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ORIGINAL ARTICLE

Treatment of thyroid disorder supported by 5-phosphodiesterase inhibitors improved erectile dysfunction in patients with hypo- and hyperthyroidism.

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Abstract

INTRODUCTION: The relationship between a poorly functioning thyroid gland and erectile dysfunction (hereinafter, "ED") has been demonstrated in many studies. If a man has thyroid problems, it can negatively affect his ability to achieve or maintain an erection. The thyroid gland produces hormones that affect metabolism and overall body function, including blood circulation. If the thyroid gland is not functioning properly, it can lead to blood circulation disorders, which can affect erectile function. There are also symptoms of thyroid disorders that can contribute to ED. Some of these symptoms include fatigue, depression, and anxiety, which can negatively affect a man's psychological side and affect his sexual performance.

OBJECTIVES AND METHODS: In our article, we present a series of patients with ED who were treated in our department and found to have some form of thyroid dysfunction.

RESULTS: After treatment for thyroid dysfunction and treatment with 5-phosphodiesterase inhibitors were implemented, erectile function improved in all patients ((Wilcoxon Signed Rank Test; Z = -4.55; p (2-tailed) < 0.001; n = 27) to the level of mild or no ED. Improvement occurred in men with hyper- and hypothyroidism. After one year of treatment, there was no difference between the two groups (t-test; t = 0.75; df = 0.25; p < 0.46).

CONCLUSION: This study shows that screening for thyroid dysfunction should be performed in all men with ED and that treating thyroid dysfunction may be an effective way to improve erectile function in men with these health problems.

Abbreviations:

ED	- erectile dysfunction
DHEA	- dehydroepiandrosterone
iPDE5	- Phosphodiesterase-5 Inhibitors
SHIM	- Sexual Health Inventory for Men
IIEF	- International Index of Erectile Function
fT4	- Free Thyroxine
TSH	- thyroid stimulating hormone

INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability (for at least six months) to achieve and maintain an erection that allows satisfactory sexual intercourse. Single situational failures or transient EDs are not a serious problem and do not require therapy (Zámečník, 2008). Treatment is indicated if more than one-quarter of attempts at sexual intercourse fail. The causes of ED are of organic origin in most cases (80%), with approximately 20% being purely psychogenic (Foresta *et al.* 2009; De Tejada IS *et al.* 2005). Psychological factors are present in all cases of ED and aggravate the problems. And conversely, men with erection problems also have an approximately threefold increased risk of suffering from depression (Wiemer *et al.* 2022). In such cases, we speak of a secondary psychogenic cause (Topak *et al.* 2023).

After sildenafil – the first pentose phosphodiesterase inhibitor (iPDE5) preparation – was launched in 1998, interest of patients and physicians in the treatment of ED increased (Lobo & Nehra 2005). Questionnaires, of which there are many, can be used to assess the degree and severity of ED. The most commonly used are: the International Index of Erectile Function (IIEF) and its five-question version IIEF-5, the Erectile Hardness Scale (EHS), the Sexual Health Inventory for Men (SHIM), the Androgen Decline in the Aging Male (ADAM) questionnaire, and the Expanded Prostate Cancer Index Composite (EPIC) (Broul *et al.* 2014). The IIEF-5 questionnaire was developed in 1997 by Rosen *et al.* (Rosen *et al.* 1997; Rosen *et al.* 1999). The entire questionnaire has 15 questions. The five-question abbreviated version of the questionnaire has proven useful in clinical practice (Ahmed Memon S *et al.* 2022). In our study, we use the Sexual Health Inventory for Men (SHIM), a validated abbreviated version of the International Index of Erectile Function (Ramanathan *et al.* 2007).

The availability of seemingly simple treatment with iPDE5 tablets may lead to overlooking the actual causes of ED. One possible cause of ED is thyroid dysfunction. The thyroid gland produces hormones that affect metabolism and overall body function, including blood circulation. If the thyroid gland does not function properly, it may lead to blood circulation disorders, which can affect erectile function (Al-Suhaimi& Khan 2022). TR alpha receptors are located in the heart and influence heart rate and systolic and diastolic myocardial function. When T3 and T4 concentrations are elevated, tachycardia and increased contractility occur, whereas when their concentrations are low, bradycardia and diastolic dysfunction occur. From a vascular point of view, hyperthyroidism causes vasodilation and increased tissue perfusion, whereas hypothyroidism has the opposite effect. Indirectly, thyroid hormones act on the myocardium through changes in the autonomic system: in their excess, sympatheticotonus predominates; in their deficiency, on the contrary, parasympatheticotonia (Zamrazil, 2015). Therefore, if a man has thyroid problems, it can negatively affect his ability to achieve and maintain an erection, both in the sense of hyperfunction (Nakova *et al.* 2022) and hypofunction (Giustina *et al.* 2022). There are also symptoms of thyroid disorders that can contribute to ED. Some of these symptoms include fatigue, depression, and anxiety, which can negatively affect a man's psychological well-being and affect his sexual performance (Anderson 2022).

