European Journal of Obstetrics & Gynecology and Reproductive Biology 234 (2019) 43–48

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Sexual function and depressive symptoms in young women with overt hyperthyroidism

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ARTICLE INFO

Article history:
Received 18 October 2018
Received in revised form 15 December 2018
Accepted 27 December 2018

Keywords:
Hyperthyroidism
Thyroid disease
Women's health
Depression

ABSTRACT

Objective: Despite high prevalence in a female population, surprisingly little is known about sexual functioning of women with thyroid hyperfunction. This study was aimed at assessing female sexual function and depressive symptoms in women with overt hyperthyroidism of autoimmune and non-autoimmune origin.

Study design: The study included three age-matched groups of young women inhabiting the Upper Silesia (a selenium-deficient and iodine-sufficient area): individuals with overt hyperthyroidism induced by Graves' disease (group A, n = 31), women with overt hyperthyroidism caused by toxic multinodular goiter or toxic adenoma (group B, n = 30) and women with normal thyroid function (group C, n = 34). Apart from measuring serum hormone levels, serum antibody titers and determining calculated parameters of thyroid homeostasis, all women completed questionnaires evaluating femalesexual function (FSFI) and depressive symptoms (BDI-II).

Results: The mean total FSFI score and all domain scores were lower while the overall BDI-II score was higher in both groups of women with overt hyperthyroidism than in the control group, and correlated with thyrotropin and free thyroid hormone levels, as well as with the SPINA-GT index. The FSFI score as well as domain scores for desire, arousal and sexual satisfaction were lower, while the BDI-II score was higher in group A than in group B. In group A, the total FSFI score, desire, arousal, sexual satisfaction and severity of depressive symptoms correlated with TRAb and TPOAb titers.

Conclusion: The obtained results suggest that excessive thyroid hormone production and thyroid autoimmunity have an additive effect on sexual functioning and mood.

Introduction

Hyperthyroidism is a condition resulting from excessive production of thyroid hormone by the thyroid gland [1]. Thyroid hyperfunction can be either overt (low serum thyrotropin levels and elevated levels of thyroxine and/or triiodothyronine) or subclinical (low serum thyrotropin levels and normal concentrations of thyroxine and/or triiodothyronine) [2]. The prevalence of overt hyperthyroidism is 0.5–0.8% in Europe, and 0.5% in the United States and the disease is characterized by strong female preponderance [3]. The most common cause of hyperthyroidism is Graves' disease, an organ-specific autoimmune disease characterized by the presence of autoantibodies that are able to stimulate thyroid follicular cells by binding to the thyrotropin receptor (thyrotropin receptor antibodies [TRAb]) [4,5].

Despite its high prevalence, surprisingly little is known about sexual functioning in patients with thyroid hyperfunction. Moreover, most studies concentrated on men who are less frequently affected by hyperthyroidism than women. Erectile dysfunction was frequently observed in men with thyroid hyperfunction [6,7]. Hyperthyroidism was found to be a common cause of acquired premature ejaculation [6,8,9], as well as was found to be associated with low total sperm count, lineal motility defects and progressive motility abnormalities [10]. After adjusting for potential confounders only overt hyperthyroidism (but not hypothyroidism) was associated with erectile dysfunction [11]. Hyperthyroidism impaired sexual desire but hypolibidemia was less expressed than in hypothyroidism [6]. Only two studies included women, providing contradictory results. Oppo et al. [12]

Abbreviations: BDI-II, Beck Depression Inventory-Second Edition; FSFI, Female Sexual Function Index; IU, international unit; SD, standard deviation; SPINA, structure parameter inference approach; TPOAb, thyroid peroxidase antibodies; TRAb, thyrotropin receptor antibodies.

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https://doi.org/10.1016/j.ejogrb.2018.12.035
0301-2115/

observed that all sexual domains scores were significantly reduced in women with hyperthyroidism, while Pasquali et al. [13], with the exception of desire, did not find any association between thyroid hyperfunction and sexual functioning. It remains also unexplained whether thyroid hyperfunction is associated with impaired mood. In some [14,15], but not all [16,17], studies, the presence of hyperthyroidism was accompanied by depressive symptoms.

