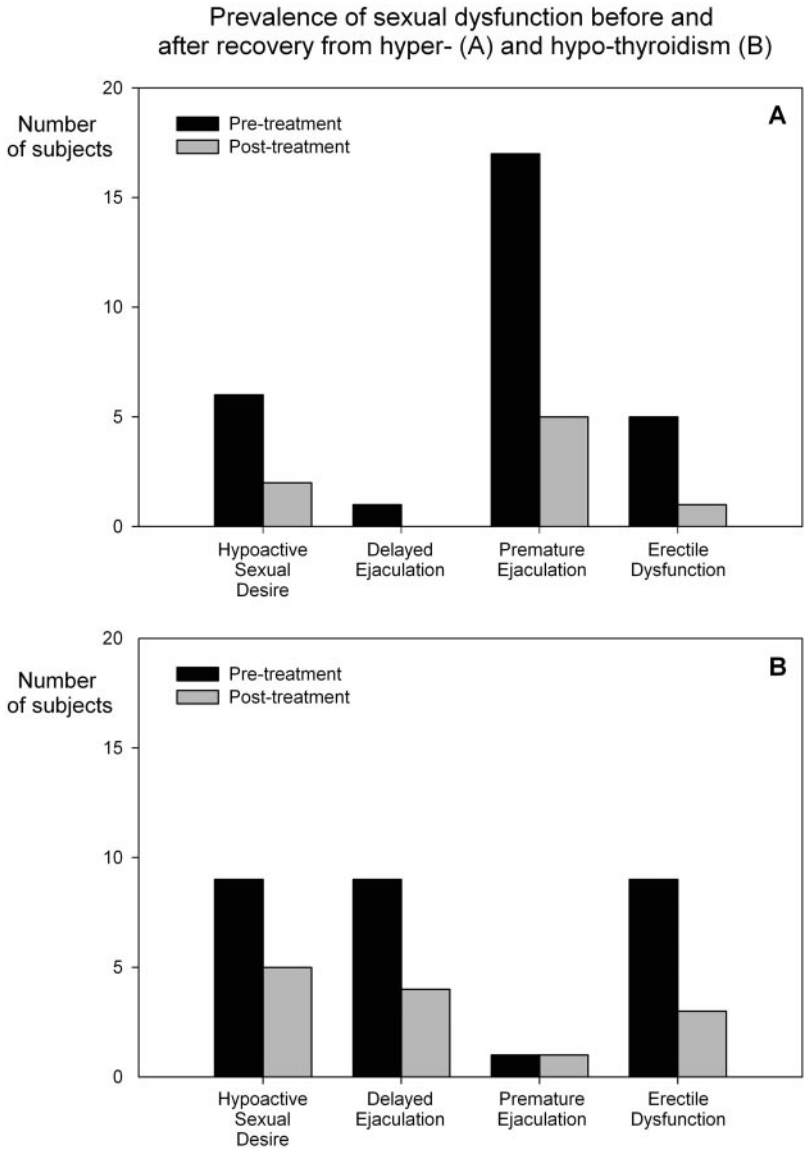

FIG. 1. Prevalence of sexual dysfunction before and after recovery from hyperthyroidism (A) and hypothyroidism (B).

were developed. Among all subjects, the best predictors of the overall improvement in IIEF were pretreatment high TSH values, posttreatment low PRL and E_2 levels, and high posttreatment fT_4. Therefore, hypothyroid patients had a greater improvement in the total IIEF score, especially when PRL levels declined with adequate T_4 replacement, compared with hyperthyroid patients that showed greater results in the IELT and control of PE.

Multivariate analysis was then performed separately in patients with thyroid hormone excess and defect. In both groups, the best predictors of posttreatment IELT were the baseline T_4 values, negatively correlated in hypothyroid patients and positively in hyperthyroid patients. This finding indicates that, despite adequate laboratory resolution of thyroid hormone imbalance, some effects lasted over time. When analyzed separately, none of the investigated variables was able to explain the variation on total IIEF score. Age, smoking, and concomitant medications had no significant effect on the response to treatment.

Discussion

Although it is well known that most endocrine diseases affect male sexuality (15) and in some cases reproduction, the relationship between thyroid hormone and sexuality has never been formally studied. We demonstrated for the first time that specific sexual disorders occur frequently in males with thyroid hypo- and hyperfunction and that most of these symptoms revert promptly as euthyroidism is restored.