The aim of this study was to examine whether and to what extent the treatment of thyroid dysfunction combined with the use of iPDE5 preparations improved ED problems in men with hyperthyroidism and hypothyroidism. We made a comparison in a cohort of our patients who had thyroid problems, were undergoing thyroid treatment, and were also taking iPDE5 preparations. The degree of ED was assessed by the SHIM questionnaire before and after treatment.

MATERIALS AND METHODS

Procedure

Respondents underwent a comprehensive medical examination, completed the SHIM questionnaire, underwent a standard laboratory test, and were prescribed one of the iPDE5 preparations (sildenafil, tadalafil, vardenafil, or avanafil). They were then referred for an endocrinological examination. After examination by an endocrinologist and after the patients started to be treated for thyroid disorders, we continued to monitor their fT4, TSH, and testosterone levels. One year after starting the treatment for thyroid dysfunction, the respondents completed the SHIM questionnaire again. In all men, their thyroid disorder was already well controlled.

Respondents

Respondents (N = 27) were selected from a cohort of patients who were treated for ED at the Department of Sexology, Masaryk Hospital in Ústí nad Labem, Krajská zdravotní, a.s between 2016 and 2022. Only the following patients were included in the study: those who had a standard examination at the beginning of treatment as well as those who were found to have hypofunction or hyperfunction of the thyroid gland. Excluding criteria were any other comorbidities – diabetes mellitus, cardiovascular diseases (myocardial infarction, coronary angioplasty, or coronary by-pass) in their history. None of the patients were taking any

Tab. 1. Age, SHIM after treatment, free thyroxine after treatment, and thyroid stimulating hormone before and after treatment of hypo- and hyperthyroid men

		Age (years)	SHIM after treatment	fT4 after treatment	TSH before treatment	TSH after treatment
Hypothyroid men	Mean	52.44	19.33	16.37	23.52	3.51
	Std. Deviation	12.00	2.28	2.77	9.25	4.31
Hyperthyroid men	Mean	51.67	19.22	15.44	0.13	2.17
	Std. Deviation	12.26	2.33	2.61	0.07	0.93

Descriptive statistics of variables that follow the normal distribution.
Hypothyroid men N = 18, Hyperthyroid men N = 9.
The treatment took one year. Patients were also taking one of the iPDE5 preparations (sildenafil, tadalafil, vardenafil, or avanafil).
fT4: free thyroxine
TSH: thyroid stimulating hormone
SHIM: Sexual Health Inventory for Men

thyroid medication prior to inclusion. Patients ranged in age from 24 to 71 years, m = 52.19±11.85SD.

Elevated fT4 levels and decreased TSH levels were diagnostic of hyperthyroidism, and elevated TSH levels and decreased fT4 levels confirmed the diagnosis of hypothyroidism. Four men in our cohort also had confirmed thyroid antibodies.

Of the 27 men selected, 9 had clinical hyperthyroidism (TSH < 0.27 mlU/l) and 18 had clinical hypothyroidism (TSH > 5 mlU/l). Of the 9 men with hyperthyroidism, five had Graves-Basedow disease and four had toxic nodular or multinodular goiter.

Sixteen of the men in our cohort were taking some medication other than thyroid medication. These were statins, beta-blockers, and antihypertensives.

Questionnaire

ED was assessed using the Sexual Health Inventory for Men (SHIM), a validated abbreviated version of the International Index of Erectile Function (Ramanathan *et al.* 2007). The SHIM Questionnaire is an abridged and slightly modified 5-item version of the 15-item International Index of Erectile Function (IIEF), designed for easy use by clinicians, to diagnose the presence and severity of ED in clinical settings (Otaola-Arca *et al.* 2022). Diagnostic evaluations of the SHIM have shown it to have high sensitivity and specificity, moderate-to high correlations with (and better reliability than) a single-item self-assessment of ED severity, and tangible correlations (as expected) with improvement in erections and with treatment satisfaction for both patient and partner (Cappelleri & Rosen 2005). The Czech version was validated by Heřmánková *et al.* in 2021 (Heřmánková *et al.* 2021). One of its questions is scored one to five points and the other 4 questions zero to five points. The total IIEF-5 score ranges from 1 to 25 points. We assessed erectile function (ED) status according to the SHIM as

