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Sexual function and depressive symptoms in young men with hypothyroidism receiving levothyroxine/liothyronine combination therapy

Funkcjonowanie seksualne i objawy depresyjne u młodych mężczyzn z niedoczynnością tarczycy leczonych terapią skojarzoną z zastosowaniem lewotyroksyny i liotyroniny

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Abstract

Introduction: Both overt and subclinical hypothyroidism are often accompanied by sexual dysfunction. Despite improving male sexual functioning, levothyroxine treatment does not always restore all its aspects. The aim of this study was to compare male sexual functioning and depressive symptoms between men with hypothyroidism receiving levothyroxine/liothyronine combination therapy and men receiving levothyroxine alone.

Material and methods: The study population consisted of 21 young levothyroxine-treated men with clinical symptoms of hypothyroidism, in whom serum thyrotropin and thyroid hormone levels were within the normal limits. In 11 of these patients, levothyroxine was replaced with levothyroxine/liothyronine combination therapy, while the remaining ones (n = 10) continued levothyroxine treatment. Beyond measuring serum levels of thyrotropin, free thyroxine, free triiodothyronine, and prolactin, before the beginning of the study and six months later, all enrolled patients completed questionnaires evaluating male sexual function (International Index of Erectile Function-15: IIEF-15) and assessing the presence and severity of depressive symptoms (Beck Depression Inventory-Second Edition — BDI-II).

Results: The study included 10 patients from each group. At baseline, erectile function, intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction, as well as the total BDI-II score did not differ between both groups. With the exception of an improvement in sexual desire, replacing levothyroxine with levothyroxine/liothyronine combination therapy did not affect sexual functioning and depressive symptoms.

Conclusions: The obtained results suggest that levothyroxine/liothyronine combination therapy has a relatively mild effect on sexual functioning in levothyroxine-treated men with normal thyrotropin and thyroid hormone levels experiencing clinical symptoms of hypothyroidism. **(Endokrynol Pol 2018; 69 (1): 16–22)**

Key words: *depressive symptoms, hypothyroidism, levothyroxine, liothyronine, sexual functioning*

Streszczenie

Wprowadzenie: Zarówno klinicznie jawnej jak i subklinicznej niedoczynności tarczycy często towarzyszy dysfunkcja seksualna. Pomimo poprawy, lewotyroksyna nie zawsze normalizuje funkcjonowanie seksualne w stanach niedoboru hormonów tarczycy. Celem badania było porównanie funkcjonowania seksualnego i objawów depresyjnych pomiędzy mężczyznami leczonymi zarówno lewotyroksyną i liotyroniną oraz mężczyznami otrzymującymi wyłącznie lewotyroksynę.

Materiał i metody: Uczestnikami badania było 21 mężczyzn leczonych lewotyroksyną odczuwających objawy kliniczne niedoczynności tarczycy, pomimo mieszczących się w granicach normy stężeniach TSH i wolnych hormonów tarczycy. U 11 z nich w miejsce lewotyroksyny włączono preparat skojarzony zawierający lewotyroksynę i liotyroninę, podczas gdy pozostałych 10 pacjentów kontynuowało leczenie lewotyroksyną. Poza oceną stężenia w surowicy: TSH, wolnej tyroksyny, wolnej trijodotyroniny i prolaktyny, w dniu rozpoczęcia badania i sześć miesięcy później, wszyscy pacjenci wypełniali kwestionariusze oceniające funkcjonowanie seksualne (IIEF-15), jak również obecność i nasilenie objawów depresyjnych (BDI-II).

Wyniki: W każdej grupie badanie ukończyło dziesięciu pacjentów. W warunkach wyjściowych funkcja erekcyjna, satysfakcja seksualna, jakość orgazmu, pożądanie, całkowita satysfakcja seksualna, jak również globalny wskaźnik BDI-II nie różniły się między grupami. Za wyjątkiem poprawy w zakresie libido, zastąpienie lewotyroksyny leczeniem skojarzonym nie wpływało na funkcjonowanie seksualne i objawy depresyjne.