The impact of thyroid hyper- and hypofunction in male sexual function is not well established. This is likely the consequence of 1) the apparent scarce clinical relevance given to male sexual symptoms compared with the systemic effects of thyroid hormones excess and defect, 2) the paucity of clinical studies because thyroid disease is less common in men, and 3) the embarrassment of patients and physicians when discussing sexual dysfunction in the traditional setting of an endocrine outpatient clinic.

Thyroid hormone disorders are known to alter the repro-

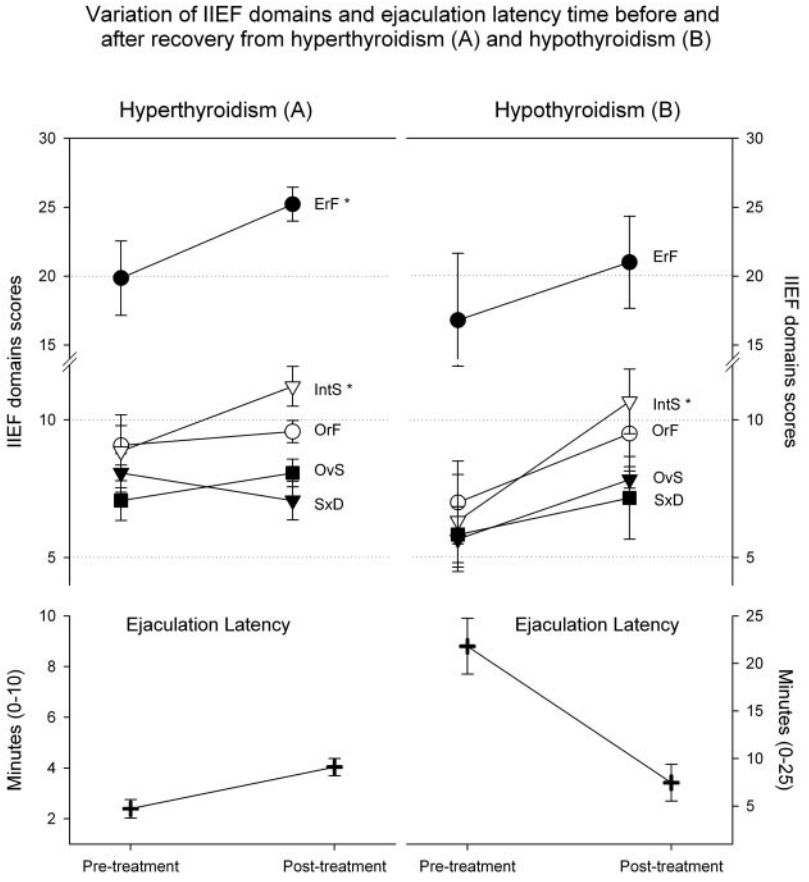

FIG. 2. Variation of IIEF domains and ejaculation latency time before and after recovery from hyperthyroidism (A) and hypothyroidism (B).

ductive axis in men (16, 17). In adult-onset hyperthyroidism, gonadotropins are often within the normal range (18), whereas SHBG is invariably elevated (19–21). In male hyperthyroidism, the increase in SHBG (22) leads to a rise in circulating tT levels (23). However, the fT is generally not affected (24). In our subjects, all reproductive hormones were within or very close to the reference range, despite that consistent fluctuations were observed with the normalization of thyroid hormones. These changes may have affected the free/bound fractions and the androgen/estrogen ratios.

TABLE 2. Spearman's correlations among serum hormones and sexual dysfunction

	TSH	T_3	fT_3	T_4	fT_4	PRL	tT	fT	E_2	SHBG
Baseline evaluation										
PE	-0.45^a	0.33^a	0.45^b	0.41^b		-0.37^a	0.77^b	-0.38^a		0.54^a
DE	0.69^b	-0.54^b	-0.50^b	-0.60^b	-0.51^b	0.48^b	-0.50^a	0.41^a		-0.47^a
ED					-0.36^a					
HSD	0.63^b		-0.38^b	-0.43^b	-0.32^a	0.31^a	-0.52^a			-0.60^b
IELT	0.74^b	-0.57^b	-0.66^b	-0.67^b	-0.52^b	0.61^b	-0.69^b		-0.46^a	-0.72^b
IIEF domains										
ErF										
IntS										
OrF	-0.77^b				0.45^b	-0.50^a				0.36^a
SxD	-0.56^a			0.53^b	0.48^a				0.50^a	0.63^b
OvS									0.48^a	
Response to treatment										
IELT	-0.68^b	0.49^b	0.61^b	0.59^b	0.46^a	-0.62^b	0.79^b		0.55^a	0.75^b
ErF										
IntS									-0.47^a	
OrF	0.81^b		-0.52^a	-0.49^a	-0.45^a	0.51^a		0.43^a		
SxD	0.69^b	-0.63^b	-0.60^b	-0.68^b	-0.58^b	0.70^b	-0.49^a	0.39^a		-0.59^b
OvS									-0.47^a	

