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Evaluation of a three-month trial of thyroxine replacement in symptomatic subclinical hypothyroidism: An impact on clinical presentation, quality of life and adoption of long-term therapy

Evaluacija tromesečne supstitucije levotiroksinom u simptomatskoj supkliničkoj hipotireozi: uticaj na kliničku sliku, kvalitet života i prihvatanje dugoročne terapije

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Abstract

Background/Aim. Although subclinical hypothyroidism (SCH) is frequently a biochemical diagnosis, some symptoms and signs of overt disease may be present, influencing our decision to start the treatment with levothyroxine (LT4). The aim of this study was to examine the effect a 3-month LT4 treatment on clinical presentation and quality of life in symptomatic SCH with thyroid-stimulating hormone (TSH) < 10 mIU/L. We also considered whether treatment discontinuation additionally improves reliability of these findings. **Methods.** Clinical parameters (disease-specific score) and quality of life (Short Form-36 questionnaire) were measured in 35 patients with persistent symptomatic SCH (TSH 7.0 ± 2.1 mIU/L) before the intervention (LT4 substitution), 3 months after the euthyroid state had been achieved and 3 months after cessation of LT4 substitution. **Results.** The median of the Zulewski index significantly decreased after the treatment with LT4: 5.0 (4.0–7.0) vs. 3.0 (2.0–5.0) ($p < 0.001$) representing a reduction of symptoms. The most common ailments before the treatment were dry skin (71.4%), hoarseness (65.7%) and rough skin (54.3 %). After the treatment, there was a significant reduction in the frequency of constipation ($p = 0.004$), dry skin ($p = 0.022$), hoarseness ($p = 0.002$), decreased sweating ($p = 0.006$), and delayed Achilles reflex ($p = 0.002$). Quality of life was not changed significantly after LT4 treatment. In the group of 18 patients who discontinued the treatment, many symptoms and signs reappeared with the TSH increasing (6.8 ± 1.1 mIU/L): periorbital edema, constipation, weight gain, decreased sweating, slow motion and delayed Achilles reflex. The median of the Żulewski index after discontinuation of LT4 was 6.0 (4.0–9.0) ($p = 0.010$). Also, there was a statistically significant reduction in the general health score, and vitality, role emotional and mental health scores. **Conclusion.** Clinical score, based on symptoms and signs, is a sensitive and reproducible test for objective estimation of LT4 treatment effects in symptomatic SCH patients with TSH <10 mIU/L and supports individually adjusted treatment. Symptomatic SCH is not necessarily associated with a quality of life impairment that may be significantly improved by LT4 treatment. Changes in general health, vitality, mental health and emotional role after LT4 cessation suggest that some aspects of life quality can be affected by subtle variations in thyroxine availability.

Key words:
hypothyroidism; thyroxine; surveys and questionaires; withholding treatment; disease progression; quality of life.

Apstrakt

Uvod/Cilj. Mada je supklinički hipotiroidizam (SCH) najčešće biohemijska dijagnoza, neki simptomi i znaci manifestne bolesti mogu biti prisutni i uticati na našu odluku o započinjanju lečenja levotiroksinom (LT4). Cilj ove studije bio je da se ispita efekat tromesečne supstitucije LT4-om na kliničku sliku i kvalitet života u simptomatskoj SCH sa