Wnioski: Uzyskane wyniki sugerują, iż terapia skojarzona lewotyroksyną i liotyroniną ma stosunkowo niewielki wpływ na funkcjonowanie seksualne mężczyzn odczuwających objawy niedoczynności tarczycy pomimo prawidłowego stężenia TSH i hormonów tarczycy. **(Endokrynol Pol 2018; 69 (1): 16–22)**

Słowa kluczowe: *objawy depresyjne, niedoczynność tarczycy, lewotyroksyna, liotyronina, funkcjonowanie seksualne*

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Introduction

Impaired sexual functioning is frequently observed in men with thyroid disorders. Erectile dysfunction has been reported more frequently in men with either hypothyroidism or hyperthyroidism than in men with normal thyroid function [1, 2], but after adjusting for potential confounders only frank hyperthyroidism was found to be associated with erectile dysfunction [3]. Unlike erectile function, libido was more disturbed in men with hypofunction than in men with hyperfunction of the thyroid gland [1, 4]. Moreover, hypothyroidism often results in delayed ejaculation, while elevated thyroid hormone levels are frequently accompanied by premature ejaculation [1, 5, 6]. Finally, hypothyroidism was found to impair sperm count, morphology, and motility [7], while hyperthyroidism leads to low total sperm count, lineal motility defects and progressive motility abnormalities [8]. Much less is known about the effect of treatment on various aspects of sexual functioning in men with thyroid disorders. The restoration of normal hypothalamic-pituitary-thyroid axis activity in men with hypothyroidism and hyperthyroidism improved erectile functioning [1, 2]. In our recent study [9], levothyroxine administered to patients with hypothyroidism produced a beneficial effect on the domains of male sexual functioning, the activity of which was disturbed, and the strength of this effect depended on the degree of thyroid hypofunction and thyroid autoimmunity. However, in patients with overt hypothyroidism post-treatment erectile functioning was still worse than in healthy subjects.

Despite biochemical euthyroidism, some hypothyroid patients receiving levothyroxine treatment report persisting symptoms of clinical hypothyroidism. There are conflicting animal and human data indicating that the addition of liothyronine to levothyroxine therapy may reverse these symptoms and improve quality of life [10, 11]. However, in some studies the combination therapy was found to bring benefits to patients with a low quality of life [12, 13].

To the best of our knowledge, no previous study has investigated the effect of liothyronine, administered alone or in combination with levothyroxine, on sexual functioning. Therefore, this study was aimed at comparing whether replacing levothyroxine with levothyroxine/liothyronine combination therapy affects sexual functioning and depressive symptoms in young men experiencing clinical symptoms of hypothyroidism in whom serum thyrotropin levels were within the normal limits.

Material and methods

This research study included young males (18–45 years old) who, because of hypothyroidism were treated with levothyroxine (75–150 μg/daily) for at least six months before the study onset. To be admitted to the study, they had to meet the following inclusion criteria: (a) the presence of at least three clinical symptoms of hypothyroidism (easy fatigue, loss of energy, weight gain, cold intolerance, dry skin, muscle pain, inability to concentrate, or constipation) and (b) normal thyroid function, defined as serum thyrotropin levels above 0.4 but less than 4.5 mU/L, combined with serum levels of free thyroid hormones within the reference range.

The exclusion criteria were as follows: hypogonadism, prolactin-secreting tumours, diabetes, multiple sclerosis, prostatitis, psychiatric problems, cardiovascular disease, impaired renal or hepatic function, vasculogenic or neurogenic disorders known to impair sexual functioning, developmental or acquired anomalies of the male reproductive system, as well as previous operations that might have affected sexual function.

Before enrolment, all patients were informed about the benefits and harms of levothyroxine/liothyronine combination therapy and gave written, informed consent to participate in the study. The study protocol was approved by our institutional Review Board.

On the basis of patient preference, the participants were then allocated to one of two groups. In the first one (n = 11), levothyroxine was replaced with levothyroxine/liothyronine combination therapy (a preparation containing both levothyroxine and liothyronine in a weight proportion of 5:1 (a molar proportion of 4.2:1), while the second group (n = 10) continued treatment with the same daily dose of levothyroxine. Both levothyroxine/liothyronine combination therapy and levothyroxine alone were administered orally once daily, 30–60 minutes before breakfast for six months, without any changes in dosage throughout the study. Compliance with medication usage was assessed at each visit by interrogation and pill count.