The clinical diagnosis, the baseline scores of the IIEF domains, and their change during treatment were correlated with hormone values at presentation (baseline). Responses to treatment were calculated as the posttreatment score minus the baseline score for each subject (individual variations).

[a] $P < 0.05$.

[b] $P < 0.01$.

In male myxedematosus sufferers, a hypergonadotropic state has been repeatedly reported (25, 26), although hypogonadotropic hypogonadism (25) or normal LH and FSH serum levels (27) have also been described. Hypothyroidism is also frequently associated with high PRL levels. In our cohort of hypothyroid patients, we found that PRL was significantly correlated to TSH and dropped when adequate T_4 replacement was given. Interestingly, higher posttreatment PRL levels, as well as higher E_2 levels, were associated with lower improvements in indices of sexual function at follow-up. Whether these associations are truly responsible for the persistence of sexual dysfunction secondary to other causes of impaired sexual function or a result of a suboptimal control of thyroid disease could not be ruled out.

Thyroid status profoundly affects mood and relational life, and patients with thyroid hormone disorders may experience a variety of sexual symptoms. We explored four major conditions, HSD, PE, DE, and ED, in a group of hyper- and hypothyroid patients. Patients were recruited prospectively over a limited time period, leading to a discrepancy in the size of the two groups, with a significantly smaller number of hypothyroid men. This has weakened the conclusions drawn on this group of subjects. However, the findings have also been analyzed jointly with the hyperthyroid subjects to provide a unitary model for the effect of thyroid hormones on the physiology of male sexual function. Because sexual function is one of the most complex human characteristics, and sexual dysfunctions are almost always multifaceted and multifactorial, involving physical, but also intrapsychic and relational factors, not all patients with thyroid disease experience a sexual dysfunction and not all patients with hyper- and hypothyroidism reaching euthyroidism recovered from a previous sexual dysfunction.

It is well known that hypothyroidism provokes somnolence, lethargy, and depression (17), whereas hyperthyroidism is associated with nervousness, emotional lability, and hyperkinesia (16). The HSD, which has been found in both hypothyroidism and hyperthyroidism at higher prevalence than the 6% described in the general population of Southern Europe (14), may be related to this. Additionally, the higher PRL levels observed in hypothyroid subjects may have affected the central machinery of sexual drive (28) as previously shown (29). In our cohort of patients, we were unable to confirm the increase in libido sometimes anecdotally described in hyperthyroid patients (16).

The main sexological complaint found in our cohort of hyperthyroid patients was PE, whereas in hypothyroid subjects, it was DE. Although the first is considered the most frequent sexual complaint, affecting around 20% of the normal population (30), the latter is an infrequent symptom (<5% of general population) (31) and, for this reason, not well studied. Surprisingly, both ejaculatory dysfunctions reverted upon achievement of euthyroidism in the absence of any other treatment for the sexual symptom. Although these can be considered secondary effects of treatment on mood, such a response on PE and DE was beyond all expectations, suggesting a direct involvement of thyroid hormones on the physiology of ejaculation.

ED, found at higher prevalence in our patients compared with the 8% estimated for the age-matched population (14), could be considered secondary to ejaculatory dysfunctions or to HSD, being present in both hypo- and hyperthyroidism. Alternatively, in hyperthyroid patients, ED might have been precipitated by an increased adrenergic tone that, in predisposed subjects, leads to an insufficient corpora cavernosa relaxation and venocclusive mechanism.

Because the relationship between thyroid hormones and ejaculatory mechanisms is currently unknown, three possible sites of action have been hypothesized: the sympathetic nervous system, the serotoninergic pathway, and the endocrine/paracrine system.