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vrednostima tiroidnog stimulišućeg hormona (TSH) < 10 mIU/L. Takođe, razmatrano je da li prekid lečenja dodatno doprinosi pouzdanosti dobijenih nalaza. **Metode.** Klinički parametri (bolest-specifičan upitnik) i kvalitet života (Short Form-36 upitnik – SF-36) procenjivani su kod 35 bolesnika sa perzistentnom simptomatskom SCH (TSH 7,0 ± 2,1 mIU/L) pre intervencije (LT4), tri meseca nakon postizanja zadovoljavajućeg kvaliteta supstitucije i tri meseca nakon prekida lečenja. **Rezultati.** Medijana Zulewski indeksa bila je značajno snižena nakon lečenja LT4-om: 5,0 (4,0–7,0) vs. 3,0 (2,0–5,0) ($p < 0,001$), što je bilo praćeno smanjenjem tegoba. Najučestalija tegoba pre tretmana bila je suva koža (71,4%), nagluvost (65,7%) i gruba i perutava koža (54,3%). Nakon lečenja, zabeležen je značajan pad u učestalosti opstipacije ($p = 0,004$), suve kože ($p = 0,022$), nagluvosti ($p = 0,002$), smanjenog znojenja ($p = 0,006$) i produženog Ahilovog refleksa ($p = 0,002$). Kvalitet života nije značajno promenjen ovim tretmanom. U grupi od 18 bolesnika koji su prekinuli lečenje, sa porastom TSH (6,8 ± 1,1 mIU/L) brojni simptomi i znaci su se ponovo javili: periorbitalni edem, opstipacija, porast telesne mase, smanjeno znojenje, usporenost i produžen Ahilov refleks. Medijana Žulewski indeksa nakon prekida uzimanja LT4 iznosila je 6,0 (4,0–9,0) ($p = 0,010$). Takođe, došlo je do značajnog pada u skorovima SF-36 upitnika koji se odnose na opšte zdravstveno stanje, vitalnost, emocionalnu komponentu i mentalno zdravlje. **Zaključak.** Klinički skor baziran na simptomima i znacima je senzitivan i reproducibilan test za objektivizaciju procene efekata supstitucije LT4-om kod bolesnika sa simptomatskom SCH (TSH < 10 mIU/L), što govori u prilog individualnom pristupu u lečenju. Simptomatska SCH nije neophodno udružena sa oštećenim kvalitetom života, ali on može biti značajno poboljšan lečenjem. Promene u opštem zdravstvenom statusu, vitalnosti, mentalnom stanju i emocionalnoj ulozi nakon prekida lečenja sugerišu da neki aspekti kvaliteta života mogu biti zahvaćeni suptilnim promenama u nivou dostupnog tiroksina.

Ključne reči:
hipotireoidizam; tiroksin; ankete i upitnici; lečenje, prekid; bolest, progresija; kvalitet života.

Introduction

Subclinical hypothyroidism (SCH) is defined as normal serum free thyroxine (FT4) and elevated thyroid-stimulating hormone (TSH), suggesting mild thyroid hypofunction. Normal serum thyroid hormone levels may not adequately represent its effects on peripheral tissues in each individual with SCH [1]. In the majority of cases, SCH is a biochemical diagnosis, and mild symptoms and signs of hypothyroidism seem to be present in about 30% of patients [2]. Although the number and intensity of the symptoms may vary widely, when they are present in patients with TSH < 10 mIU/L, it is suggested that a 3-month trial of levothyroxine (LT4) therapy with the assessment of response can be carried out [3]. In the elderly, avoidance of the treatment is advised since such a mild increase of TSH is found to be associated with the greater longevity and unchanged quality of life [4–5]. Rationale for the trial approach in symptomatic patients younger than 65–70 years is based on many interventional studies which demonstrated an improvement of symptoms and potential benefit from LT4 treatment [6–10]. However, in a smaller number of randomized studies, no evidence for symptoms improvement was found [11, 12].

Generally, benefit of the treatment depends on the degree of thyroid failure in SCH and the risk for progression to overt hypothyroidism. Relevant factors for treatment decision even in the absence of symptoms are serum TSH values, thyroid antibody (tAb) levels, goitre size and comorbidities [3, 13]. Complaints of patients with mild hypothyroidism may be occasionally misleading, since they are similar to those of the general age-matched population. Prevalence of SCH in the general population is high, with a peak of 17% reported in women and older adults [14]. For this reason, it is useful to objectify effects of both SCH and its resolution in treated patients by the clinical scale for the hypothyroidism assessment. Health-related quality of life (HR-QOL) questionnaires may provide additional tool for the assessment of the need for therapy of SCH and the evaluation of its effects.

The aim of our study was to evaluate the reliability and relevance of present symptoms and signs of hypothyroidism in the group of SCH patients with TSH < 10 mIU/L, and their relationship to the quality of life on three different occasions: before treatment, after a 3-month trial with LT4 and after the treatment withdrawal. We also considered patients' opinion on the treatment benefit. We used general questionnaire of World Health Organization (WHO) for the subjective assessment of the health status, Short Form-36 (SF-36).