Recently, we have found that mild hypothyroidism was associated with impaired female sexual functioning and impaired mood, as well as that sexual dysfunction was particularly pronounced in women in whom thyroid hypofunction was secondary to autoimmune thyroiditis [18]. To the best of our knowledge, no similar data are available for thyroid hyperfunction. Therefore, the primary study objective was to compare female sexual function and depressive symptoms in young women with overt hyperthyroidism of autoimmune and non-autoimmune origin and their peers with normal thyroid function. The secondary study objective was to evaluate whether sexual dysfunction and depressive symptoms are reciprocally interrelated, as well as to assess whether sexual dysfunction and depressive symptoms may be explained by differences in the degree of dysfunction of the hypothalamic-pituitary-thyroid axis, severity of autoimmune disease, calculated parameters of thyroid homeostasis and androgen status.

Materials and methods

Study population

The participants of the study (n = 95) were chosen among premenopausal women with recently diagnosed and previously untreated overt hyperthyroidism. The women were considered premenopausal if they were aged between 20 and 45 years and had regular menstrual bleeding within the previous 3 months. These patients were diagnosed in our Department because of weight loss, tachycardia, intolerance to heat, excessive sweating or diarrhea. Overt hyperthyroidism was defined as suppressed serum thyrotropin levels (below 0.1 mIU/L) coexisting with free thyroid hormone levels above the upper limit of the normal range (free thyroxine above 23 pmol/L and/or free triiodothyronine above 6.5 pmol/L). On the basis of TRAb titers and thyroid ultrasound imaging characteristics, women with overt hyperthyroidism were divided into two groups: women with Graves' disease (TRAb titers above 1.8 U/L) (group A, n = 31) and women with toxic multinodular goiter or toxic adenoma (group B, n = 30). The study also enrolled 34 age-matched women with the same clinical symptoms but with serum levels of thyrotropin and free thyroid hormones, as well as serum thyroid antibody titers within the reference range (group C).[1]

The exclusion criteria were as follows: coexistence of positive TRAb titers and thyroid nodules; other forms of thyrotoxicosis; subclinical hyperthyroidism; euthyroid sick syndrome; thyroid cancer; hyperprolactinemia; type 1 or type 2 diabetes; hypogonadism; adrenal disorders; osteoporosis; acute or chronic infection; impaired renal or hepatic function; cardiovascular, neurologic or psychiatric disorders; developmental or acquired anomalies of the female reproductive system, a past history of major pelvic surgery or of other operations that might have affected sexual functioning; sexual inactivity, as well as any pharmacotherapy.

The study protocol was approved by the local ethics committee and each woman gave a written informed consent before participation in the study.

[1] Assuming a power of 80% and a level of significance of 0.05, to detect a 20% difference in all aspects of female sexual functioning each study group must have included at least 28 women.

Laboratory assays

All blood samples were taken between 8.00 and 9.00 a.m. after a 12-h overnight fast in a quiet, temperature-controlled room (24–25 °C). Before blood collection, the participants had been resting in a quiet room for at least 30 min in the seated position. All measurements were performed in duplicate by staff blinded to patients' identity and clinical details. Before submission of our manuscript, we also retrospectively measured total testosterone and sex hormone-binding globulin levels in randomly selected stored serum samples of 15 women from group A, 14 women from group B and 16 women from group C. Serum levels of thyrotropin, free thyroid hormones (free thyroxine and free triiodothyronine), total testosterone and sex hormone-binding globulin, as well as titers of thyroid peroxidase antibodies (TPOAb) were determined by direct chemiluminescence using acridinium ester technology (ADVIA Centaur XP Immunoassay System, Siemens Healthcare Diagnostics, Munich, Germany). Titers of TRAb were measured by immunoassay with chemiluminescent detection (Immulite 2000XPi, Siemens Healthcare, Warsaw, Poland). The structure parameters of thyroid homeostasis were calculated using SPINA-Thyr 4.0.1 for Windows software. Jostel's thyrotropin index was calculated as follows: ln [thyrotropin] + 0.1345 x free thyroxine [19]. The SPINA-GT index was calculated using the following formula: β_T x (D_T + thyrotropin) x (1 + K_{41} x standard concentration of thyroxine-binding globulin + K_{42} x standard concentration of transthyretin x free thyroxine) / (α_T x thyrotropin) [20]. The SPINA-GD index was calculated as follows: β_{31} x (K_{M1} + free thyroxine) (1 + K_{30} x standard concentration of thyroxine-binding globulin) x free triiodothyronine/ (α_{31} x free thyroxine) [21]. Constants in the equations were as follows: $\beta_T = 1.1 \times 10^{-6}$/s, D_T = 2.75 mU/L, $K_{41} = 2 \times 10^{10}$ L/mol, standard concentration of thyroxine-binding globulin = 300 nmol/L, $K_{42} = 2 \times 10^{8}$ L/mol, standard concentration of transthyretin = 4.5 mmol/L, α_T = 0.1/L, $\beta_{31} = 8 \times 10^{-6}$/s, $K_{M1} = 5 \times 10^{-7}$ mol/L, $K_{30} = 2 \times 10^{9}$ L/mol and α_{31} = 0.026/L [20,21]. The free androgen index was calculated using the following formula: (total testosterone [nmol/L] x100)/sex hormone-binding globulin [nmol/L].

