Systematic review and meta-analysis for the value of thyroid disorder screening in men with ejaculatory dysfunction

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Abstract

Abstract Objective: To demonstrate evidence from available clinical studies to clarify the scientific points that have been achieved in relation to thyroid disorders and ejaculatory dysfunction. Data sources: Clinical trial articles published in English on Medline. Eligibility criteria: Clinical studies that investigated the association of thyroid disorders with the ejaculatory function of subjects and the trials evaluating the effect of thyroid dysfunction treatment on the ejaculatory function of the subjects were eligible. Synthesis methods: We searched Medline with "ejaculation" and different combinations of "thyroid," "serum TSH," "serum T3," "serum T4" keywords in PubMed. Results: Standardized mean serum thyroid-stimulating hormone (TSH) levels in premature ejaculation (PE) sufferers differed from non-PE control subjects (p=.05). Hyperthyroidism was associated with increased odds among PE subjects (OR=2.0, p=.03). Delayed ejaculation was seen with increased odds in hypothyroid patients compared with hyperthyroidism patients (OR=57, p=.0001). Serum TSH and mean intra-vaginal ejaculation latency time (IELT) of the subjects showed a correlation both before and after treatment for thyroid disorder. Treatment of thyroid disorders improved the mean IELT measures of the subjects. The overall estimate of the effect of hyperthyroidism treatment on mean IELT was .64 (p=.0001) in the random-effects model. Limitations: The low quality and quantity of evidence from available studies limited the interpretation of our study findings. Conclusions: The causal relationship between ejaculatory dysfunction and thyroid disorders remains to be clarified. Sufferers of delayed ejaculation acquired PE subjects, and PE sufferers who have accompanying erectile dysfunction and/or anxiety may benefit from thyroid disorder investigation.

Introduction

A higher prevalence of hyperthyroidism in patients with premature ejaculation (PE) has been reported; treatment of hyperthyroidism in a small group of patients resulted in improved outcomes by means of patient-reported outcome (PRO) measures related to PE and the mean intra-vaginal ejaculation latency time (IELT) of the subjects (Carani et al., 2005; Cihan, Demir, et al., 2009; G. Corona et al., 2004). On the other hand, delayed ejaculation (DE) has been observed in a large proportion of hypothyroidism patients; the mean IELT is also improved with the treatment of the thyroid disorder itself (Carani et al., 2005). In the same decade, it has also been clarified that there is no association with very low prevalence rates between thyroid dysfunction and lifelong PE in patients with normal erectile function (Waldinger, Zwinderman, Olivier, & Schweitzer, 2005). The aforementioned findings led to recommendations such as "thyroid hormone disorders should be suspected in ejaculatory disorders" with low certainty (Buvat et al., 2010). However, evidence from animal studies supports the presence of at least modulatory effects of thyroid hormones on the ejaculatory reflex operated from the central nervous system (Cahangirov et al., 2011; Cihan, Murat, et al., 2009; Cinar et al., 2018). We aimed to clarify the clinical evidence supporting the possible causality between thyroid dysfunction and EjD and the scientific background that supports the investigation of thyroid function in patients suffering from EjD.

Methods

Protocol and registration: The study protocol was established and recorded in the International Prospective Register of Systematic Reviews (Prospero: CRD42020198387).

Eligibility criteria: Studies investigating the proportion of human subjects with accompanying thyroid disorders among PE or DE sufferers or vice versa, correlation studies evaluating serum TSH with IELT and/or PRO measures of the EjD sufferers and measuring treatment effects that aim to establish a euthyroid state on the IELT and/or PRO measures of thyroid dysfunction sufferers were considered for this review. Both studies performed in the population and hospital settings were eligible in the case of appropriate ethical review board approval.

Information sources and search: An electronic data search was performed on Medline (via PubMed) without any time limit. A query by the different combinations of the following keywords: "ejaculation" and "thyroid," "serum TSH," "serum T3," and "serum T4"was performed on July 3rd 2020 and updated on November 3rd 2020.