1–7	Severe ED
8–11	Moderate ED
12–16	Mild to Moderate ED
17–21	Mild ED

Statistics

Data were analyzed with IBM SPSS Statistic 29. Data normality was assessed using the Shapiro-Wilk test and the Kolmogorov-Smirnov test with Lilliefors Significance Correction. T-test (parametric test) was used for normally distributed data. For data that did not follow the normal distribution, Wilcoxon Signed Rank Tests (non-parametric 2-sided tests) were performed. We use the t-test to compare the SHIM of hyperthyroid men to the SHIM of hypothyroid men before treatment. Then we use the Wilcoxon Signed Rank Test to compare

Tab. 2. SHIM before treatment, increase in SHIM scores (Δ SHIM), and free thyroxine before treatment of hypo- and hyperthyroid men

		SHIM before treatment	Δ SHIM	fT4 before treatment
Hypothyroid men	Median	13.00	6.50	4.50
	Range	15.00	10.00	8.80
Hyperthyroid men	Median	12.00	8.00	27.30
	Range	13.00	8.00	15.50

Descriptive statistics of variables that did not follow the normal distribution.
Hypothyroid men N = 18, Hyperthyroid men N = 9.
The treatment took one year. Patients were also taking one of the iPDE5 preparations (sildenafil, tadalafil, vardenafil, or avanafil).
fT4: free thyroxine
SHIM: Sexual Health Inventory for Men

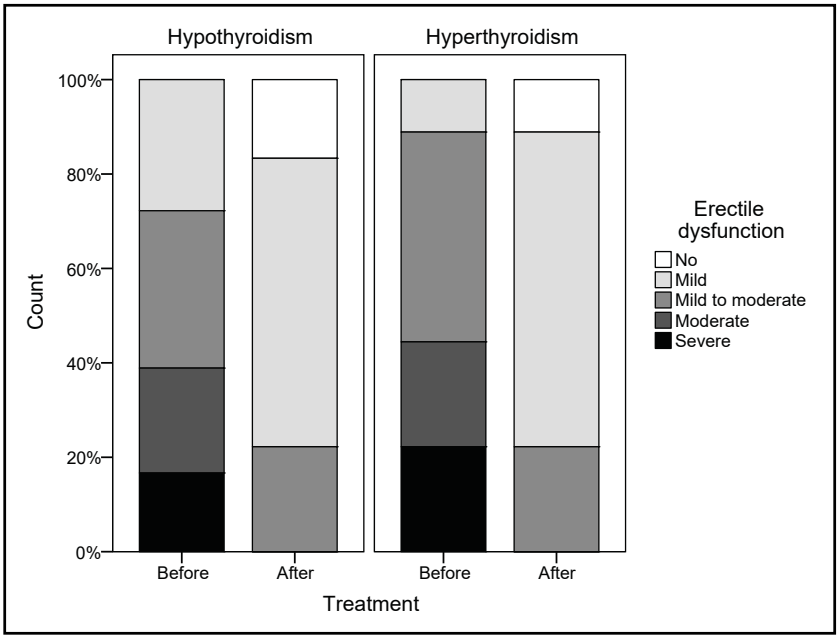

Fig. 1. SHIM score before and after treatment. Degree of ED according to SHIM score before and after the treatment of thyroid dysfunction in patients with hypo- and hyperthyroidism (N = 18 and 9). Respondents were also taking one of the iPDE5 preparations (sildenafil, tadalafil, vardenafil, or avanafil). After the treatment, complete, severe, and moderate ED did not occur in hyper- or hypothyroid patients.

the SHIM before and after treatment for all men. Finally, we compared the improvement (ΔhSHIM) between the two groups of men by t-test.

Power analysis of t-test was managed via IBM SPSS Statistic 29. We used G*Power Version 3.1.9.6. for power analysis of the Wilcoxon Signed Rank Test. The asymptotic relative efficiency (A.R.E.) method was used to compute power of Wilcoxon tests. The method is based on comparison of efficiency of the Wilcoxon test with the t-test. Minimal theoretical value of efficiency ratio 0.846 was used to achieve maximal margin of conservatism. Since the distributions of analysed variables are most similar to uniform distribution having efficiency ratio 1, the true power of the Wilcoxon test lies between the conservative estimate and estimate or t-test power.