Questionnaires

Immediately after blood collection and the ultrasound, all women considered for enrollment were asked to fill in questionnaires assessing (a) their demographic characteristics, smoking, physical activity, education, occupational activity, stress exposure, the number of sexual partners, the number and duration of marriages, as well as the number of deliveries and abortions; (b) sexual functioning (Female Sexual Function Index, FSFI); and (c) the presence and severity of depressive symptoms (the Beck Depression Inventory Second Edition: BDI-II).

The FSFI is a 19-item standardized multidimensional self-reported measure of female sexual function in the last four weeks, with a specific focus on six domains: desire (questions 1 and 2), arousal (questions 3–6), lubrication (questions 7–10), orgasm (questions 11–13), satisfaction (questions 14–16) and pain (questions 17–19) [22,23]. Questions are scored on a 5-point or 6-point Likert scale ranging from 0 to 5 or 1 to 5 within each domain with the option of "no sexual activity" (0) for four of the domains (arousal, lubrication, orgasm, and satisfaction). The overall score, being the sum of the scores for each item multiplied by a domain factor (0.6 for desire, 0.3 for arousal and lubrication, and 0.4 for orgasm, satisfaction, and pain), may range from 2 to 36, with lower values indicating higher symptom burden. A total score of less than 26.55 is assumed to indicate sexual dysfunction [22,23].

BDI-II is a valid and reliable measure of depressive state, consisting of 21 items rated on a scale from 0 (not present) to 3 (severe) [24] and corresponding well to a clinical diagnosis of

depressive disorders outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [25]. All scores are added to yield the total BDI-II score, which can range from 0 to 63. Based on the overall BDI-II score, patients are classified as having no/minimal depression (0–13), mild depression (14–19), moderate depression (20–28), or severe depression (29–63) [24].

Statistical analysis

Although all potential participants underwent laboratory investigation and completed the questionnaires, only data of women meeting the inclusion and exclusion criteria, as well as data of the control subjects were statistically analyzed. Owing to the skewed distributions, all parameters were natural log-transformed to achieve normality and homogeneity of variance. The study groups were compared using analysis of covariance followed by Bonferroni post hoc tests after consideration of age, smoking, body mass index, waist circumference, marital status, education, occupational activity, type of work, profession, physical activity, stress exposure as well as blood pressure as potential confounders. Categorical variables were analyzed by χ^2test. Associations were calculated using the Pearson partial correlation coefficient (r). All *p*-values were corrected for multiple testing using Benjamini and Hochberg's false discovery rate. Differences were described as statistically significant if p-values after correcting for multiple testing were below 0.05.

Results

General characteristics of the study groups

At study entry, all groups were comparable with respect to age, smoking, education, occupational activity, a type of work, stress exposure, the number and duration of marriages, the number of deliveries, the number of abortions and the number of sexual partners. Systolic blood pressure was higher, while the body mass index, physical activity and diastolic blood pressure were lower in groups A and B than in group C (Table 1).

Expectedly, thyrotropin levels and Jostel's thyrotopin index were lower, while free thyroid hormone levels, the SPINA-GT index and SPINA-GD index were higher in groups A and B than in group C. Group A differed from the remaining groups of patients in serum titers of TRAb and TPOAb. Circulating levels of free triiodothyronine, as well as a value of the SPINA-GD index were higher in group A than in group B. Serum levels of testosterone and sex hormone-binding globulin were higher, while the free androgen index was lower in women with hyperthyroidism than normal thyroid function, as well as higher in women from group A than women from group B (Table 2).