All measurements were performed at baseline and at the end of the study. Venous blood samples were taken from the antecubital vein at 8 a.m. (12 hours after the last meal) in a quiet, temperature-controlled room (24–25°C). Serum levels of thyrotropin, free thyroxine, free triiodothyronine and prolactin were determined by direct chemiluminescence using acridinium ester technology (ADVIA Centaur XP Immunoassay System, Siemens Healthcare Diagnostics, Munich, Germany). All assays were performed in duplicate to minimise analytical errors.

Immediately after blood collection, all participants were asked to complete questionnaires assessing (a) their demographic characteristics, smoking, physical activity, education, occupation, stress exposure, the number of sexual partners, the number and duration

of marriages, as well as systolic and diastolic blood pressure; (b) sexual functioning for heterosexual men (the International Index of Erectile Function-15: IIEF-15); and (c) depression severity (the Beck Depression Inventory Second Edition: BDI-II).

IIEF-15, a reliable, cross-culturally valid and psychometrically sound measure of sexual functioning in men [14, 15], consists of 15 items divided into five collective sexual domains evaluating various dimensions of male sexual functioning: erectile function (questions 1 to 5 and 15), intercourse satisfaction (questions 6–8), orgasmic function (questions 9 and 10), sexual desire (questions 11 and 12), and overall satisfaction; from sexual activity (questions 13 and 14) in the last four weeks. Each answer is rated on a scale ranging from 0 to 5 or 1 to 5 (higher scores are suggestive of better sexual function). Domain scores are obtained from the sum of the items in each domain. Minimum domain scores are: 0 for intercourse satisfaction, and orgasmic function, 1 for erectile function, and 2 for sexual desire and overall satisfaction, while maximum ones are: 10 for orgasmic function, sexual desire and overall satisfaction, 15 for intercourse satisfaction and 30 for erectile function. Erectile dysfunction, defined as an overall erectile function score less than 26, is classified as: severe (no more than 10), moderate (11–16), mild to moderate (17–21), or mild (22–25) [14, 15].

The BDI-II is a 21-item self-report questionnaire with items rated on a four-point Likert scale from 0 (not present) to 3 (severe) [16]. The questions are adjusted to correspond with the diagnostic criteria for depressive disorders outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [17]. The total score, being the sum of the individual scores, can range from 0 to 63. Higher total scores indicate more severe depressive symptoms. Based on the overall BDI-II score, depressive symptoms are classified as minimal (0–13), mild (14–19), moderate (20–28), or severe (29–63) [16].

Because of the skewed distributions, values were natural-log transformed to achieve a normal distribution. Comparisons between the groups were performed using Student's *t*-test for independent samples. Student's paired *t* test was used to compare differences between the means of variables within the same group. Qualitative variables were compared using the χ^2 test. Pearson's *r*-tests were used to test correlations. A probability value of *p* less than 0.05 was regarded as statistically significant.

Results

One patient receiving levothyroxine/liothyronine combination therapy was withdrawn from the study because of adverse effects (tachycardia, irritability, tremor and heat intolerance). The study finally included 10 men receiving the combination therapy and 10 men treated with levothyroxine alone, and only the data of these patients were included in the final analyses.

At baseline, both groups of men were comparable with respect to age, smoking, education, physical activity, occupational activity, a type of work, the number of sexual partners, the number and duration of marriages, stress exposure, and blood pressure (Table I). The mean serum levels of thyrotropin, free thyroid hormones, and prolactin did not differ between the groups (Table II). There were no significant differences between both groups in baseline sexual functioning (Table III) and in depressive symptoms (Table IV). Mild to moderate and mild erectile dysfunction were found in one (10%) and three (30%) patients treated later with levothyroxine, as well as in one (10%) and three (30%) patients who were switched to the combination therapy. No cases of severe or moderate erectile dysfunction were reported.