Study selection: Initial screening via review keywords on PubMed was performed by the first author and title and abstract of the journal articles were evaluated for eligibility. Randomized and non-randomized studies on human subjects that declare ethical approval and clearly report all of the components of the population, interventions, comparators, and outcome measures of the trial were eligible for our review. Reviews and meta-analyses of existing data were not included in the current study. Irrelevant reports were removed, and candidate studies for the scope of the current review were finally evaluated for eligibility with their full-text files. Finally, the relevance of the studies was assessed with both review authors not blinded to the names and institutions of the study authors. The study flow diagram is shown in Figure 1 and characteristics of the included studies are shown in Table 1.

Risk of bias in individual studies: We established the risk of bias assessment tool for eligible studies specific to the current review and classified all of the included studies according to their grade and type of bias according to GRADE recommendations for evaluation of certainty of the evidence (Table 2) (Guyatt et al., 2008).

Summary measures: We rendered the presence of EjD, either PE or DE, as a dichotomous qualitative outcome measure. The mean PRO measures of the subjects and the mean of the IELT measurements in the reviewed studies were quantitative outcome measures.

Primary outcomes

We defined three primary outcomes for the current review:

I. Relative risk or odds ratio of EjD diagnosis among the studied subjects according to the presence of accompanying thyroid dysfunction.

II. Correlation measure and direction between serum TSH and IELT with or without PRO measures related to ejaculation in the subjects.

III. Proportional improvement in the IELT and/or PRO measures related to ejaculation of the subjects in studies investigating the quantitative effects of treatment for accompanying thyroid dysfunction.

Secondary outcomes

The time interval between the achievement of euthyroid status and observed effects on ejaculatory function among subjects in the studies, presence of need for further treatment except intervention aimed at euthyroidism for related EjD, treatment-related sexual side effects (de novo ED or loss of libido, etc.), and economic aspects of treatment to achieve changes in ejaculatory function were the secondary outcomes if reported in eligible studies.

Synthesis of results: Data of eligible articles were extracted into Excel sheets and analyzed for quality, the quantity of the measured effect, the direction of the effect, and rated according to the possible risk of bias.

Additional analysis: The random effects model was used for all measures obtained from eligible studies. Measures of intervention effect on outcomes with change over time or differences between groups were the main aim of the current meta-analysis. We initially evaluated the consistency of standardized correlation coefficients between the IELT and serum TSH measurements of the subjects across studies. Observed effect measures (p values) with 95% confidence intervals, measured effects of thyroid dysfunction treatment with odds ratios, and PRO and IELT measurements were analyzed. While different methods were anticipated to be used in the measurement of IELT and PRO measures of the heterogeneous group of subjects across the eligible studies, a standardized mean difference was used to estimate the overall size of the effect on the measured variable. We have used "Review Manager (RevMan)" computer program Version 5.4 for windows from "Cochrane Collaboration, 2020" and Open Meta program (http://www.cebm.brown.edu/open_meta) during our study conduction. Both of these programs have already been launched for the use of external reviewers.

Results

The odds ratio of hyperthyroidism among PE patients compared with control subjects was 2.0 (0.6-6.9 at 95% CI, p=.03). The odds ratio of PE among hyperthyroid patients compared with euthyroid subjects was 2.2 (1.1-4.5 at 95% CI, p=.0001). The odds ratio of PE among hyperthyroid patients compared with hypothyroid subjects was 13.2 (5.6-31.4 at 95% CI, p=.006). The odds ratio of DE among hypothyroid patients compared with hyperthyroid subjects was 57.4 (16.9-194.5 at 95% CI, p=.0001). Table-3 summarizes the findings from interventional studies.

The standardized mean serum TSH difference between PE and non-PE subjects in the random-effects model had an estimate of effect of -0.45 (lower and upper bound: -0.91 and 0.006; SE: 0.23; p=0.05) (Figure 2.A). The effect of treatment of hyperthyroidism on mean IELT in the random-effects model was as an overall estimate of effect of 0.64 (lower and upper bound: 0.27 and 1.02; SE: 0.19; p<0.001) (Figure 2.B). The effect of treatment of hyperthyroidism on the prevalence of PE in the binary random-effects model was as an overall estimate of effect of 0.13 (lower and upper bound: 0.05 and 0.33; p<0.001) (Figure 2.C).