Assessment of sexual function

Sexual dysfunction was found in 25 women (81%) from group A, 14 women (47%) from group B and 6 women (18%) from group C. The mean total FSFI score and all domain score were lower in women overt hyperthyroidism than in women with normal thyroid function. There were differences between groups A and B in the overall FSFI score and in domain scores for desire, arousal and sexual satisfaction (Table 3).

Assessment of depressive symptoms

The overall BDI-II score, as well as a percentage of women with total and mild depressive symptoms (but not with moderate and severe depressive symptoms) were higher in groups A and B than in group C, as well as higher in group A than group B (Table 4).

Correlations

The mean total FSFI score inversely correlated with the total BDI-II score (r=-0.41; $p = 0.0008$) and with the number of women with total and mild depressive symptoms (r values between -0.24; $p = 0.0416$ and -0.36; $p = 0.0084$). The overall BDI-II score inversely correlated with domain scores for sexual desire (r=-0.40; $p = 0.0002$), arousal (r=-0.36; $p = 0.0053$), lubrication (r=-0.32; $p = 0.0153$), orgasm (r=-0.29; $p = 0.0236$), sexual satisfaction (r=-0.34; $p = 0.0124$) and dyspareunia (r=-0.28; $p = 0.0317$). The total FSFI score and all domain scores positively correlated with: (a) serum levels of thyrotropin (r values between 0.24; $p = 0.0438$ and 0.39; $p = 0.0004$) and (b) the free androgen index (r values between

Table 1
Sociodemographic characteristics of the study population.

	Group A[1]	Group B[2]	Group C[3]	*p* value Group A vs. Group B	*p* value Group A vs. Group C	*p* value Group B vs. Group C
Number of patients	31	30	34	–	–	–
Age [years; mean (SD)]	31 (6)	30 (6)	30 (5)	0.52	0.47	1.00
Body mass index [kg/m^2; mean (SD)]	21.3 (2.0)	21.7 (2.3)	26.0 (3.7)	0.47	<**0.0001**	<**0.0001**
Smokers [%]/**Number of cigarettes a day** [n; mean (SD)]/**Duration of smoking** [months, mean (SD)]	23/11 (5)/ 82 (35)	27/10 (6)/85 (32)	29/9 (6)/79 (30)	0.77/0.48/0.72	0.63/0.15/0.71	0.86/0.51/0.44
Physical activity: total/once a week/several times a week/ once a month [%]	39/13/10/16[a]	43/10/13/20[a]	82/32/35/15	0.79	**0.03**	**0.01**
Primary or vocational/secondary/university education [%]	26/35/39	26/37/37	27/32/41	0.95	0.90	0.75
Occupational activity/Blue-collar/white-collar/pink-collar workers [%]	74/26/26/23	70/23/23/23	74/24/24/26	0.99	0.95	0.99
Number of sexual partners [n; mean (SD)]	2.2 (1.1)	2.0 (1.0)	2.1 (0.9)	0.46	0.69	0.68
Number of marriages [n; mean (SD)]/ **duration of marriages** [months; mean (SD)]	1.2 (0.8)/49 (17)	1.1 (0.6)/50 (19)	1.1 (0.7)/47 (18)	0.58/0.79	0.65/0.59	1.00/0.52
Number of deliveries [n; mean (SD)]/ **Number of abortions** [n; mean (SD)]	1.7 (0.8)/0.4 (0.4)	1.6 (0.7)/0.4 (0.4)	1.6 (0.6)/0.5 (0.4)	0.61/1.00	0.57/0.32	1.00/0.34
Stress exposure [%, mean (SD)]	81	83	82	0.93	0.95	0.97
Systolic blood pressure [mm Hg; mean (SD)]	134 (14)	132 (15)	115 (10)	0.46	<**0.0001**	<**0.0001**
Diastolic blood pressure [mm Hg; mean (SD)]	72 (6)	72 (5)	78 (7)	1.00	**0.0005**	**0.0002**

SD - standard deviation.
[1] women with overt hyperthyroidism due to Graves' disease.
[2] women with overt hyperthyroidism caused by toxic multinodular goiter or toxic adenoma.
[3] women with normal thyroid function.
[a] $p < 0.001$ *vs.* group C.

Table 2
Serum hormone levels, antibody titers and thyroid function tests in the study population.

