RESEARCH LETTER

Effect of free triiodothyronine concentration on the quality of life of patients treated with levothyroxine

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Introduction An association between thyroid insufficiency and disturbances of mood and cognition has been observed in clinical studies.[1] Moreover, even subclinical hypothyroidism has been shown to affect psychological well-being, while supplementation of levothyroxine (LT_4)—to improve patients' quality of life (QoL). In everyday clinical practice, we often observe patients who still present with symptoms indicating thyroid insufficiency (suggesting an inadequate dose of LT_4), despite having normal thyroid-stimulating hormone (TSH) levels.

In a community-based study, Saravanan et al[2] proved that the QoL in euthyroid patients treated with LT_4 was lower than that in the control group. Some authors have suggested that thyroid autoimmunity may influence patients' psychological well-being independently of thyroid function.[3] In addition, antithyroperoxidase (anti-TPO) antibodies may contribute to psychological morbidity in euthyroid individuals. On the other hand, we should consider the possibility that free thyroid hormones are directly responsible for mood.[4]

In view of recent studies showing that LT_4 therapy is associated with lower free triiodothyronine (FT_3) concentrations despite lower TSH levels, we may hypothesize that TSH monitoring does not fully reflect restoration of thyroid function in those patients.[5] The aim of our study was to examine whether an increase in the dose of LT_4, resulting in higher FT_3 levels in patients who initially presented with hypothyroid symptoms despite having normal TSH, helps relieve their symptoms.

Patients and methods This was a prospective case-control study. From March 2014 to September 2014, consecutive patients with hypothyroidism during a course of benign thyroid disease were enrolled to the study. All patients complained of symptoms characteristic of thyroid hormone insufficiency, despite having adequate TSH concentrations. Autoimmune thyroid disease was diagnosed when at least 1 antithyroid autoantibody titer was elevated (antithyroglobulin antibodies, anti-TPO antibodies) along with the presence of sonographic signs of chronic inflammation on a thyroid ultrasound.

The exclusion criteria were any comorbidities or use of medications that could interfere with the absorption or assessment of thyroid hormones or TSH (ie, cancer, insufficiency of the pituitary gland, heart, liver, and kidney diseases; medications: hormonal replacement therapy or oral contraceptives, proton pump inhibitors or histamine H_2-receptor antagonists, metformin, steroids, liothyronine, calcium, and iron preparations). TSH, free thyroxine (FT_4), and FT_3 levels were measured in every patient before and 4 to 6 months after increasing the dose of LT_4. Blood samples were drawn in the morning, before the ingestion of the patient's usual LT_4 medication. The QoL was assessed with the Polish version of the thyroid-specific questionnaire, ThyPRO. ThyPROpl was prepared according to standard methodology for translation of patient-reported outcomes.[6] Patients were asked to answer ThyPROpl before the dose of LT_4 was increased and 4 to 6 months after.

TSH, FT_4, and FT_3 levels were measured using the electrochemiluminescence technique (Roche Diagnostics GmbH, Mannheim, Germany; reference ranges: TSH, 0.27–4.2 mU/l; FT_4, 11.5–21.0 pmol/l; FT_3, 3.9–6.7 pmol/l). Anti-TPO antibodies were measured by a radioimmunoassay (Roche Diagnostics GmbH; reference range <34 IU/ml).

Statistical analysis A statistical analysis was performed with MedCalc version 15.8 (MedCalc Software bvba, Ostend, Belgium). Normality was analyzed by the Shapiro–Wilk test. Variables with normal distribution were compared using the paired samples *t* test. When data did not follow normal distribution, comparisons of analyzed

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TABLE 1 Scores of patients before (score 1) and after (score 2) the dose of levothyroxine (LT_4) was increased