RESULTS

Over the past 7 years (patients treated between 2016 and 2022), we have detected a total of 51 men with hyperthyroidism or hypothyroidism at our institution using standard screening. Of these respondents, one-third had hyperthyroidism and two-thirds had hypothyroidism. Only 27 men met the inclusion criteria and were enrolled in the study (Tables 1,2). These patients

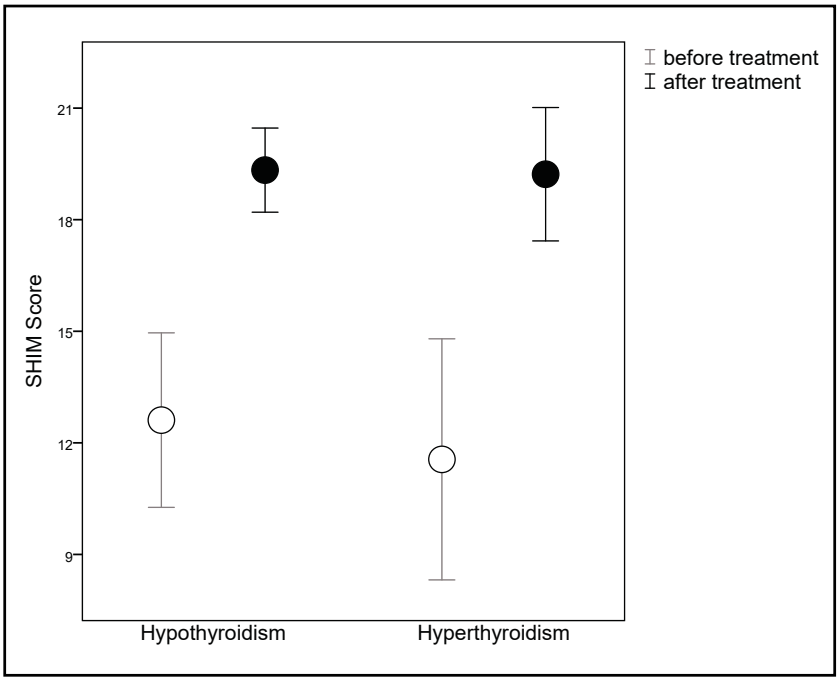

Fig. 2. SHIM mean and confidence interval. Mean SHIM test before (dashed) and after (full) treatment for hypo- and hyperthyroidism (N = 18 and 9). The confidence interval for mean 95% is shown. Respondents were concurrently taking one of the iPDE5 preparations (sildenafil, tadalafil, vardenafil, or avanafil). There was no difference between men with hypo- and hyperfunction when comparing improvements between these groups.

started treatment with phosphodiesterase inhibitors after complexing the SHIM questionnaire and before starting thyroid treatment.

Before the treatment, all responders had a SHIM score less than or equal to 19. Mean SHIM scores did not differ between hyper- and hypothyroid men (mean hyper = 11.56, SD = 4.22; mean hypo = 12.61, SD = 4,72; t-test; t = -0.57; df = 25; $p < 0.58$) but the power was low (Power: Test of Mean Difference, Power = 0.085, N1 = 9, N2 = 18, Effect Size = 0.23, $p < 0.05$; Sample Size: Test of Mean Difference, Power = 0.8, N1 = 221, N2 = 442, Effect Size = 0.23).

One year after the initiation of the treatment for thyroid dysfunction (and thyroid dysfunction was under control), we observed an increase in SHIM scores, both in men with hypo- and hyperthyroid function (Wilcoxon Signed Rank Test; Z = -4.55; p (2-tailed) < 0.001; n = 27) (Fig. 1, 2). The mean difference in SHIM was 7.04, SD = 3.04; min = 2; max = 12; n = 27.) Power lies between 0.84 – 1 (see chapter "Statistics", Test of Mean Difference, Power = 1.0, N = 27, Effect Size = 2.31, $p < 0.05$; Sample Size: Test of Mean Difference, Power = 0.8, N = 4, Effect Size = 2.31) (Tables 1,2).

We showed no difference between men with hypo- and hyperfunction when comparing improvements between these groups (t-test; t = 0.75; df = 25; $p < 0.46$), but the power was weak (Test of Mean Difference, Power = 0.11, N1 = 9, N2 = 18, Effect Size = 0.31, $p < 0.05$; Sample Size: Test of Mean Difference, Power = 0.8, N1 = 126, N2 = 251, Effect Size = 0.31).