Variable	Group A[1]	Group B[2]	Group C[3]	*p* value Group A vs. Group B
Thyrotropin [mIU/L; mean (SD)]	0.02 (0.01)	0.02 (0.02)	1.40 (1.05)	1.00
Free thyroxine [pmol/L; mean (SD)]	36.4 (6.2)	35.6 (5.9)	16.2 (2.8)	0.61
Free triiodothyronine [pmol/L; mean (SD)]	18.2 (5.8)	12.5 (4.0)	4.4 (1.1)	<**0.0001**
Thyrotropin receptor antibodies [U/L; mean (SD)]	5.5 (1.5)	0.1 (0.1)	0.1 (0.1)	<**0.0001**
Thyroid peroxidase antibodies [U/mL; mean (SD)]	211 (203)	16 (10)	14 (8)	<**0.0001**
Jostel's thyrotropin index [mean (SD)][4]	1.0 (0.2)	0.9 (0.2)	2.5 (0.3)	0.08
SPINA-GT index [pmol/s; mean (SD)][5]	382.70 (45.23)	374.29 (42.87)	3.65 (0.46)	0.46
SPINA-GD index [nmol/s; mean (SD)][6]	46.23 (5.62)	32.47 (4.83)	25.11 (3.56)	<**0.0001**
Total testosterone [nmol/L; mean (SD)][7]	2.43 (0.51)	2.05 (0.46)	1.68 (0.50)	**0.04**
Sex hormone-binding globulin [nmol/L; mean (SD)] [7]	115.8 (30.4)	80.1 (19.3)	53.2 (20.1)	**0.0009**
Free androgen index [%; mean (SD)][7]	2.10 (0.46)	2.56 (0.53)	3.16 (0.58)	**0.02**

SD - standard deviation.
[1] women with overt hyperthyroidism due to Graves' disease.
[2] women with overt hyperthyroidism caused by toxic multinodular goiter or toxic adenoma.
[3] women with normal thyroid function.
[4] Reference range: 1.3–4.1 [19].
[5] Reference range: 1.4–8.7 pmol/s [20].
[6] Reference range: 20–60 nmol/s [20].
[7] data of 15 women from group A, 14 women from group B and 16 women from group C.

Table 3
Female sexual function in the study population.

Variable	Group A[1]	Group B[2]	Group C[3]	*p* value Group A vs. Group B	*p* value Group A vs. Group C	*p* value Group B vs.Group C
FSFI score [mean (SD)]	26.42 (3.89)	28.85 (3.26)	32.03 (3.41)	**0.0106**	<**0.0001**	**0.0003**
FSFI score $\leq$ **26.55** [%]	81	47	18	**0.04**	**0.002**	**0.04**
Sexual desire [mean (SD)]	4.10 (0.59)	4.80 (0.76)	5.25 (0.62)	**0.0002**	<**0.0001**	**0.0114**
Sexual arousal [mean (SD)]	4.44 (0.57)	4.87 (0.72)	5.34 (0.64)	**0.0121**	<**0.0001**	**0.0075**
Lubrication [mean (SD)]	4.32 (0.68)	4.68 (0.80)	5.41 (0.53)	0.0629	<**0.0001**	**0.0001**
Orgasm [mean (SD)]	4.47 (0.79)	4.73 (0.65)	5.19 (0.52)	0.1664	<**0.0001**	**0.0026**
Sexual satisfaction [mean (SD)]	4.46 (0.64)	4.92 (0.75)	5.46 (0.58)	**0.0124**	<**0.0001**	**0.0019**
Dyspareunia [mean (SD)]	4.63 (0.71)	4.85 (0.72)	5.38 (0.60)	0.2343	<**0.0001**	**0.0021**

SD - standard deviation.
[1] women with overt hyperthyroidism due to Graves' disease.
[2] women with overt hyperthyroidism caused by toxic multinodular goiter or toxic adenoma.
[3] women with normal thyroid function.

Table 4
Depressive symptoms in the study population.

