Int. J Med. Pharm. Res. (P-ISSN: 2958-3675 | E-ISSN: 2958-3683)
Available on: https://ijmpr.in/

International Journal
of Medical and Pharmaceutical Research

ORGINAL ARTICLE **OPEN ACCESS**

Consistent outcomes from treating prolonged hypothyroid disorders with an administration of LT4 and LT3

Dipak Paudel[1], Tanisha Vinod[2], Tshetiz Dahal[3]

[1]Consultant Physician, Department of Internal Medicine, Civil Service Hospital, Kathmandu, Nepal
[2]Medical Student, Researcher, Manipal University College, Malaysia
[3]General Physician, Clinical Researcher, Lugansk State Medical University, Ukraine

OPEN ACCESS

***Corresponding Author**
Dipak Paudel
Consultant Physician, Department of Internal Medicine, Civil Service Hospital, Kathmandu, Nepal

Received: 12-01-2025
Accepted: 18-02-2025
Available online: 28-02-2025

A B S T R A C T

Objective: Although the effectiveness and adverse effects of long-term therapy are still mostly unknown, patients are increasingly using and seeking LT4/LT3 combination treatment for persistent hypothyroid symptoms. The purpose of this study was to assess the quality of life (QoL) and hypothyroid symptoms of the patient group that was affected by LT4/LT3 in a long-term manner.

Methodology: A cross-sectional study of 66 hypothyroid patients who had starting LT4/LT3 combination medication earlier was conducted. The patients were divided into two groups based on their current treatment: T3 responders, who were still getting LT4/LT3 treatment, and T3 non-responders, who had stopped LT3 treatment since it was not working. Hypothyroid symptoms were measured using a validated symptom score, and QoL was assessed using ThyPRO. The article presents a real-world study that shows dissatisfied people being treated at an outpatient clinic.

Results: The subjects started LT4/LT3 combination therapy 5.4 years ago, and their median age was 56. Twelve patients stopped LT3 treatment because it was ineffective, whereas fifty-four patients remained to undergo LT4/LT3 therapy. The QoL of the patients in the T3 responder group was similar to that of the background population. Remarkably, the T3 responder group's symptom scores were comparable to those of Nepalese women with overt hypothyroidism. In the T3 responder group, 38% of patients had thyroid stimulating hormone (TSH) levels below 0.4 mU/L, which suggests over-treatment.

Conclusion: Patients still had numerous symptoms even though LT4/LT3 medication was well-tolerated, had no adverse effects, and had a great quality of life.

Keywords: Hypothyroid, Hypothyroidism, Liothyronine, Quality of life.

INTRODUCTION

It is widely known that individuals treated with levothyroxine (LT4) frequently have chronic hypothyroid symptoms even after being deemed "well-treated" based on thyroid function blood tests (1, 2). Hypothyroidism is a prevalent condition. According to population-based research, the quality of life (QoL) is lower for 34% of hypothyroid patients treated with LT4 than for 26% of the general population. Furthermore, 12% of thyroid-healthy people experience depression, but 18% of LT4-treated patients do (3). Additionally, individuals treated with LT4 are more likely to receive disability benefits and earn less money (4). The main product of the thyroid gland is thyroxine (T4), which has a seven-day half-life. A deiodinase enzyme transforms T4 into triiodothyronine (T3), which is more powerful and has a shorter half-life of one day. Given that the thyroid and hypothalamic cells convert T4 to T3 more efficiently than cells in other organs, it is possible that some individuals receiving LT4 alone do not create T3 directly in the thyroid gland. This implies that even if a patient receiving LT4 has normal TSH levels on hypothalamic and pituitary examination, they may still have "tissue" hypothyroidism (2). It is debatable whether liothyronine (LT3) should be used in addition to LT4 to treat certain types of hypothyroid patients who have chronic symptoms.