Discussion

Summary of evidence

Despite the limitations of the available studies, we clarified that patients with hyperthyroidism have at least two-fold increased odds for PE. Patients with hypothyroidism had more increased odds for DE compared to hyperthyroidism subjects. Hyperthyroidism is much more common in patients with PE; however, the latter association is not true for lifelong PE sufferers who have normal erectile function. Current evidence indicates that serum TSH levels in men are correlated with their ejaculation latency control ability by means of time in both hypothyroid and hyperthyroid subjects. From the treatment aspect, relieving the thyroid disorder by itself improves both IELT control and subjective PRO measures related to ejaculation at least 2 months after the achievement of euthyroidism in men. Several aspects of erectile function and the accompanying anxiety of the subjects also improved with the treatment of thyroid disorders only.

With respect to the memory of Waldinger, who emphasized the necessity of large cohorts (for example, to identify at least 55 lifelong PE patients, you need at least 100,000 screened subjects) to demonstrate the natural distribution of serum TSH among lifelong PE and non-PE subjects, we are still far from clarifying the contribution of thyroid hormone axis distortions to the ejaculatory reflex machinery with currently available clinical studies (Waldinger et al., 2005). For instance, if a case-control study aimed to reveal the proportions of thyroid disorders among EjD sufferers, at least 833 subjects for each group are needed to achieve 80% power with 95% CIs according to power analysis for sample size with a known prevalence. Therefore, the lack of large population-based comparative studies, excessive heterogeneity across available studies, absence of standardization in the evaluation of both objective (IELT) and subjective measures related to ejaculation, erectile function, anxiety, etc., has led to a deficiency in the overall completeness of our study evidence. The absence of placebo effect elaboration and results of long-term follow-up studies with the presence of selection bias also lowered the quantity of evidence for interventional studies available in the current review.

The association of hyperthyroidism and PE with increased odds for each other has been confirmed in our study, which is in agreement with previous reports (Giovanni Corona, Jannini, Vignozzi, Rastrelli, & Maggi, 2012a; Gabrielson et al., 2019). Considering that only one study by Waldinger is available, the absence of this association among a subgroup of patients who have lifelong PE has also been confirmed in our study (Giovanni Corona, Jannini, Vignozzi, Rastrelli, & Maggi, 2012b; Waldinger et al., 2005). On the other end of the ejaculatory axis, DE has been shown to be strongly associated with hypothyroidism, which has been reported in previous reviews, as evidenced by one available study (Carani et al., 2005; Di Sante et al., 2016; Gabrielson et al., 2019). Finally, the median age of the available studies that demonstrate the aforementioned associations is in the forties, which agrees with the previous argument that thyroid disorders may be a relevant risk factor for sexual problems in young adults (Gabrielson et al., 2019).

The higher prevalence of anxiety among acquired PE patients and hyperthyroid patients has been demonstrated with currently available data (Cihan, Demir, et al., 2009; Culha, Tuken, Gonultas, Cakir, & Serefoglu, 2020). However, the exact role of anxiety (direct or indirect role) on the ejaculatory disturbance due to underlying thyroid dysfunction is another issue that still remains to be clarified.

Treatment of thyroid dysfunction by itself has led to significant improvements in the majority of patients with respect to ejaculatory latency control, PRO measures related to ejaculation and accompanying erectile function domains, and anxiety levels, which is demonstrated in the available studies in our study and has already been reported in previous reviews (Bates, Kohn, & Pastuszak, 2020; Sansone, Romanelli, Jannini, & Lenzi, 2015). Surgically treated hyperthyroid patients demonstrated much more improvement in their ejaculatory control outcomes compared with other treatment groups, which should also be emphasized again for planning future trials (Cihan, Demir, et al., 2009). However, as shown by Bates et al., although there are statistically significant and desired improvements in the IELT of subjects suffering from a thyroid disorder, a small but perhaps clinically significant proportion of patients still complain of EjD (Bates et al., 2020). Therefore, we concluded that the relevance and different dimensions of treatment effects with targeting euthyroidism alone on the EjD in patients with thyroid disorder should be validated with large, longitudinal studies with longer follow-up evaluations.

Limitations

The lack of blinding of the authors during data extraction and synthesis in the current review may have contributed to the potential bias. However, heterogeneity of the available studies was the major limitation during the meta-analysis process of our study.