Most of the manifestations of thyrotoxicosis and sympathetic nervous system activation overlap. This may suggest a similar action of both systems on ejaculation, a reflex largely dependent on sympathetic and parasympathetic tone. However, plasma catecholamines and their urinary metabolites are usually normal in hyperthyroidism (32). On the other hand, there are studies showing that thyroid hormones augment sensitivity to β-adrenergic agonists by increasing the β-adrenoceptor density and G_s/G_i protein ratio with an overactivation of adenylate cyclase (33, 34). This leads to an increased sympathetic activity with normal circulating catecholamine levels. In hyperthyroid patients, the increased adrenergic tone may precipitate both PE and ED, either acting directly on smooth muscle contractility/relaxation or indirectly on anxiety and irritability. The opposite may occur in hypothyroid patients (35).

Considering the neuropsychic reactions to thyroid hormone excess (hyperkinesia, nervousness, anxiety, and emotional lability), PE may be a nonspecific disease-related complaint, disappearing when a euthyroid state is achieved. However, in light of the widespread distribution of thyroid hormone nuclear receptors within the brain, it can be hypothesized that iodothyronines specifically alter the central serotoninergic pathway (36), leading to diminished ejaculation control. In animals with experimentally induced hypothyroid states, increased serotonin (5-HT) turnover in the brain stem is consistently reported (37–40), and thyroid hormone replacement is associated with increased cortical 5-HT concentrations and augmentation of serotonergic neurotransmission by desensitization of the 5-HT inhibitory 5-hydroxytryptamine$_{1a}$ autoreceptor (autoinhibition) (37–39). Finally, DE is a common and therapeutically useful side effect of serotoninergic drugs, indicating that this pathway is fundamental for ejaculatory control (31, 41).

Another way thyroid hormone may affect the ejaculatory mechanism could be through estrogen metabolism. Hyperthyroidism increases SHBG, which binds androgens with higher affinity than estrogens, leading to a relative hyperestrogenism, which, at least in our cohort of patients, was present (when compared with euthyroidism) but never outside normal values. The increased androgen to estrogen conversion rate may be the mechanism for gynecomastia seen in about 10% of thyrotoxic men (42). It has been demonstrated in hypogonadic rabbits that estrogens, but not androgens, fully restore oxytocin-induced epididymal contractility, upregulating oxytocin receptor gene and protein expression, and that deprivation of endogenous estrogens induces oxytocin hyporesponsiveness (43–45). Because oxytocin is strictly involved in the ejaculatory mechanism (46), both

centrally (47) and peripherally (48), this may account for the close correlation between hyperthyroidism and PE.

Finally, thyroid hormone receptors have been described in the animal (49) and human testis (50) and may also be present in other male genital tract structures triggering ejaculation. The latter possibility is currently under investigation in our laboratories.

In conclusion, most patients with a chronic thyroid disease experience some sexual symptoms, such as PE in hyperthyroidism, DE in hypothyroidism, and HSD and ED in both conditions. This novel finding is of interest for the endocrinologist, who gains new clinical symptoms potentially useful for the diagnosis and follow-up of male thyroid disorders, and for the medical sexologist, who should screen patients complaining of ejaculatory dysfunction, at least by clinical examination and/or by measuring TSH.