Our team reported a blinded cross-over research in 2009 that assessed LT4/LT3 combination therapy in a subset of 59 hypothyroid patients with ongoing symptoms (all of whom had an s-TSH >20 at diagnosis). Using the SF-36 QoL score, it was found that patients receiving LT4/LT3 combination therapy had improved QoL scores on seven of the eleven scales. According to that study, 36% of patients had no choice, 15% preferred LT4 mono-therapy, and 49% preferred

combination therapy (P = 0.002) (5). Similarly, 48% of respondents chose LT4/LT3 combination treatment, 27% preferred LT4 mono-therapy, and 25% had no choice in a treatment preference analysis that included data from ve cross-over trials (n = 228) (1). There is currently no proof of the effects of LT4/LT3 combination therapy as measured by QoL and depression scores using SF-36, GHQ, BDI, POMS, or SCL-90 questionnaire items, according to a 2022 meta-analysis that comprised 18 research (6). Furthermore, LT4 and LT4/LT3 combination treatment did not differ in two recent high-quality randomised-controlled trials (7,8). But a sizeable portion of patients still experience chronic symptoms, which prompts doctors to employ LT4/LT3 combo treatment. 78% of participants in an online poll conducted by the patient association British Thyroid Foundation reported having a low quality of life (9). A small number of register-based studies have been conducted on the side effects and long-term effects of LT4/LT3 combo medication. However, they all have drawbacks, such as failing to show links between adverse effects and TSH levels or T3 dose (10, 11, 12, 13).

Additionally, there is currently a dearth of information assessing the treatment's long-term impacts on quality of life and hypothyroid symptoms, as well as a more thorough account of the patient's experience with the consequences of LT3 treatment. Thyroid specialists work to provide safe solutions to patients' requests for individualised care. Nevertheless, there are currently no tools available to determine whether people need treatment and what the best course of action is. In order to assess the long-term effects of LT4/LT3 treatment on quality of life and hypothyroid symptoms, estimate side effects (such as atrial fibrillation, osteoporosis, and general symptoms), and evaluate medication changes, this study sought to describe the patient group receiving LT4/LT3 combination therapy in a real-life study that shows dissatisfied patients as they are met in an outpatient clinic.

METHODS

Design

Patients who had previously started LT4/LT3 therapy were the subjects of the cross-sectional investigation. Testing if certain genetic variants may predict which patients would benefit from LT4/LT3 treatment was the main goal. In order to respond to this question, we were unable to include enough patients

Patients

Patients were gathered from Kathmandu Hospital's endocrinology department. They had started LT4/LT3 therapy with the intention of adhering to the ETA recommendations for LT4/LT3 combination therapy (1). After thoroughly discussing the nature and goal of every surgery, each patient provided written consent. The two populations listed below were used to recruit patients.

Population 1: Patients with persistent hypothyroid symptoms who started LT4/LT3 therapy between 2018 and 2024 were systematically gathered from the outpatient clinic at the Kathmandu Hospital's Department of Endocrinology. 46 of the 113 patients that were invited were invited.

Population 2: In the outpatient clinic in 2024, 34 people were invited to participate in a screening of patients who had received LT4/LT3 treatment for at least a year or who had attempted LT4/LT3 therapy without success (20 included). Prior to treatment, a persistently high serum TSH level was considered hypothyroidism. If a patient complained of ongoing symptoms (fatigue, impaired memory and cognitive function, joint and muscle pain, and weight gain), they were encouraged to begin combination therapy.

Comparing T3 responders with non-responders

The patients were divided into two groups based on their current treatment: T3 responders, who were still getting LT4/LT3 treatment, and T3 non-responders, who had stopped LT3 treatment since it was not working.

Prior blood tests and the patient's medical history

During the appointment, the patients responded to a questionnaire about their medication, potential adverse effects of LT3, and comorbid conditions (stress, depression, osteoporosis, and cardiac illness, including hypertension, arthritis, and cancer). Thyroid hormone replacement dosages and prior thyroid function tests (serum TSH and T4) were confirmed using an electronic diary system.

Scores for symptoms and quality of life

Patients completed questionnaires about their quality of life and hypothyroid symptoms during the appointment. sThyPRO was used to measure QoL (16, 17). We made advantage of ThyPRO's nine sub-scales. Each score was created by adding up pertinent items and converting them linearly to a range of 0–100, where 100 denoted the highest number of symptoms or effects on quality of life (17). Fig. 2 was created by comparing the QoL ratings of patients with a median age of 50 years (Q1–Q3: 37–62 years old) to historical data from the general population (18).