Variable	Group A[1]	Group B[2]	Group C[3]	*p* value Group A vs. Group B	*p* value Group A vs. Group C	*p* value Group B vs. Group C
BDI-II score [mean (SD)]	15.8 (3.8)	13.1 (3.6)	7.8 (3.2)	**0.006**	<**0.0001**	<**0.0001**
depressive symptoms [n (%)]	17 (55)	9 (30)	2 (6)	**0.04**	**0.001**	**0.03**
mild symptoms [n (%)]	16 (52)	8 (27)	2 (6)	**0.05**	**0.002**	**0.04**
moderate symptoms [n (%)]	1 (6)	1 (6)	0 (0)	0.98	–	–
severe symptoms [n (%)]	0 (0)	0 (0)	0 (0)	–	–	–

SD - standard deviation.
[1] women with overt hyperthyroidism due to Graves' disease.
[2] women with overt hyperthyroidism caused by toxic multinodular goiter or toxic adenoma.
[3] women with normal thyroid function.

0.27; $p = 0.0352$ and 0.39; $p = 0.0007$), as well as inversely correlated with: (c) serum levels of free thyroxine (r values between -0.23; $p = 0.0472$ and -0.41; $p = 0.0002$); (d) serum levels of free triiodothyronine (r values between -0.26; $p = 0.0388$ and -0.43; $p = 0.0001$); (e) the SPINA-GT index (r values between -0.27; $p = 0.0350$ and -0.37; $p = 0.0042$); and (f) the SPINA-GD index (r values between -0.23; $p = 0.044$ and -0.36; $p = 0.0079$). Moreover, there were also correlations between: (a) TRAb and the total FSFI score or domain scores for desire, arousal and sexual satisfaction (r values between -0.35; $p = 0.0092$ and -0.43; $p = 0.0003$); (b) TPOAb and the total FSFI score and domain scores for desire, arousal and sexual satisfaction (r values between -0.31; $p = 0.0187$ and -0.43; $p = 0.0002$); (c) TRAb and the overall BDI-II score (r=0.31, $p = 0.0216$); (d) TPOAb and the overall BDI-II score (r=0.34, $p = 0.0105$); (e) the overall BDI-II score and the body mass index (r=-0.30; $p = 0.0231$); (f) the overall BDI-II score and physical activity (r=-0.35; $p = 0.0082$); as well as between (g) the overall BDI-II score and systolic blood pressure (r=0.28; $p = 0.0482$). No other correlations were found.

Discussion

This study has shown that overt hyperthyroidism impairs all aspects of female sexual functioning, as well as leads to the development of depressive symptoms. The presence of correlations between various aspects of female sexual functioning and serum levels of thyrotropin and thyroid hormones, as well as between female sexual functioning and the SPINA-GT, reflecting

the maximum stimulated amount of thyroxine that the gland can produce in a given time-unit [20], indicates that the degree of sexual dysfunction depends on severity of thyroid hyperfunction. In opposition to the previous reports [12,13], the strength of our study is its population being a relatively homogeneous group of untreated women. Using very strict inclusion and exclusion criteria enabled us to reduce bias resulting from the presence of confounding risk factors, which may have potentially affected questionnaire results. Moreover, the impact of subjectivity on the obtained results was limited by the study protocol, according to which, at the time of completing the questionnaires, neither the individuals nor the investigators were aware of the thyroid status of the patient.

We can only speculate why hyperthyroidism makes women susceptible to sexual dysfunction. Thyroid hormone overproduction leads to the development of cardiovascular complications including systolic hypertension, congestive heart failure, impaired vascular elasticity of large and small arteries, atrial fibrillation and supraventricular tachycardia [26,27], which may disrupt blood flow through genital organs during sexual intercourse. Alternatively, the obtained results may be secondary to the effect of elevated levels of thyroid hormones on androgen production, protein binding and metabolism. Interestingly, in the stored serum samples obtained from participants of our study, although total testosterone levels were higher, the free androgen index was lower in women with hyperthyroidism than in women with normal thyroid function and correlated with the SPINA-GT index. Moreover, it is possible that a high risk of sexual dysfunction is associated with the development of neuromuscular complications of hyperthyroidism and polyneuropathy, the severity of which depends the degree of hyperthyroidism [28]. It cannot be also totally excluded that impaired sexual functioning reflected decreased physical activity, observed in patients with thyroid hyperfunction participating in our study.