In both treatment groups, the body mass index and systolic and diastolic blood pressure were similar on the first and in the last day of the study.

No changes in serum concentrations of all investigated hormones were observed in patients who continued levothyroxine therapy. Levothyroxine/liothyronine combination therapy increased serum levels of free triiodothyronine and tended to decrease ($P = 0.083$) serum levels of thyrotropin. The combination therapy did not affect serum levels of free thyroxine and prolactin. At the end of the study, levels of free triiodothyronine were higher, while levels of thyrotropin tended to be lower ($P = 0.092$) in patients receiving the combination therapy than in those receiving levothyroxine alone (Table II).

Continuation of levothyroxine treatment did not affect any aspect of male sexual functioning (Table III), and did not affect the total BDI score and the percentage of patients with total, mild, moderate, and severe depressive symptoms (Table IV). Replacing levothyroxine with levothyroxine/liothyronine improved sexual desire but did not affect erectile function, intercourse satisfaction, orgasmic function, and overall satisfaction. At the end of the study, both groups differed in sexual desire (Table III). The overall BDI-II score, as well as the percentage of men with total, mild, moderate, and severe depressive symptoms did not change throughout the study and at the end of the study did not differ between the groups (Table IV).

At study entry, erectile function, intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction inversely correlated with the overall BDI-II score (*r* values between –0.27 [$P < 0.05$] and –0.40 [$P < 0.001$]). Desire inversely correlated with serum thyrotropin levels ($r = –0.30$, $P < 0.05$) and serum

Table I. *Sociodemographic characteristics of the study population*
Tabela I. *Socjodemograficzna charakterystyka uczestników badania*

	Levothyroxine	Levothyroxine/ /Liothyronine
Number of patients	10	10
Age [years; mean (SD)]	35 (6)	36 (5)
Body mass index [kg/m^2; mean (SD)]	27.1 (2.3)	26.9 (2.5)
Smokers [%]/Number of cigarettes a day [n; mean (SD)]/Duration of smoking [months, mean (SD)]	30/12(5)/275 (53)	30/11(6)/284 (61)
Physical activity: total/once a week/several times a week/ once a month [%]	90/40/30/20	90/30/30/30
Primary or vocational/secondary/university education [%]	10/50/40	10/40/50
Occupational activity/blue-collar/white-collar/pink-collar workers [%]	100/50/50/0	100/60/40/0
Number of sexual partners [n; mean (SD)]	2.1 (1.1)	2.2 (1.0)
Number of marriages [n; mean (SD)]/ duration of marriages [months; mean (SD)]	1.0 (0.7)/65 (14)	1.1 (0.6)/70 (18)
Stress exposure [%, mean (SD)]	70	80
Systolic blood pressure [mm Hg; mean (SD)]	130 (15)	132 (12)
Diastolic blood pressure [mm Hg; mean (SD)]	82 (7)	83 (6)

Table II. *The effect of thyroid hormone supplementation on serum hormone levels in men*
Tabela II. Wpływ stosowania egzogennych hormonów tarczycy na stężenie hormonów w surowicy uczestników badania

	Levothyroxine	Levothyroxine/ Liothyronine
Thyrotropin [mIU/L; mean (SD)]		
Baseline	2.3 (0.8)	2.2 (0.7)
At the end of the study	2.1 (0.8)	1.7 (0.6)
Free thyroxine [pmol/L; mean (SD)]		
Baseline	16.5 (2.5)	16.7 (3.0)
At the end of the study	16.2 (2.8)	16.9 (3.1)
Free triiodothyronine [pmol/L; mean (SD)]		
Baseline	4.5 (0.7)	4.3 (0.6)
At the end of the study	4.4 (0.6)	5.1 (0.7)[a,b]
Prolactin [ng/mL; mean (SD)]		
Baseline	14 (5)	14 (7)
At the end of the study	12 (5)	10 (5)

[a]$P < 0.05$ vs. baseline value; [b]$P < 0.05$ vs. the other group of patients

prolactin levels ($r = –0.32$, $P < 0.05$), and positively correlated with serum thyroxine ($r = 0.24$, $P < 0.05$) and triiodothyronine levels ($r = 0.34$, $P < 0.05$). Moreover, the BDI-II score correlated with the body mass index ($r = 0.48$, $P < 0.001$), as well as with systolic ($r = 0.38$, $P < 0.01$) and diastolic ($r = 0.37$, $P < 0.01$) blood pressure. Combination therapy-induced changes in desire correlated with its effect on free triiodothyronine levels ($r = 0.31$, $P < 0.05$). No other correlations were found.