Score for symptoms

Additionally, we computed the alternative symptoms score, in which the existence of a symptom was coded as a yes/no binary variable (several items resembled those in the ThyPRO questionnaire). Thirteen hypothyroidism-related symptoms—such as fatigue, dry skin, mood swings, constipation, palpitations, restlessness, wheezing, globulus sensation, difficulty swallowing, hair loss, dizziness, and anterior neck pain—are included in this score, which has been previously validated (19, 20, 21). The percentage of patients with the symptom is used to display the results. To create Fig. 3, the symptoms of patients with overt hypothyroidism (n = 108) and euthyroid controls (n = 216) from the Dan Thyr research (19, 20, 21) were matched by age and gender.

Measurement of TSH Blood

TSH was obtained during the visit, and a Siemens Atellica®IM Analyser was used in the local laboratory to perform a two-site chemiluminescent immunometric test to measure plasma TSH (reference level: 0.4–4.8 mU/L). At TSH levels of 1.04 and 10.7 mU/L, the coefficient of variance was 2.5 and 5%, respectively. As is customary, an electrocardiogram was measured.

Analysis of statistics

Medians and ranges or n (%) are used to display the data. ANOVA or the chi-squared test were used to compare the groups. When appropriate, Bonferroni corrections were used.

Ethical Approval

The Kathmandu Hospital Ethics Committee accepted the study under the number NP-KH25342476.

RESULTS

Findings Population under study 147 patients from the Kathmandu Hospital who were identified from two specific cohorts were invited. When the patients were discharged from the outpatient clinic, 110 of them were registered as T3 responders (evaluated at least 12 months after starting LT4/LT3 treatment) and 37 as T3 non-responders. These included 66 patients (64 female) who started LT4/LT3 therapy between 2018 and 2024 (Fig. 1). The patients ranged in age from 28 to 77 years, with a median age of 56. They had been on LT4/LT3 therapy for a median of 5.6 years (range: 0.7–11) before to the trial. A total of 49 patients (74%) had comorbidities over the previous ten years: 17% had depression, 46% had a stressful time (34% required sick leave), 3% had osteoporosis, and 16% had cancer (breast, bladder, skin, uterus, renal, lung, colon, and melanoma) (Table 1). Of the patients included, six had undergone surgery, two had subacute thyroiditis, 41 had postpartum thyroiditis, and 41 had been initially diagnosed with spontaneous autoimmune hypothyroidism.

Figure 1 : 147 patients' flow diagrams who had previously started LT4/LT3 medication because of ongoing hypothyroid symptoms from LT4 mono-therapy.

Level of Education

Thirty-three had extensive education (more than 12 years), 25 had lesser education (10–12 years), and eight had fewer than ten years.

Tests for TSH

Prior to starting LT4, TSH most likely had subclinical hypothyroidism (22). Three had TSH levels < 0.01 mU/L, twelve had TSH levels between 0.1 and 0.4 mU/L, and fifty-one had TSH levels within the normal range after switching from mono-therapy to combined LT4/LT3 medication. One had an increased TSH, 25 of 66 (38%) had a TSH below the reference range (16 had an unmeasurable TSH), and 40 (60%) had a TSH within the normal range at the time of the research. One had an increased TSH, 25 of 66 (38%) had a TSH below the reference range (16 had an unmeasurable TSH), and 40 (60%) had a TSH within the normal range at the time of the research. Four patients (33%) in the T3 non-responder group and 23 patients (43%) in the T3 responder group showed evidence of a suppressed TSH.

LT3 treatment was stopped in these patients due to lack of effect. Back on LT4. †Data available on 46 patients, 43 of 54 LT4/LT3 treated patients and 3/12 LT4 treated patients. ‡One patient was initiating LT4 on TSH 3.4 but had during follow-up a low dose of LT4 TSH levels above the normal range. §The difference between T4/T3 ratio when initiating T3 and at the actual study ns (P = 0.99).

Table 1 : Data from a cross-sectional research conducted five years after 66 patients started LT4/LT3 combo medication.