Methods

This prospective, open-label study was a part of a larger study that evaluated different effects of thyroxine substitution in SCH [15]. It included 35 consecutive symptomatic patients with persistent (3–6 months) untreated SCH with TSH < 10 mIU/L, caused by chronic autoimmune thyroiditis (positive tAbs and/or typical ultrasound scan). All patients had at least two symptoms of hypothyroidism. The exclusion criteria were: previous history of thyroid disease and treatment, conditions and drugs that affect thyroid, past or current serious medical diseases that might affect study parameters, smoking and patient's refusal to participate in the study. All criteria were configured to avoid the confounding effects of other factors on clinical presentation of SCH, quality of life in SCH and biochemical parameters in SCH. The group was ranked by disease-specific score for hypothyroidism clinical grading validated by Zulewski and al. [6]. The score includes 12 symptoms and signs (periorbital edema, constipation, weight gain, cold skin, paresthesia, dry skin, rough/flaky skin, hoarseness, decreased sweating, slow motion, hearing loss, delayed Achilles reflex); the maximum score is 12 and the sum is interpreted as follows: less than 3 points – clinically eu-

thyroid patients; 3–5 points – intermediate, more than 5 points – symptoms and signs of overt hypothyroidism [6].

Quality of life was assessed using a self-administered SF-36 questionnaire validated in Serbian language [16–17]. SF-36 provides data on general health status and well-being, both physical and mental. The higher total SF-36 score represents a better quality of life.

The study design included two phases. After the initial investigation, in the first phase, LT4 treatment was started in doses sufficient to normalize TSH. Three months after TSH normalization, all measurements were repeated. In the second phase, patients were asked to stop the treatment with LT4 and three months later, thyroid function, degree of hypothyroidism and quality of life were reassessed. The Ethics Committee of the Faculty of Medicine of the Belgrade University approved the study protocol. All patients gave informed consent before participating in the study.

Serum FT4 (12–20 pmol/L), FT3 (3.95–6.8 pmol/L), and TSH (0.3–4.0 mIU/L) levels were measured by the commercially available automated chemiluminescence system and associated kits (ACS: 180, Chiron Diagnostics, East Walpole, MA, USA); tAbs (TPO Ab and Tg Ab) were measured by RIA method (Inep, Belgrade, Serbia); normal level for TPO Abs is < 35 U/mL.

Data were analyzed using methods of descriptive and analytical statistics. To assess the significance of differences we used the Mc Nemar test for categorical variable and the paired *t*-test or Wilcoxon test for numerical variables. The Spearman's correlation coefficient was used to analyze the relationship between study variables. Central tendency was presented by mean and median and variability by standard deviation and interquartile range. The $p < 0.05$ was considered statistically significant. All statistical analyses were performed in SPSS 20.0 (SPSS Inc., Chicago, Illinois).

Results

Our study included 29 female and 6 male patients (82.9% vs. 17.1%, r4spectively), mean age 51.6 ± 15.4 years. The anthropometric data and thyroid status before and after therapy are shown in Table 1.

Doses sufficient to normalize TSH were ranged from 25 mcg to 75 mcg daily, with a mean dose of 50 mcg.

After correction of TSH, the median of the Zulewski index was reduced significantly ($p < 0.001$) from 5.0 (4.0–7.0) before the treatment to 3.0 (2.0–5.0) after the treatment, representing a reduction of symptoms and signs in the whole group of patients. A distribution of all three Zulewski index degrees is presented in Table 2. Before the treatment, most patients fell into intermediate and overt hypothyroidism groups. After the treatment, the highest frequencies were recorded in clinically euthyroid and intermediate categories.

LT4 treatment significantly reduced the percentage of patients with symptoms and signs of overt hypothyroidism and significantly increased the number of individuals classified as intermediate and euthyroid ones. The frequency of symptoms and signs of hypothyroidism before and after the substitution are shown in Table 3.

The most common ailments before the treatment were dry skin (71.4%) and hoarseness (65.7%). After the treatment, there was a significant reduction in the frequency of constipation ($p = 0.004$), dry skin ($p = 0.022$), hoarseness ($p = 0.002$), decreased sweating ($p = 0.006$), and delayed Achilles reflex ($p = 0.002$) (Figure 1). The frequency of weight gain was reduced, but that was close to statistical significance ($p = 0.057$).