DISCUSSION

We found striking improvement in the SHIM score in patients who received thyroid treatment combined with phosphodiesterase inhibitors. We did not find a difference in SHIM score before the treatment in hyper- and hypothyroid men, but the power analysis showed that a much larger sample is needed to find differences between the two groups (221 and 442 respondents according to power analysis). Similarly, we did not find differences between the two groups in improvement. Here, the sample should be larger too (i.e. 126 and 251 respondents). So the comparison of the two groups should be viewed as a pre-study.

These findings did not change the essence of our study. i.e. proof that the combination of thyroid treatment and usage of phosphodiesterase inhibitors was effective. The improvement was so pronounced that we could demonstrate it in even a smaller group of responders. On the other hand, the need for larger groups of patients for finding the differences between hyper- and hypothyroid men suggested that the difference may be small and may have lower importance for medical practice.

In our cohort, we confirmed that the SHIM score increased by 6.5 points after treatment of thyroid disorder. This can be considered a significant improvement. For comparison, in the study by Hao Su *et al.* (Su *et al.* 2022), there was a 4.53-point increase in IIEF-5 score in patients treated with atorvastatin compared with the control group. In the study by Durmus and Oki (Durmus & Ok 2022), there was a decrease in IIEF score in patients with Mondor disease after 6 months from 19.24 to 19.09. A study by Elliot *et al.* (Elliott *et al.* 2023) showed that there was a decrease in IIEF-5 score of 5.02 points in patients after acetabulum fracture.

All men in our study showed improvement (Fig. 1, 2). The respondents moved from complete, severe, and moderate dysfunction to mild or no ED. Two men had a pre-treatment SHIM score of 4, i.e., they suffered from complete ED. After the treatment, in 11 men the SHIM score even climbed to 21 or more. Hyper- and hypothyroid men did not differ in the severity of ED before treatment. Nor did they differ in the degree of improvement. Thus, treatment helped both groups similarly.

A healthy, sexually functional man should have normal libido, normal erectile function, intact hypothalamic-pituitary hormonal axis, spermatogenesis, and ejaculatory function (Lewis *et al.* 2004). A study by Krassas *et al.* confirmed the association between libido, erectile function, and hypo/hyperthyroid function (Krassas *et al.* 2002). Our study also suggests that impaired thyroid function is related to the development of ED. Studies by Bliesener, Gray, and O'Connor (Bliesener *et al.* 2005; Gray *et al.* 2005; O'Connor *et al.* 2004) have come to the same conclusion. The occurrence of ED in middle-aged and older men is quite common. This was confirmed in a study by Wespes, where 52% of men aged 40 to 70 years reported suffering from some degree of ED. 17% of men had mild, 25% had moderate, and 10% had complete ED (Wespes 2002).

The mechanism by which impaired thyroid function causes ED was studied by Lundberg and Kaufman. According to them, ED is caused by a complex interplay between the state of the splanchnic pelvic nerves or nervi erigentes, cognitive decline, and the stress associated with the disease (Lundberg *et al.* 2000; Kaufman & Vermeulen 1998). Thus, abnormalities of endocrine function certainly affect erectile function. In patients with hypothyroidism, these changes were described in a study by Werner, where it was shown that hypothyroidism was associated with a decrease in serum testosterone, dehydroepiandrosterone (DHEA), and DHEA sulfate (Refetoff 2020).

In another study, Krassas *et al.* also confirmed an increase in SHIM score in men treated for thyroid disorders. No difference in SHIM scores was found between hyper- and hypothyroid patients. In patients with hypothyroidism, SHIM scores correlated positively with fT4 levels and negatively with TSH levels. In contrast, SHIM scores did not correlate with either FT4 or TSH levels in patients with hyperthyroidism. After treatment of thyroid dysfunction, a significant increase