Domain	Score 1	Score 2	*P* value
goiter symptoms	20.5 (10.8–42.7)	14 (4.6–25)	0.0013
hyperthyroid symptoms	37.5 (20.75–47.68)	19 (14.83–28.8)	0.0004
hypothyroid symptoms	50 (31.3–75)	38 (31.1–47.5)	0.0011
eye symptoms	31.3 (18.8–39.3)	19 (12.5–25)	0.0001
tiredness	57.1 (50–61.8)	35.7 (25–53.6)	0.0001
cognitive complaints	37.5 (16.7–54.3)	25 (8.2–34.4)	<0.0001
anxiety	50 (19.8–58.3)	29.2 (12.5–44)	0.0002
depressive symptoms	39.3 (32.1–53.6)	28.6 (18.73–40.3)	0.0003
emotional susceptibility	57.1 (50–61.8)	35.7 (25–53.6)	0.0001
impaired social life	12.5 (0–33.4)	6.3 (0–14.1)	0.0005
impaired daily life	29.2 (19.2–55.2)	16.7 (8–26)	<0.0001
impaired sex life	50 (12.9–75)	25 (4.7–38.4)	0.0001
cosmetic complaints	33.3 (4.2–50)	20.8 (3.2–34.4)	0.0021
overall quality of life	50 (25–75)	25 (0–50)	0.0001

A *P* value of less than 0.05 is considered statistically significant.

Data are presented as median (interquartile range).

parameters were performed with the Wilcoxon test. The strength of the relationship between analyzed parameters was measured with the Spearman's correlation coefficient test. Results were presented as medians and interquartile ranges (IQRs). All tests were performed 2-tailed and were considered as significant at a *P* value of less than 0.05.

Results A total of 423 patients underwent screening, of whom 46 reported complaints indicating thyroid insufficiency. Owing to the exclusion criteria, 37 patients were finally enrolled in the study, and 33 female patients were able to complete the study (median age, 51 years [IQR, 37.8–64 years]; age range, 18–75 years). The study flow chart is presented in Supplementary material online. At baseline, the median levels of TSH, FT_4, and FT_3 were 1.93 μU/ml (IQR, 1.1–2.29 μU/ml), 16.52 pmol/l (IQR, 15.58–18.35 pmol/l), 3.94 pmol/l (IQR, 3.74–4.29 pmol/l), respectively. These serum levels were achieved by the daily administration of 79 ±38 μg of LT_4. Eighteen women had Hashimoto thyroiditis, 11 were thyroidectomized, and 8 had been treated with radioiodine (median thyroid volumes were 9.4 ml [IQR, 7.2–12.6 ml]; 1.26 ml [IQR, 0.7–3.6 ml]; and 5.1 ml [IQR, 2.8–6.0 ml], respectively). The median anti-TPO antibody titer of Hashimoto patients was 156 IU/ml (IQR, 89–186 IU/ml).

The daily dose of LT_4 was increased to 110 ±40 μg (P <0.0001; paired t test). The median TSH level after increasing the dose of LT_4 was 0.50 μU/ml (IQR, 0.24–1.04 μU/ml); of FT_4, 19.76 pmol/l (IQR, 18.12–20.88 pmol/l); and of FT_3, 4.67 pmol/l (IQR, 4.38–5.11 pmol/l). After the dose increase, 10 of 33 patients had TSH levels below the reference range (0.1–0.26 mU/l), but their TSH levels were not completely suppressed.

There were significant differences in FT_3 levels (P <0.0001; Wilcoxon test), FT_4 levels (P <0.0001; paired t test), and TSH levels (P <0.0001; paired t test) before and after the increase of the LT_4 dose.

Four to six months after the increase in the LT_4 dose, scores improved significantly in hypothyroid symptoms, anxiety, cognitive complaints, tiredness, depressive symptoms, emotional susceptibility, impaired daily life, impaired social life, impaired sex life, cosmetic complaints, and goiter symptoms (**TABLE 1**).

The FT_3 concentration before and after the increase of LT_4 dose was inversely associated with several QoL outcomes (Spearman's correlation coefficient test): anxiety (r = –0.3; P = 0.02), depressivity (r = –0.3; P = 0.03), emotional susceptibility (r = –0.5; P = 0.0001), goiter symptoms (r = –0.3; P = 0.01), and tiredness (r = –0.4; P = 0.001). There was also a tendency for the association between the FT_3 level and impaired sex life (r = –0.3; P = 0.055). The FT_4 concentration was significantly associated with depressivity (r = –0.3; P = 0.02) and cosmetic complaints (r = –0.3; P = 0.006). The TSH level significantly correlated with depressivity (r = 0.25; P = 0.045) and cosmetic complaints (r = 0.3; P = 0.002).