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References

1. **Jannini EA, Ulisse S, D'Armiento M** 1995 Thyroid hormone and male gonadal function. Endocr Rev 16:443–459
2. **Read S, King M, Watson J** 1997 Sexual dysfunction in primary medical care: prevalence, characteristics and detection by the general practitioner. J Public Health Med 19:387–391
3. **Corona G, Petrone L, Mannucci E, Jannini EA, Mansani R, Magini A, Giommi R, Forti G, Maggi M** 2004 Psycho-biological correlates of rapid ejaculation in patients attending an andrologic unit for sexual dysfunctions. Eur Urol 46:615–622
4. **Fabbri A, Jannini EA, Gnessi L, Moretti C, Ulisse S, Franzese A, Lazzari R, Fraioli F, Frajese G, Isidori A** 1989 Endorphins in male impotence: evidence for naltrexone stimulation of erectile activity in patient therapy. Psychoneuroendocrinology 14:103–111
5. **Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A** 1997 The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49:822–830
6. **American Psychiatric Association** 1995 Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: American Psychiatric Association
7. **NIH Consensus Conference** 1993 Impotence. NIH Consensus Development Panel on Impotence. JAMA 270:83–90
8. **Apfelbaum B** 2005 Retarded ejaculation. In: Leiblum SR, Rosen RC, eds. Principles and practice of sex therapy. 3rd ed. New York: The Guilford Press; 205–241
9. **Waldinger MD, Hengeveld MW, Zwinderman AH** 1994 Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. Am J Psychiatry 151:1377–1379
10. **Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B** 2004 Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. Int J Impot Res 16:369–381
11. **Korenman SG** 1995 Advances in the understanding and management of erectile dysfunction. J Clin Endocrinol Metab 80:1985–1988
12. **Screponi E, Carosa E, Di Stasi SM, Pepe M, Carruba G, Jannini EA** 2001 Prevalence of chronic prostatitis in men with premature ejaculation. Urology 58:198–202
13. **Padma-Nathan H, Giuliano F** 2001 Oral drug therapy for erectile dysfunction. Urol Clin North Am 28:321–334
14. **Nicolosi A, Laumann EO, Glasser DB, Moreira Jr ED, Paik A, Gingell C** 2004 Sexual behavior and sexual dysfunctions after age 40: the global study of sexual attitudes and behaviors. Urology 64:991–997
15. **Lombardo F, Gandini L, Santulli M, Jannini EA, Dondero F, Lenzi A** 2003 Endocrinological diagnosis in sexology. J Endocrinol Invest 26(Suppl):112–114
16. **Davies TF, Larsen PR** 2003 Thyrotoxicosis. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, eds. Williams textbook of endocrinology. 10th ed. Philadelphia: Saunders, Elsevier; 374–421
17. **Larsen PR, Davies TF** 2003 Hypothyroidism and thyroiditis. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, eds. Williams textbook of endocrinology. 10th ed. Philadelphia: Saunders, Elsevier; 423–455
18. **Rojdmark S, Berg A, Kallner G** 1988 Hypothalamic-pituitary-testicular axis in patients with hyperthyroidism. Horm Res 29:185–190
19. **Ridgway EC, Longcope C, Maloof F** 1975 Metabolic clearance and blood production rates of estradiol in hyperthyroidism. J Clin Endocrinol Metab 41:491–497
20. **Rosner W, Aden DP, Khan MS** 1984 Hormonal influences on the secretion of steroid-binding proteins by a human hepatoma-derived cell line. J Clin Endocrinol Metab 59:806–808
21. **Sarne DH, Refetoff S, Rosenfield RL, Farriaux JP** 1988 Sex hormone-binding globulin in the diagnosis of peripheral tissue resistance to thyroid hormone: the value of changes after short term triiodothyronine administration. J Clin Endocrinol Metab 66:740–746
22. **Olivo J, Southren AL, Gordon GG, Tochimoto S** 1970 Studies of the protein binding of testosterone in plasma in disorders of thyroid function: effect of therapy. J Clin Endocrinol Metab 31:539–545
23. **Ruder H, Corvol P, Mahoudeau JA, Ross GT, Lipsett MB** 1971 Effects of induced hyperthyroidism on steroid metabolism in man. J Clin Endocrinol Metab 33:382–387
24. **Gordon GG, Southren AL, Tochimoto S, Rand JJ, Olivo J** 1969 Effect of hyperthyroidism and hypothyroidism on the metabolism of testosterone and androstenedione in man. J Clin Endocrinol Metab 29:164–170
25. **Wortsman J, Rosner W, Dufau ML** 1987 Abnormal testicular function in men with primary hypothyroidism. Am J Med 82:207–212
26. **Jaya KB, Khurana ML, Ammini AC, Karmarkar MG, Ahuja MM** 1990 Reproductive endocrine functions in men with primary hypothyroidism: effect of thyroxine replacement. Horm Res 34:215–218
27. **Corrales Hernandez JJ, Miralles Garcia JM, Garcia Diez LC** 1990 Primary hypothyroidism and human spermatogenesis. Arch Androl 25:21–27
28. **Cohen LM, Greenberg DB, Murray GB** 1984 Neuropsychiatric presentation of men with pituitary tumors (the 'four A's'). Psychosomatics 25:925–928
29. **Corona G, Mannucci E, Petrone L, Giommi R, Mansani R, Fei L, Forti G, Maggi M** 2004 Psycho-biological correlates of hypoactive sexual desire in patients with erectile dysfunction. Int J Impot Res 16:275–281
30. **Jannini EA, Lenzi A** 2005 Ejaculatory disorders: epidemiology and current approaches to definition, classification and subtyping. World J Urol 23:68–75
31. **Jannini EA, Simonelli C, Lenzi A** 2002 Disorders of ejaculation. J Endocrinol Invest 25:1006–1019
32. **Bilezikian JP, Loeb JN** 1983 The influence of hyperthyroidism and hypothyroidism on α- and β-adrenergic receptor systems and adrenergic responsiveness. Endocr Rev 4:378–388
33. **Seppet EK, Kaasik A, Minajeva A, Paju K, Ohisalo JJ, Vetter R, Braun U** 1998 Mechanisms of thyroid hormone control over sensitivity and maximal contractile responsiveness to β-adrenergic agonists in atria. Mol Cell Biochem 184:419–426
34. **Williams LT, Lefkowitz RJ, Watanabe AM, Hathaway DR, Besch Jr HR** 1977 Thyroid hormone regulation of β-adrenergic receptor number. J Biol Chem 252:2787–2789
35. **Polikar R, Kennedy B, Maisel A, Ziegler M, Smith J, Dittrich H, Nicod P** 1990 Decreased adrenergic sensitivity in patients with hypothyroidism. J Am Coll Cardiol 15:94–98
36. **Sandrini M, Vitale G, Vergoni AV, Ottani A, Bertolini A** 1996 Effect of acute and chronic treatment with triiodothyronine on serotonin levels and serotonergic receptor subtypes in the rat brain. Life Sci 58:1551–1559
37. **Bauer M, Heinz A, Whybrow PC** 2002 Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. Mol Psychiatry 7:140–156
38. **Kulikov AV, Jeanningro R** 2001 The effects of hypothyroidism on 5-HT1A and 5-HT2A receptors and the serotonin transporter protein in the rat brain. Neurosci Behav Physiol 31:445–449
39. **Henley WN, Bellush LL, Tressler M** 1998 Bulbospinal serotonergic activity during changes in thyroid status. Can J Physiol Pharmacol 76:1120–1131
40. **Sjoberg S, Eriksson M, Nordin C** 1998 L-Thyroxine treatment and neurotransmitter levels in the cerebrospinal fluid of hypothyroid patients: a pilot study. Eur J Endocrinol 139:493–497
41. **Waldinger MD** 2002 The neurobiological approach to premature ejaculation. J Urol 168:2359–2367
42. **Ridgway EC, Maloof F, Longcope C** 1982 Androgen and oestrogen dynamics in hyperthyroidism. J Endocrinol 95:105–115
43. **Filippi S, Vannelli GB, Granchi S, Luconi M, Crescioli C, Mancina R, Natali A, Brocchi S, Vignozzi L, Bencini E, Noci I, Ledda F, Forti G, Maggi M** 2002 Identification, localization and functional activity of oxytocin receptors in epididymis. Mol Cell Endocrinol 193:89–100
44. **Filippi S, Luconi M, Granchi S, Vignozzi L, Bettuzzi S, Tozzi P, Ledda F, Forti G, Maggi M** 2002 Estrogens, but not androgens, regulate expression and