However, the most important finding of our study was that unfavorable changes in sexual functioning were more pronounced if thyroid hyperfunction resulted from Graves' disease than from single toxic nodules or toxic multinodular goiter. This finding suggests that excessive thyroid hormone production and thyroid autoimmunity have an additive effect on sexual functioning. Two various mechanisms seem to explain the obtained results. According to the first one, differences between women with Graves' disease and with nodular thyroid disease should be attributed to various hormonal status of both groups of patients. In our study, groups A and B differed in serum levels of free triiodothyronine, as well as in the SPINA-GD index, reflecting the activity of deiodinases (mainly of type I deiodinase) outside the brain and other isolated compartments [20,21]. In line with this explanation, both serum triiodothyronine levels and the SPINA-GD correlated with the total FSFI score, as well as with domain scores for desire, arousal and sexual satisfaction. Interestingly, desire and, to a lesser extent, arousal are more dependent on proper hormone balance than other aspects of female sexual functioning [29]. The obtained results may have been partially explained by changes in free testosterone, playing the most important role in regulation of sexual behavior in women [30]. In our study, the highest levels of total testosterone, correlating with triiodothyronine levels, were observed in women with Graves' disease. This finding is in line with previous reports showing that liothyronine stimulated steroid hormone production in porcine follicular cells [30], was superior to levothyroxine in affecting steroid hormone production by bovine granulosa and theca cells [31], as well as decreased aromatase activity [32]. However, because of a simultaneous increase in sex hormone-binding globulin, the free androgen index, reflecting the pool of free testosterone [33], was lower in women with hyperthyroidism, particularly in women with Graves' disease, than in women with normal thyroid function.

According to the alternative explanation, differences in sexual functioning between patients with Graves' disease and nodular thyroid disease are secondary to thyroid autoimmunity. In line with this explanation, in women with Graves' disease (but not in the remaining study groups), the FSFI score and all domains scores correlated with TRAb and TPOAb titers. Moreover, a deteriorating effect of autoimmune thyroiditis on sexual functioning observed previously [18], was found even in women in whom serum levels of thyrotropin and free thyroid hormones were within the reference range. The lack of correlations between antibody titers and testosterone levels, as well as between antibody titers and the free androgen index suggests that an eventual impact of inflammation on sexual function does not seem to be mediated by steroid hormones.

Various aspects of female sexual functioning moderately correlated with the presence and severity of depressive symptoms. What is more, depressive symptoms were much more frequently observed in women with excessive thyroid hormone production, particularly if hyperthyroidism was secondary to Graves' disease. This finding indicates that either sexual dysfunction has an unfavorable effect on mood or is secondary to poor well-being observed in women with thyroid hyperfunction. Apart from its association with sexual disturbances, depressive symptoms may have been associated with low self-esteem of the participants of our study, resulting from weight loss, a fear of being negatively perceived by the local community, as well as from feeling of being ill. In line with these explanations, the overall BDI-II score negatively correlated with the body mass index and physical activity, as well as positively with systolic blood pressure. Finally, mood disturbances in women with thyroid hyperfunction may have resulted from the hyperthyroidism-induced changes in monoamine content in discrete brain regions [34]. In turn, a particularly high risk of the development of depression in women with Graves's disease may be a consequence of a proinflammatory state, found in this clinical entity [35] and having a negative impact on well-being [36]. This explanation is supported by finding correlations between the BDI score and antibody titers.

There are some limitations that should be kept in mind during interpreting the obtained results. Firstly, a small number of patients limits the statistical significance of the findings. Secondly, because the Upper Silesian population is characterized by low selenium status [37] and adequate iodine intake [38], it cannot be excluded that the impact of hyperthyroidism on sexual functioning and depressive symptoms may be different in women inhabiting selenium-sufficient and/or iodine-deficient areas. Thirdly, despite being well-validated, the utility of FSFI and BDI-II questionnaires (as other self-report inventories) is limited by their subjectivity. Finally, the study protocol does not allow to conclude whether similar effects are observed in postmenopausal women, not participating in our study.

In conclusion, overt hyperthyroidism has an unfavorable effect on female sexual functioning and mood and the degree of these disturbances depends on hypothalamic-pituitary-thyroid axis activity and the results of thyroid function tests. Sexual dysfunction and depressive symptoms are particularly pronounced in women with Graves' disease, correlating with its severity, which suggests that excessive thyroid hormone production and thyroid autoimmunity have an additive effect on sexual functioning and mood. Because of study limitations, the obtained results should be confirmed in a large clinical trial.

Conflict of interest

None declared.

Institutional approval

The study was approved by the Bioethical Committee of the Medical University of Silesia.

Acknowledgements

This work was not supported by any external sources of funding.

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