Conclusions

Implications for practice: Acquired PE subjects and PE sufferers who have accompanying erectile dysfunction and/or anxiety may benefit from thyroid disorder investigation. Screening men for thyroid disease may also be useful in patients with DE.

Implications for research: With current knowledge of available studies, we are still far from establishing any conclusion on a causal relationship between EjD and thyroid disorders. Available evidence suggests Dopaminergic pathways in the central nervous system that mediates the emission phase of the ejaculation might be a good research area for experimental studies that aimed to clarify the interrelation between thyroid disorder and ejaculatory dysfunction in men. Further longitudinal studies with a good sample size estimation based on the population-based prevalence rates of thyroid disorders, using standardized diagnostic tools (PRO related to ejaculation, measured IELT, etc.) and an appropriate length of follow–up evaluations may enhance the quality of scientific evidence on this emerging topic.

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Table 1. Characteristics of the included studies

	Country	*Design*	*Setting*	*Participants*	*Diagnosis of EjD*	*Cut-offs for serum TSH measurement*	*Intervention*	*Funding*
Culha MG (Culha et al., 2020)	Turkey	Case series (prospective)	Hospital	Acquired PE sufferers	ISSM definition	Not stated	no	none
Khan HL(Khan et al., 2018)	Pakistan	Case-control study	Hospital	PE with Diabetes mellitus vs. non-PE (control)	DSM-4TR definition and estimated IELT (with 3 min cut-off)	0.4-4.5 mcIU/ml	no	none
Canat L (Canat, Erbin, Canat, Dinek, & Çaşkurlu, 2017)	Turkey	Case-control study	Hospital	PE sufferers without ED vs. non-PE (control)	PEDT	Not stated	no	none

	Country	*Design*	*Setting*	*Participants*	*Diagnosis of EjD*	*Cut-offs for serum TSH measurement*	*Intervention*	*Funding*
Öztürk MI (Öztürk et al., 2012)	Turkey	Case-control study	Hospital	PE patients vs. non-PE (control)	Measured IELT	0.4-4 mIU/L	no	none
Corona G (G Corona et al., 2011)	Italy	Retrospective cohort	Hospital	PE or DE sufferers following admission to sexual health unit	Study specific PRO for EjD and estimated IELT	TSH < 0.2 mIU/L for hyperthyroidism	no	none
Cihan A (Cihan, Demir, et al., 2009)	Turkey	Prospective cohort	Hospital	Hyperthyroid male patients who admitted to Endocrinology outpatient clinic	DSM-4TR and measured IELT	0.4mcIU/ml cut-off for Hyperthyroidism	Specific treatment of hyperthyroidism with medication, surgery or RAI	none
Carani C (Carani et al., 2005)	Italy	Prospective cohort	Hospital	Hyperthyroid and Hypothyroid male patients who admitted to Endocrinology clinic	DSM-4TR and measured IELT	0.3-5.0 mcIU/ml	Medical tx of thyroid dysfunction (Metimazole, L-Thyroxine plus Propanolol and Benzodiazepine's in some cases)	yes

	Country	*Design*	*Setting*	*Participants*	*Diagnosis of EjD*	*Cut-offs for serum TSH measurement*	*Intervention*	*Funding*
Waldinger MD (Waldinger et al., 2005)	Netherlands	Case series (prospective)	Hospital	Patients who admitted to Andrology Unit recruited according to presence of lifelong PE and absence ED	Estimated IELT	0.3 -4.0 mcIU/ml	no	none
Corona G (G. Corona et al., 2004)	Italy	Cross-sectional	Hospital	Patients who admitted to sexual health unit	Study specific PRO for PE	TSH < 0.2 mIU/L for hyperthyroidism	no	yes
Abbreviations	*Abbreviations*	*Abbreviations*	*Abbreviations*	*Abbreviations*	*Abbreviations*	*Abbreviations*	*Abbreviations*	*Abbrevi*
DE:	DE:	DE:	Delayed ejaculation	Delayed ejaculation	Delayed ejaculation	Delayed ejaculation	Delayed ejaculation	Delayed ejaculat
ED:	ED:	ED:	Erectile dysfunction	Erectile dysfunction	Erectile dysfunction	Erectile dysfunction	Erectile dysfunction	Erectile dysfunc
EjD:	EjD:	EjD:	Ejaculatory dysfunction	Ejaculatory dysfunction	Ejaculatory dysfunction	Ejaculatory dysfunction	Ejaculatory dysfunction	Ejacula dysfunc
IELT:	IELT:	IELT:	Intravaginal ejaculation latency time	Intravaginal ejaculation latency time	Intravaginal ejaculation latency time	Intravaginal ejaculation latency time	Intravaginal ejaculation latency time	Intravaginal ejacula-tion latency time
PE:	PE:	PE:	Premature ejaculation	Premature ejaculation	Premature ejaculation	Premature ejaculation	Premature ejaculation	Premat ejaculat
PRO:	PRO:	PRO:	Patient reported outcome	Patient reported outcome	Patient reported outcome	Patient reported outcome	Patient reported outcome	Patient reporte outcom