Discussion

This study shows for the first time that levothyroxine administered together with liothyronine exhibits a slightly better effect on sexual functioning than levothyroxine administered alone, and that levothyroxine-treated men with hypothyroidism coexisting with impaired desire may benefit more from levothyroxine/liothyronine combination therapy than from levothyroxine monotherapy.

Table III. *The effect of thyroid hormone supplementation on sexual functioning in men*
Tabela III. *Wpływ stosowania egzogennych hormonów tarczycy na funkcjonowanie seksualne uczestników badania*

Variable	Levothyroxine	Levothyroxine/ /Liothyronine
Erectile function [mean (SD)]		
Baseline	25.7 (2.8)	25.4 (3.7)
At the end of the study	25.5 (2.9)	26.1 (2.3)
Erectile dysfunction [%]		
Baseline	40	40
At the end of the study	40	30
Intercourse satisfaction [mean (SD)]		
Baseline	11.1 (2.4)	10.9 (2.0)
At the end of the study	11.2 (1.5)	11.7 (1.9)
Orgasmic function [mean (SD)]		
Baseline	6.9 (1.4)	7.0 (1.6)
At the end of the study	7.1 (1.6)	7.5 (1.2)
Sexual desire [mean (SD)]		
Baseline	7.0 (1.2)	7.2 (1.4)
At the end of the study	7.2 (1.3)	8.5 (0.8)[a, b]
Overall satisfaction [mean (SD)]		
Baseline	7.3 (1.4)	7.5 (1.3)
At the end of the study	7.4 (1.3)	7.9 (1.4)

[a]$P < 0.05$ vs. baseline value; [b]$P < 0.05$ vs. the other group of patients

Table IV. *The effect of thyroid hormone supplementation on depressive symptoms in men*
Tabela IV. *Wpływ stosowania egzogennych hormonów tarczycy na objawy depresyjne uczestników badania*

Variable	Levothyroxine	Levothyroxine/ /Liothyronine
BDI-II score [mean (SD)]		
Baseline	13.1 (3.1)	13.0 (2.7)
At the end of the study	13.2 (3.2)	12.3 (2.4)
depressive symptoms [n (%)]		
Baseline	3 (30)	3 (30)
At the end of the study	3 (30)	2 (20)
mild symptoms [n (%)]		
Baseline	3 (30)	3 (30)
At the end of the study	3 (30)	2 (20)
moderate symptoms [n (%)]		
Baseline	0 (0)	0 (0)
At the end of the study	0 (0)	0 (0)
severe symptoms [n (%)]		
Baseline	0 (0)	0 (0)
At the end of the study	0 (0)	0 (0)

The present findings are in contrast with our previous research, which showed that impaired erection was the only sexual dysfunction observed in men with subclinical hypothyroidism as well as a domain most seriously affected in patients with overt hypothyroidism [9]. Moreover, correlations between erectile functioning and thyrotropin and free thyroid hormone levels were stronger than for the remaining domains of IIEF-15 [9]. These differences may reflect the direct impact of chronic levothyroxine treatment (participants of the previous study were levothyroxine-naïve) and/or different inclusion criteria. The previous study included men with biochemical hypothyroidism, suggesting hypothalamic-pituitary-thyroid axis hypofunction. The presence of clinical symptoms in the participants of the present study suggests that at least some of them were characterised by either low tissue levels of thyroid hormones and/or by impaired thyroid hormone action at the level of the brain and/or peripheral tissues. This interpretation is in agreement with the results of animal studies [18, 19]. In thyroidectomised rats, levothyroxine restored tissue content of thyroid hormones only in a few tissues and structures, (the cerebral cortex, cerebellum, and brown adipose tissue). In order to restore euthyroidism in the remaining structures levothyroxine had to be administered together with liothyronine [18, 19].