	Patients treated with LT4/LT3 combination (*n* = 54)	LT4 treated patients (*n* = 12)*	*P* values
Diagnosis of hypothyroidism			
Year of initiating LT4 treatment	2008 (1985–2017)	2009 (1982–2018)	0.61
Serum TSH†	10.5 (3.4–150)‡	6.8 (6.6–17)	
Sex (F/M)	52/2	12/0	0.51
Shifting from LT4 to LT4/LT3 combination			
Year of shifting regime	2014 (2012–2018)	2013 (2013–2019)	0.58
TSH at new regime	0.74 (0.01–3.08)	0.84 (0.2–2.2)	0.96
Medication when initiating LT3 treatment			
LT4 dose (μg)	128.6 (71.4–250)	100 (75–200)	0.27
LT3 dose (μg)	7.5(5–20)	5.0(5–10)	**0.050**
LT4/LT3 ratio	16.7 (5–28.6)	17.1(10.0–20.0)	0.43
Cross-sectional study			
Age	56 (40–77)	58 (28–69)	0.81
BMI	29 (20–45)	27 (22–45)	0.69
TSH	0.61 (<0.01–5.28)	0.53 (0.07–3.16)	0.96
Time between T3 initiation and cross-sectional study (years)	5.4 (1.7–10.9)	5.9 (0.71–3.4)	0.80
Medication at cross-sectional study			
T4 dose (μg)	100 (50–200)	100 (50–171.4)	
LT3 dose (μg)	8.75 (2.5–35)		
LT4/LT3 ratio	13.4 (3–37)§		
Comorbidity within 10 years before the cross-sectional study			
Depression	7 (13%)	4 (33%)	0.09
Stress	28 (52%)	3 (25%)	0.50
Stress needing sick leave	20 (37%)	3 (25%)	
Known osteoporosis	2 (4%)	0	
Hypertension	5 (9%)	5 (42%)	0.005
Cancer	9 (17%)	1 (8%)	0.12

Data

are presented as either n (%) or the median (range). Statistical significance (P <0.05) is indicated by bolded values.

Medication

The median LT4/LT3 ratio was 17, with the LT3 dose at the start of the LT4/LT3 combination treatment being 7.5 μg (range: 5–20 μg).

ThyPRO's evaluation of QoL

When adjusted for multiple testing, the difference between T3 non-responders and T3 responders was not statistically significant, but overall, QoL and depression measures indicated a tendency toward lower QoL in the former group (Table 2). QoL was comparable to and significantly better than historical data on LT4-treated patients with persistent complaints (15), when comparing T3 responders to historical data on a sample of the general population with similar age (18). Refer to Figure 2.

QoL was comparable to and significantly better than historical data on LT4-treated patients with persistent symptoms (15) when comparing T3 responders to historical data on a sample of the general population with comparable age (18). Refer to Figure 2. Better scores were observed in the anxiety score (10 vs 18, P = 0.010), emotional susceptibility score (13 vs 21, P = 0.021), and ThyPRO composite score (17 vs 23, P = 0.044) in the T3 responders of those with a TSH <0.4 mU/L (38% of the patients) compared to TSH ≥0.4 mU/L
However, these differences were not statistically significant when controlling for multiple testing.
Still receiving combo treatment. † Returning to LT4, P < 0.05 indicates statistical a-significance.

ThyPRO	Responders (*n* = 54)*	Non-responders (*n* = 12)†	*P* values‡
Overall QoL impact	25 (0–75)	44 (13–94)	0.036
Tiredness	42 (8–92)	67 (8–92)	0.092
Cognitive complaints	21 (1–85)	29 (7–52)	0.50
Anxiety	10 (1–71)	18 (1–56)	0.58
Depression	14 (0–71)	26 (0–71)	0.063
Emotional susceptibility	21 (7–77)	32 (7–68)	0.15
Impaired social life	0 (0–50)	0 (0–25)	0.86
Impaired daily life	15 (0–62)	19 (0–89)	0.17
ThyPRO composite score	20 (3–73)	27 (3–55)	0.094

Table 2 : QoL measured by ThyPRO for 66 patients initiating LT4/ LT3 combination therapy and participating in a cross-sectional study 5 years later.