functional activity of oxytocin receptor in rabbit epididymis. Endocrinology 143:4271–4280
45. **Filippi S, Morelli A, Vignozzi L, Vannelli GB, Marini M, Ferruzzi P, Mancina R, Crescioli C, Mondaini N, Forti G, Ledda F, Maggi M** 2005 Oxytocin mediates the estrogen-dependent contractile activity of endothelin-1 in human and rabbit epididymis. Endocrinology 146:3506–3517
46. **Filippi S, Vignozzi L, Vannelli GB, Ledda F, Forti G, Maggi M** 2003 Role of oxytocin in the ejaculatory process. J Endocrinol Invest 26(Suppl):82–86
47. **Carmichael MS, Humbert R, Dixen J, Palmisano G, Greenleaf W, Davidson JM** 1987 Plasma oxytocin increases in the human sexual response. J Clin Endocrinol Metab 64:27–31
48. **Maggi M, Malozowski S, Kassis S, Guardabasso V, Rodbard D** 1987 Identification and characterization of two classes of receptors for oxytocin and vasopressin in porcine tunica albuginea, epididymis, and vas deferens. Endocrinology 120:986–994
49. **Jannini EA, Dolci S, Ulisse S, Nikodem VM** 1994 Developmental regulation of the thyroid hormone receptor α1 mRNA expression in the rat testis. Mol Endocrinol 8:89–96
50. **Jannini EA, Crescenzi A, Rucci N, Screponi E, Carosa E, de Matteis A, Macchia E, d'Amati G, D'Armiento M** 2000 Ontogenetic pattern of thyroid hormone receptor expression in the human testis. J Clin Endocrinol Metab 85:3453–3457

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