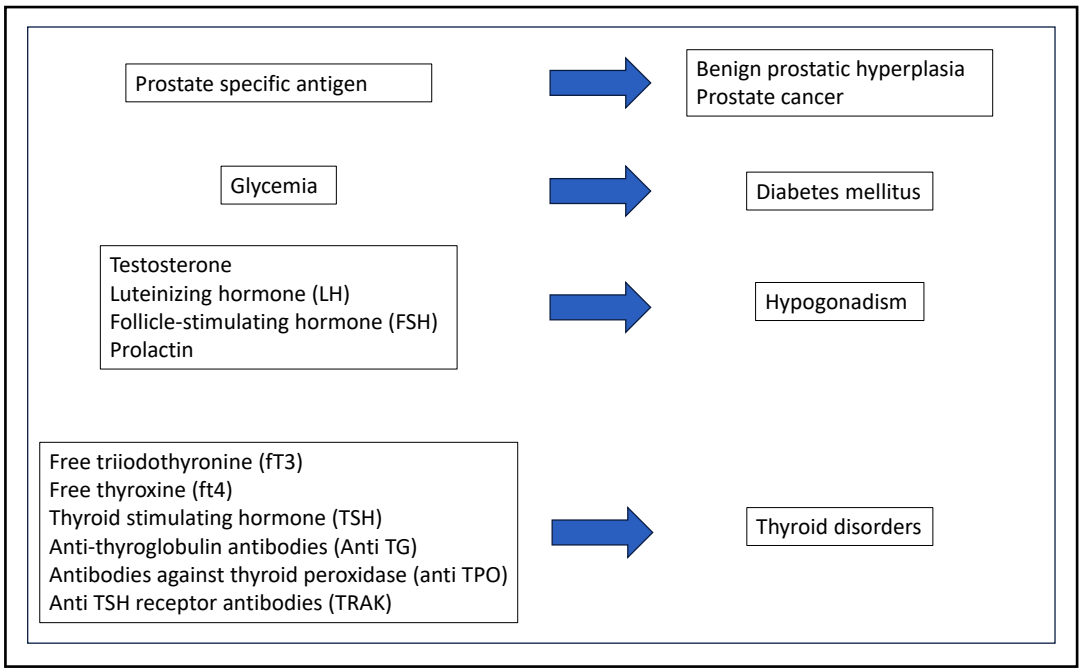

Fig. 3. Diagram of possible causes of ED. The left column shows the standard laboratory tests performed at the first examination of men in our department. On the right, possible causes of dysfunction are listed.

of SHIM scores was noted in both hyperthyroid and hypothyroid patients (Krassas *et al.* 2008).

In our study, correction of thyroid function led to restoration of erectile function in most patients. Therefore, we recommend screening for thyroid dysfunction in all men with ED (Fig. 3, recommended standard investigations and causes of ED). At the same time, however, it should be said that thyroid dysfunction is not a contraindication to the use of iPDE5 medications. Thus, these drugs should be taken at the beginning of the treatment of ED.

We provide values of free thyroxine and thyroid stimulating hormone (Tables 1, 2) that might be of interest for clinical practice. The standard laboratory tests that we do in our department are glucose, prostate specific antigen (PSA), testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH), anti-thyroglobulin antibodies (anti TG), antibodies against thyroid peroxidase (anti TPO), and anti TSH receptor antibodies (TRAK). We dare to recommend this procedure. Figure 3 shows the causes of ED diagnosed by these laboratory tests. These are mainly benign prostatic hyperplasia, diabetes mellitus, hypogonadism, and thyroid dysfunction.

Limitations of the study

One of the limitations of the study is the relatively small number of respondents. However, the results of the study are conclusive even in this sample. Another limitation is the fact that all the patients received the treatment, so a comparison sample was not available. However, our results can be compared on a standardized questionnaire before and after the treatment and compared with other studies.

CONCLUSIONS

It is important to emphasize that treating the primary cause of ED, in this case thyroid dysfunction, can lead to improved erectile function. Therefore, thyroid screening should be part of the diagnostic process in men with ED. If thyroid dysfunction is detected, appropriate treatment should be implemented and monitored for improvement in erectile function.

However, in some patients, concomitant treatment of ED may be necessary and need not be delayed until the thyroid dysfunction is properly treated. The iPDE5 preparations such as sildenafil, tadalafil, vardenafil, and avanafil are effective in the treatment of ED and can be started even before the treatment of thyroid dysfunction. However, each case should be assessed individually, and treatment plans should be proposed in accordance with the patient's medical condition and needs.

ED is very common in men with thyroid dysfunction. Treatment of this primary cause may affect normal erectile function. We recommend screening for thyroid dysfunction in all men with ED. Treatment of ED with iPDE5 agents need not be delayed and can be initiated prior to the initiation of treatment for thyroid dysfunction.

AUTHOR CONTRIBUTIONS

MB designed the research study. MB, PK, and KŽ performed the research. MB and EJ analyzed the data. MB and EJ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding authors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was performed in accordance with Declaration of Helsinki and the Krajská zdravotní, a.s. guidelines and regulations. The ethics of the research were approved by the Institutional Review Board of 315/1.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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