Table 1

The anthropometric data and thyroid status before and after therapy with levothyroxine

Parameters	Before (n = 35) mean ± SD	After (n = 35) mean ± SD	*p*-value (*t*-test)
Body mass (kg)	72.6 ± 18.4	71.4 ± 16.6	0.030
Body mass index (kg/m^2)	25.5 ± 4.0	24.9 ± 4.0	0.320
Waist circumference (cm)	87.1 ± 16.0	85.7 ± 16.2	0.422
Free thyroxine – FT4 (pmol/L)	13.4 (12.5–14.7)	16.6 (15.4–18.8)	< 0.001*
Thyroid-stimulating hormone – TSH (mIU/L)	7.0 ± 2.1	3.0 ± 1.0	< 0.001
Free triiodothyronine – FT3 (pmol/L)	1.7 ± 0.2	1.6 ± 0.2	0.019
Thyroid peroxidase antibodies – TPO Abs (U/mL)	208.4 (16.2–903.1)	25.4 (0.1–87.5)	< 0.001*

SD – standard deviation; **p* – value from the Wilcoxon test.

Table 2

Zulewski index before and after therapy with levothyroxine

Zulewski index	Before (n = 35) n (%)	After (n = 35) n (%)
1–2 (clinically euthyroid patients)	4 (11.4)	13 (37.1)
3–5 (intermediate)	16 (45.7)	18 (51.4)
> 5 (symptoms and signs of overt hypothyroidism)	15 (42.9)	4 (11.4)

Table 3

The frequency of symptoms and signs asassessed by the Zulewski score before and after therapy with levothyroxine

Simptoms and signs	Before (n = 35) n (%)	After (n = 35) n (%)	*p*-value
Periorbital edema	17 (48.6)	13 (37.1)	0.388
Constipation	15 (42.9)	6 (17.1)	0.004
Weight gain	17 (48.6)	9 (25.7)	0.057
Cold skin	16 (45.7)	16 (45.7)	0.999
Paresthesia	15 (42.9)	13 (37.1)	0.774
Dry skin	25 (71.4)	16 (45.7)	0.022
Rough / flaky skin	19 (54.3)	18 (51.4)	0.999
Hoarseness	23 (65.7)	10 (28.6)	0.002
Decreased sweating	11 (31.4)	1 (2.9)	0.006
Slow motion	10 (28.6)	8 (22.9)	0.625
Hearing loss	11 (31.4)	6 (17.1)	0.125
Delayed Achilles reflex	11 (31.4)	1 (2.9)	0.002