Discussion There have been numerous studies that investigated the effect of thyroid dysfunction on patients' QoL, but only a few addressed the question about the possible effect of serum concentrations of free thyroid hormones on the well-being of euthyroid patients. We hypothesized that in "biochemically euthyroid" patients on LT_4 therapy reporting symptoms of thyroid gland insufficiency, an increase of LT_4 dose may improve their symptoms. To detect the differences, we used the ThyPROpl questionnaire, which is a comprehensive instrument specifically reflecting

all aspects of life affected by benign thyroid disorders. It was originally developed and validated by Torquil Watt in Denmark and has been translated into many languages.

Initially, patients' scores indicated that Tiredness and Emotional Susceptibility were the most affected domains, and the Impaired Social Life domain was the least affected. Our results suggested that the QoL of patients on LT_4 therapy is associated with FT_3 and FT_4 levels, and an increase in the concentrations of free thyroid hormones, particularly FT_3, leads to an improvement of the symptoms. Saravanan et al[7] observed the association of FT_4 levels with the patients' QoL measured by the General Health Questionnaire and Thyroid Symptoms Questionnaire (TSQ), but did not find any relationship with FT_3. It should be emphasized that we were able to detect changes in the patients' QoL because we used a sensitive, reliable, and validated questionnaire, ThyPRO, which covers a broad spectrum of patients' complaints caused by benign thyroid diseases. The TSQ used by Saravanan et al[7] has not been validated, and this may explain why the authors were not able to detect the effect of FT_3 on the QoL.

FT_3 is the active form of thyroid hormones; it is transported across the cell membrane in the central nervous system (CNS) by carriers: monocarboxylate transporter (MCT8) and organic anion-transporting polypeptide (OATP1C1).[8] MCT8 is mainly responsible for highly specific transport of T_3 into the intracellular compartment, regulating the bioavailability of T_3 in the CNS. The intracellular T_3 availability is also determined by the action of deiodinases, including D_3, which predominantly prevents excessive neuronal T_3 concentrations. D_2 produces T_3 from T_4, and T_4 is probably mainly transported by OATP1C1. T_3 binds to nuclear receptors (TRα and TRβ) and controls the expression of target genes. High expression of TRα and TRβ was found in brain regions responsible for mood and cognition (amygdala and hippocampus).[4] The exact mechanism of how thyroid hormones influence brain functions is still being investigated, but undoubtedly, an imbalance of thyroid hormones resulting from an inadequate dose of LT_4 has an adverse effect on patients' mood, cognition, and well-being. Interestingly, despite the increase in the dose of LT_4, no patients experienced symptoms of overdose, and the high tolerability of such therapy was reported by patients on the hyperthyroid scale.

In our study, the LT_4 dose escalation did not lead to a further increase in FT_3 concentrations in 1 patient. Recently, Midgley et al[9] also described this paradoxical effect, explaining that a higher LT_4 dose might inhibit the conversion efficiency in some patients. Identifying those patients is important in clinical practice, since they might be candidates for combined T_3/T_4 therapy.

Patients with concomitant coronary heart disease or arrhythmias are more likely to have several complaints. However, these complaints might be related to cardiovascular disease, rather than reflecting an inadequate dose of LT_4. Furthermore, in severe cases, low FT_3 concentrations might be explained by euthyroid sick syndrome. Therefore, in our opinion, dose escalation in patients with cardiovascular diseases is not plausible and reasonable.

It is still debatable whether low serum TSH concentrations in patients treated with LT_4 is associated with increased risk of cardiovascular disease or arrhythmias. In a population-based study, LT_4 therapy was safe in patients with low TSH levels (defined as 0.04–0.4 mU/l).[10]

Our results might be interpreted in a broader context of the role of TSH measurement in the monitoring of patients on LT_4 therapy. Recently, Hoermann et al[5,11] proved that both TSH and FT_3 levels are lower in LT_4-treated patients, suggesting that the reference range for TSH in this group of patients should be revised. Our findings provide some support for those postulates, and we suggest that the levels of free thyroid hormones should also be measured to assess the adequacy of replacement therapy, particularly in symptomatic patients. We have also previously reported the beneficial effect of such an approach among LT_4-treated women with Hashimoto thyroiditis diagnosed with idiopathic infertility.[12]

Limitation of the study The main limitation of our study is the sample size. However, it was a prospective study among patients without any relevant comorbidities, and we used a validated disease-specific questionnaire to measure changes in the QoL.

Supplementary material online Supplementary material online is available with the online version of the manuscript at www.pamw.pl.

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