	Country	*Design*	*Setting*	*Participants*	*Diagnosis of EjD*	*Cut-offs for serum TSH measurement*	*Intervention*	*Funding*
PEDT:	PEDT:	PEDT:	Premature ejaculation diagnostic tool	Premature ejaculation diagnostic tool	Premature ejaculation diagnostic tool	Premature ejaculation diagnostic tool	Premature ejaculation diagnostic tool	Premat ejacula- tion diagnos tic tool
RAI:	RAI:	RAI:	Radioactive Iodine	Radioactive Iodine	Radioactive Iodine	Radioactive Iodine	Radioactive Iodine	Radioac Iodine
TSH:	TSH:	TSH:	Thyroid stimulating hormone	Thyroid stimulating hormone	Thyroid stimulating hormone	Thyroid stimulating hormone	Thyroid stimulating hormone	Thyroid stimu- lating hormon

Table.2 Risk of bias assessment

	Confounding	*Selection of participants*
Culha MG,2020	MR	MR
Khan HL,2018	SR	MR
Canat L,2017	MR	SR
Öztürk MI, 2012	LR	MR
Corona G,2010	MR	MR
Cihan A,2009	LR	LR
Carani C, 2005	LR	LR
Waldinger MD, 2005	SR	SR
Corona G,2004	MR	MR
Abbreviations:	LR: low Risk, MR: Moderate risk, SR: Serious risk, NI: No information	LR: low Risk, MR: Moder

Table 3. Summary of findings of interventional studies

Patients and population: Men with thyroid disorder

Patients and population: Men with thyroid disorder	Patients and population: Men with thyroid disorder	Patients and popu

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Patients and population: Men with thyroid disorder

Setting: Hospital	
Intervention: Thyroid disorder treatment only.	*Intervention:* Thyroid disorder treatment only.

&

Patients and population: Men with thyroid disorder

Setting: Hospital	
Intervention: Thyroid disorder treatment only.	*Intervention:* Thyroid disorder treatment only.

&

Patients and population: Men with thyroid disorder

Setting: Hospital	
Intervention: Thyroid disorder treatment only.	*Intervention:* Thyroid disorder treatment only.

&

Patients and population: Men with thyroid disorder

Setting: Hospital	
Intervention: Thyroid disorder treatment only.	*Intervention:* Thyroid disorder treatment only.

&

Patients and population: Men with thyroid disorder

Setting: Hospital	
Intervention: Thyroid disorder treatment only.	*Intervention:* Thyroid disorder treatment only.

&

Patients and population: Men with thyroid disorder

Setting: Hospital	
Intervention: Thyroid disorder treatment only.	*Intervention:* Thyroid disorder treatment only.

&

Patients and population: Men with thyroid disorder

Setting: Hospital	
Intervention: Thyroid disorder treatment only.	*Intervention:* Thyroid disorder treatment only.

Figure legends.

Figure 1. Study flow diagram

Figure 2-A. The forest plot of mean difference for serum TSH among PE and non-PE subjects in available studies

Figure 2-B. The forest plot of the treatment effect of Hyperthyroidism on mean IELT

Figure 2-C. The forest plot of the treatment effect of Hyperthyroidism on the prevalence of PE