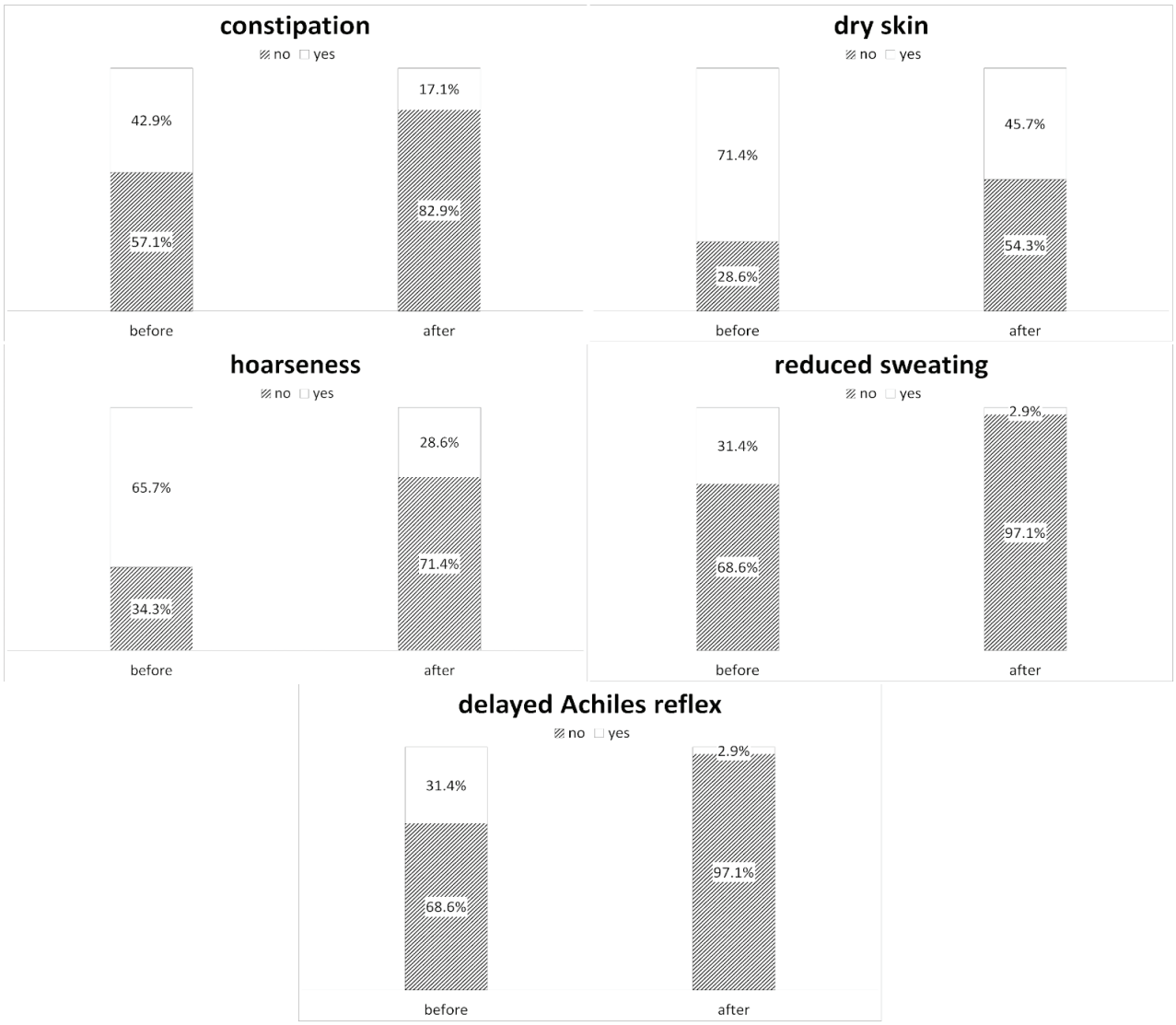

Fig. 1 – The frequency of constipation, dry skin, hoarseness, decreased sweating and delayed Achilles reflex in patients with subclinical hypothyroidism before and after therapy with levothyroxine.

There was no correlation among changes in the Zulewski index and changes of TSH, FT4, FT3, thyroid autoantibodies (TPO Abs) levels and average dose of levothyroxine (Table 4).

Table 4
The correlation of changes in the Zulewski index with changes in TSH, FT4, FT3, TPO Abs and the average dose of levothyroxine

Thyroid hormones	Zulewski index	
	r	*p*
Thyroid-stimulating hormone (TSH)	-0.105	0.550
Free thyroxine (FT4)	-0.057	0.752
Free triiodothyronine (FT3)	0.103	0.589
Thyroid peroxidase antibodies (TPO Abs)	0.330	0.061
Average dose of levothyroxine	0.165	0.343

***r* – Spearman's rank correlation coefficient.**

We also estimated the quality of life by SF-36 before and after LT4 substitution. The results are shown in Table 5.

Emotional roles improved the most after the therapy, the change being close to statistical significance ($p = 0.065$). The improvement of other scores was not significant.

In the phase 2, all 35 patients were asked to give their opinion about treatment benefit based on symptom correction and to stop the treatment in order to re-evaluate the effects of LT4 therapy. Among them, 17 patients were quite satisfied with the improvement of their symptoms and were not willing to stop the treatment. The remaining 18 patients accepted additional checking and continued the study. There were no statistically significant differences in any measured parameters between these two groups of patients. In the group of patients who discontinued treatment, many symptoms and signs reappeared (Table 6) with the increase of TSH (6.8 ± 1.1 mIU/L). Patients had no insight into their earlier test responses.