In light of previous observations, the impact of levothyroxine/liothyronine combination therapy on male sexual functioning is undoubtedly interesting. Although no data are available for men, macroprolactinaemia and vitamin D insufficiency, representing mild endocrinopathies, were accompanied by isolated hypolibidaemia in women [20, 21]. In turn, more severe forms of prolactin excess and of hypovitaminosis D were associated with disturbances of other aspects of sexual functioning [20, 21]. What is more, irrespectively of gender, serum androgen levels correlated better with desire than with other domains of male and female sexual functioning [22–24]. This may suggest that discrete abnormalities in the production and/or metabolism of hormones playing a role in the regulation of sexual functioning secondary to tissue hypothyroidism may, at least partially, explain the beneficial effect of levothyroxine/liothyronine combination therapy in our study. In line with this hypothesis, hypothyroid rats were characterised by a decreased number and impaired morphology of Leydig cells [25], while thyroid hormone supplementation increased testicular testosterone production [25, 26]. Certainly, it cannot be ruled out that impaired desire may be a consequence of an effect on cardiovascular homeostasis and/or on nervous regulation of the sexual response [27, 28].

The molar proportion of thyroxine to triiodothyronine (4.2:1) in a preparation used in the present study reflects serum levels of both hormones. However, it is lower than the molar proportion of daily secretion of thyroxine and triiodothyronine (14:1) by the human thyroid gland [20, 29]. This fact suggests a relative excess of liothyronine, which, unlike levothyroxine, is characterised by a short half-life, leading to widely varying serum levels of this hormone [30]. Taking into account the presence of correlations between the impact of the combination therapy on desire and on free triiodothyronine levels, we may assume that an increase in triiodothyronine levels observed exclusively in men receiving both thyroid hormones contributes to the improvement in sexual functioning. Unfortunately, fluctuations in triiodothyronine concentrations may also explain why one patient had to prematurely terminate the study due to symptoms suggestive of hyperthyroidism.

Despite the presence of correlations between sexual desire and the overall BDI-II score at baseline and during treatment, combination therapy-induced improvement in desire was not accompanied by changes in depressive symptoms. Based on these results, it seems that depressive symptoms in young levothyroxine-treated men do not justify the introduction of levothyroxine/liothyronine combination therapy. The obtained results suggest that the beneficial association of an improvement in desire induced by levothyroxine/liothyronine and mood was probably counterbalanced by a neutral effect of other factors. In line with this explanation, the BDI-II score correlated with numerous other factors, including the body mass index and blood pressure, which remained unaltered during the study. Moreover, at least in the case of the body mass index, correlations with BDI-II were stronger than for desire. Certainly, it is possible that the combination therapy, at least at the daily doses used in the current study, does not fully restore adequate thyroid hormone levels in all brain structures playing a role in the regulation of well-being.

There are some limitations of this study, the most important of which are the small number of participants and its short duration. Moreover, although well-validated, as in the case of other self-report inventories, the utility of IIEF-15 and BDI-II questionnaires is limited by their subjectivity. Furthermore, the question of whether levothyroxine/liothyronine combination therapy affects sexual functioning in levothyroxine-naïve men with uncorrected hypothyroidism remains open. Finally, because of mandatory salt iodisation, iodine intake in Poland is adequate [31]. It cannot be ruled out that iodine deficiency may modulate the impact of thyroid hormone replacement on sexual functioning.

Conclusions

In conclusion, replacement of levothyroxine with levothyroxine/liothyronine combination therapy improved sexual desire in biochemically euthyroid men with persistent symptoms of hypothyroidism and this effect correlated with treatment-induced increase in triiodothyronine levels. The obtained results suggest that this form of supplementary treatment may be helpful in men with hypoactive sexual desire disorder and a history of hypothyroidism. Because of the small sample size, our findings should be confirmed in a larger study.

Conflict of interest

The authors declare no conflict of interest.

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