Table 5
The Short Form-36 (SF-36) questionnaire scores obtained before and three months after euthyroidism had been achieved

SF-36 domain	Before (n = 35) mean ± SD	After (n = 35) mean ± SD	*p*-value (*t*-test)
Physical functioning	62.4 ± 37.3	73.1 ± 27.6	0.364
Role-physical	64.3 ± 47.1	62.1 ± 48.6	0.842
Body pain	72.8 ± 23.9	74.5 ± 25.6	0.891
General health	53.9 ± 9.2	53.8 ± 8	0.837
Vitality	75.1 ± 24.7	83.3 ± 19.2	0.182
Social functioning	64.8 ± 26.8	67 ± 23.2	0.647
Role-emotional	47.6 ± 49.4	74.3 ± 45.1	0.065
Physical health	65.6 ± 21.0	69.3 ± 19.6	0.675
Mental health	63.7 ± 19.7	72.5 ± 17.9	0.106
Total SF-36 score	64.8 ± 21.4	71.6 ± 20.2	0.379

SD – standard deviation.

Table 6
Incidence of symptoms according to the Disease-specific questionnaire with clinical assessment scale for hypothyroidism before and after stopping therapy with levothyroxine

Symptoms from the questionnaire	Before (n =18) n (%)	After (n =18) n (%)	*p*-value
Periorbital edema	4 (23.5)	12 (70.6)	0.021
Constipation	4 (23.5)	12 (70.6)	0.039
Weight gain	1 (5.9)	7 (41.2)	0.008
Cold skin	6 (35.3)	7 (41.2)	> 0.999
Paresthesia	7 (41.2)	7 (41.2)	> 0.999
Dry skin	9 (52.9)	18 (51.4)	0.688
Rough / flaky skin	10 (35.3)	7 (41.2)	0.375
Hoarseness	6 (35.3)	12 (70.6)	0.109
Decreased sweating	0 (0)	7 (41.2)	0.016
Slow motion	4 (23.5)	11 (64.7)	0.039
Hearing loss	4 (23.5)	3 (17.6)	> 0.999
Delayed Achilles reflex	0 (0)	12 (70.6)	< 0.001

Table 7
The Short Form-36 (SF-36) questionnaire scores obtained before and after stopping therapy with levothyroxine

SF-36 domain	Before (n = 18) (mean ± SD)	After ± SD (n = 18) (mean ± SD)	*p*-value (*t*-test)
Physical Function	69.4 ± 30.9	67.1 ± 25.7	0.781
Role-Physical	52.9 ± 51.4	35.3 ± 49.3	0.257
Body Pain	73.9 ± 27.2	74.1 ± 21.6	0.972
General Health	52.9 ± 10.5	71.6 ± 25.4	0.007
Vitality	82.1 ± 21.0	66.8 ± 17.8	0.01
Social Functioning	69.4 ± 26.5	82.4 ± 13.9	0.11
Role emotional	68.6 ± 46.4	43.1 ± 45.3	0.033
Mental Health	83.5 ± 21.0	68.5 ± 23.7	0.023
Physical health	66.1 ± 22.8	62.9 ± 24.3	0.535
Mental Health (dimension)	71.3 ± 20.2	66.5 ± 22.7	0.379
Total SF-36 Score	69.2 ± 23.4	63.6 ± 24.8	0.325

SD - standard deviation.

Table 8
The Zulewski index and total Short Form 36 (SF-36) questionnaire score compared between patients who continued levothyroxine treatment and those who quitted it

Score	Treatment continued (n =17)	Treatment quitted (n = 18)	*p*-value (*t*-test)
Zulewski index	3.0 (2.0–5.0)	4.0 (3.0–6.0)	0.460
Total SF-36	73.9 ± 17	69.2 ± 23.4	0.493

Note: Results are present as median (range) or mean ± standard deviation.

After the therapy discontinuation, there was a statistically significant increase in the frequency of following parameters: periorbital edema, constipation, weight gain, decreased sweating, slow motion and delayed Achilles reflex. The median of the Zulewski index on LT4 treatment was 3.0 (2.0–5.0) and three months after the therapy discontinuation it was 6.0 (4.0–9.0). There was again a statistically significant change of the score ($p = 0.010$).

Therapy withdrawal was associated with a non-significant change in the total SF-36 score, but there was a statistically significant reduction in the general health score. The significant decrease was also recorded in vitality, role emotional and mental health scores. There were no significant changes in other parameters of the SF-36 questionnaire (Table 7). Also, there were no significant differences in the Zulewski index and the total SF-36 score between the patients who continued LT4 treatment and those who quitted it (Table 8).

Discussion

The treatment of SCH, especially a mild form, is still a matter of debate. In spite of very extensive research over the last two decades, the relationship between subclinical hypothyroidism, lipid metabolism and cardiovascular diseases is still controversial. Many studies showed that mild thyroid hypofunction may represent a risk factor for metabolic and cardiovascular diseases. The largest epidemiologic Colorado study confirmed a positive relationship between serum TSH and dyslipidaemia [2]. A larger number of observational studies demonstrated that the lipid profile is unfavorably changed in SCH compared to the number of those which showed that it is unchanged [18]. Previous analyses of small interventional studies did not confirm a significant influence of LT4 on lipid profile [12, 18]. One of the largest studies which demonstrated a significant reduction of total cholesterol and low density lipoprotein cholesterol (LDL-C) on LT4 was a randomized, double-blind, cross-over study by Razvi et al. [10]. A recent meta-analysis of randomized controlled trials showed that LT4 treatment has clear benefits on total cholesterol and LDL-C in SCH patients, including those with mild SCH [19].

The relationship of SCH and cardiovascular events was also a focus of many studies. Selmer et al.[20] demonstrated, in a large population study, that a risk of major adverse cardiovascular events in SCH is elevated. Analyses of prospective cohort studies showed that SCH is associated with increased coronary heart disease mortality and an increased risk of stroke and heart failure [21]. A double-blind, placebo-controlled study by Monzani et al. [22] showed the existence of functional disorder of the left ventricle which was resolved by LT4 treatment . After the already mentioned study of Razvi et al.[10] who demonstrated the beneficial effect of LT4 on cardiovascular risk factors and endothelial function, recent meta-analysis [23] has supported the positive influence of the treatment on the progression of carotid intima-media thickness, possibly by reducing risk factors for its occurrence in SCH . The limitation of this analysis is a small number of randomized controlled trials with the overall small number of respondents included, indicating that there is still a need for larger interventional studies to confirm those findings.

Although, there are controversies about the efficacy of LT4 treatment in SCH, the drug is widely used for potential beneficial effect on symptoms, protection from asymptomatic complications or prevention of the insidious development of

overt hypothyroidism. The decision to treat SCH is mostly based on patients' TSH and tAb levels, their complaints, quality of life and present co-morbidities [3]. Unfortunately, complaints of patients with mild hypothyroidism are similar to those of the general age-matched population. Some studies estimated frequency and consistency of complaints in a large number of patients with SCH. Among the many frequent symptoms, not specific to mild hypothyroidism alone, dry skin and poor memory were the most common [2, 6, 24]. Patients with SCH may tolerate their symptoms in different ways, which also may enhance the importance of the quality of life assessment.

Clinical evaluation by the standardized score used in this study provides information about the severity of thyroid dysfunction and allows better evaluation of treatment effects. Patients with SCH may be ranged as overt hypothyroidism according to the Zulewski score (> 5) and the therapeutic target could be based not only on TSH correction but also on clinical improvement (euthyroid state defined by the Zulewski score 1–2). The majority of patients in our study were classified as clinically intermediate and hypothyroid before and showed significant improvement after the treatment, with a large number of respondents reaching the clinically euthyroid state. Some studies support our results emphasizing that SCH patients treated with LT4 improved their score when regained normal TSH, even if they did not feel many symptoms at the beginning [6–8].

To provide better objectivity in the assessment of LT4 effects in this study, patients were tested on three different occasions with the time distance. About 57% of symptomatic patients in our study were interested to suspend LT4 use and re-evaluate the influence of treatment on their ailments. This group of patients did not significantly differ from the other in any measured parameters. The retested group showed consistency in reporting symptoms of untreated SCH and the same degree of severity was measured by the Zulewski index on these two occasions. Despite a lesser confidence in the benefit of LT4 therapy in this group of patients, objective scoring demonstrated significant improvement of symptoms.

The individuals in our study mostly reported problems related to the dry, rough skin and hoarseness. In the Colorado study including 2,336 subjects with SCH, many symptoms were significantly more often reported than in euthyroid subjects, but dry skin and cognitive impairment predominated [2]. After the treatment, frequency of constipation, dry skin, hoarseness, decreased sweating and delayed Achilles reflex were significantly reduced in our study. These results are in accordance with report from two randomized controlled trials that SCH subjects treated with LT4 had significantly greater improvement in general hypothyroid symptom scores than did subjects treated with placebo [7, 8].

A few very large studies provide insight into the influence of SCH on quality of life. LifeLines Cohort study on 9,491 participants showed no significant difference in HR-QOL scores of 973 subjects with SCH compared to euthyroid controls, but also compared to the groups with overt hypothyroidism and hyperthyroidism [25]. In a cross-sectional study which included women aged 18–75 years, SCH was neither associated with lower well-being nor impaired health-related quality of life [26].

As for LT4 treatment, there are many controversies about the success of the intervention to improve the quality of life and symptoms in SCH. In the study of Jorde et al. [11], LT4 treatment was not found to improve hypothyroid symptoms and cognitive and emotional functions in subjects with SCH compared to placebo group. But, in that study, the mean TSH level in the SCH group was 5.5 mIU/L, slightly higher than normal. Also, even before LT4 treatment there were no differences between SCH patients and healthy controls in symptoms related to hypothyroidism and neuropsychological dysfunction. A double-blind, randomized, placebo-controlled trial involving 737 adults who were at least 65 years of age (TRUST study) suggested that the treatment of older patients with subclinical hypothyroidism does not change significantly quality of life or hypothyroid symptoms [27]. We recruited for our study only symptomatic patients with persistent SCH, which were otherwise healthy nonsmokers. Even though the old age was not an exclusion criterion, our study did not cover patients with SCH older than 65 years eventually, due to exclusion criteria related to their co-morbidities and the use of drugs which might influence thyroid function or biochemical parameters analyzed and presented elsewhere [15].

In our study, emotional roles were mostly improved after therapy, but the change was just close to statistical significance. Total score and many other subscales of the SF-36 questionnaire (physical and social functioning, vitality, physical and mental health) showed only a trend toward improvement. The study of Razvi et al. [10] also showed partial improvement following LT4 treatment. Some patient-reported outcomes as tiredness related symptoms were significantly improved, some others, as all subscales of the SF-36 questionnaire (apart from role emotional) just tended toward the improvement. Quality of life measured by general questionnaires in patients with unselected SCH may not be significantly disturbed or improved by LT4 treatment in the large studies. Our patients, who had at least two recognizable sustained symptoms of hypothyroidism, also did not show significant changes of their quality of life on LT4 treatment. Still, patients who stop the treatment could experience worsening of their life quality in some aspects, according to our finding.

The main limitation of our study is a small number of patients and this finding need to be confirmed in larger population of symptomatic SCH patients. Also, the lack of significant differences between groups related to the measured variables such as the Zulewski index and SF-36 questionnaire scores indicates the influence of unmeasured confounders, e.g. long-term drug compliance, and the intensity, type and duration of symptoms.

Some data suggest that the physical and mental component scores of the SF-36 questionnaire are influenced by smoking status, co-morbidity, and body mass index (BMI) or waist circumference [28]. Our study does not include smokers and patients with co-morbidities and since there were no significant changes in BMI and waist circumference (WC) during the study, the potential changes of the SF-36 questionnaire scores could be attributed to LT4 treatment *per se*.

Conclusion

Clinical score based on symptoms and signs is a sensitive and reproducible test for objective estimation of LT4 treatment effects in symptomatic SCH patients with TSH < 10 mIU/L. The improvement in clinical score may not be associated with the patient's clear sense of treatment benefit. Measured by general health-related SF-36 questionnaire, symptomatic subclinical hypothyroidism is not necessarily associated with a quality of life impairment that may be significantly improved by LT4 treatment. Still, after withdrawal from the therapy, some aspects of life quality, such as general health, vitality, mental health and emotional role, may be significantly affected according to our findings.

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