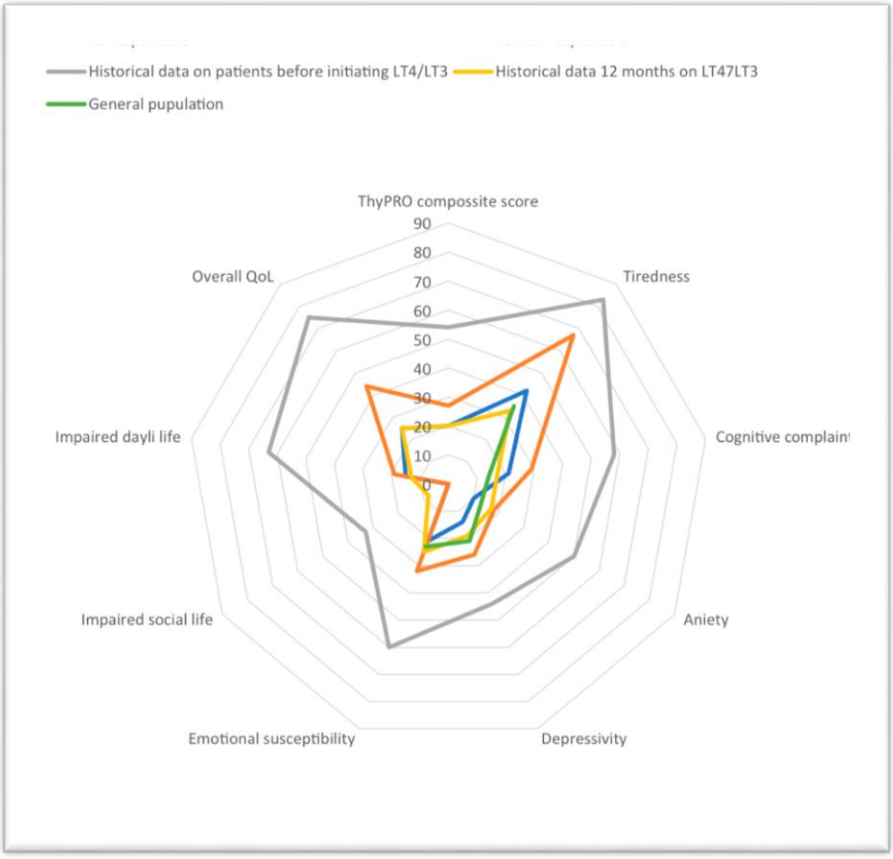

Figure 2 : The ThyPRO score, which measures quality of life, was assessed 5.4 years after starting LT4/LT3 combination therapy. Comparing historical data before starting treatment (n = 23 gray line), 12 months after starting treatment (yellow line) (15)), and the general population (n = 739 (18)) (light blue line) to T3 responders (n = 54, dark blue line) and T3

Symptoms	Responders (*n* = 54)*	Non-responders (*n* = 12)†	*P* values‡
Tiredness	89	100	0.092
Dry skin	78	92	0.27
Shortness of breath	60	40	0.24
Globulus	53	33	0.20
Restlessness	43	58	0.32
Dizziness	43	50	0.64
Hair loss	41	50	0.56
Mood lability	39	50	0.48
Constipation	33	60	0.28
Palpitation	31	58	0.08
Difficulties swallowing	33	25	0.58
Wheezing	20	8	0.33
Anterior neck pain	8	17	0.32

non-responders (discontinuing LT3 treatment due to lack of effect) (n = 12, orange line).

Still on combination. †Back on LT4 due to no effect of LT4/LT3. ‡P < 0.005 is statically significant

Table 3 : 66 patients who started LT4/LT3 combination therapy and took part in a cross-sectional study four years later had symptoms. The percentage of those who report positive symptoms is how the data are displayed.

The hypothyroid symptoms score using to evaluate symptoms.

Numerous hypothyroid symptoms were still present in both T3 responders and non-responders. Both T3 responders and T3 non-responders reported symptom scores that matched those of untreated individuals of comparable age with overt hypothyroidism (TSH >10) (19) when compared to data on recently diagnosed hypothyroidism (Table 3 and Fig. 3). Significantly higher scores with TSH <0.4 were observed in terms of mood lability when comparing the symptom scores of the T3 respondents, TSH <0.4 mU/L versus TSH ≥0.4. This was because 14% of the group with suppressed TSH answered "yes," compared to 55% in the group with TSH within the normal range (P = 0.003), and there was a tendency in the restlessness score (P = 0.03).

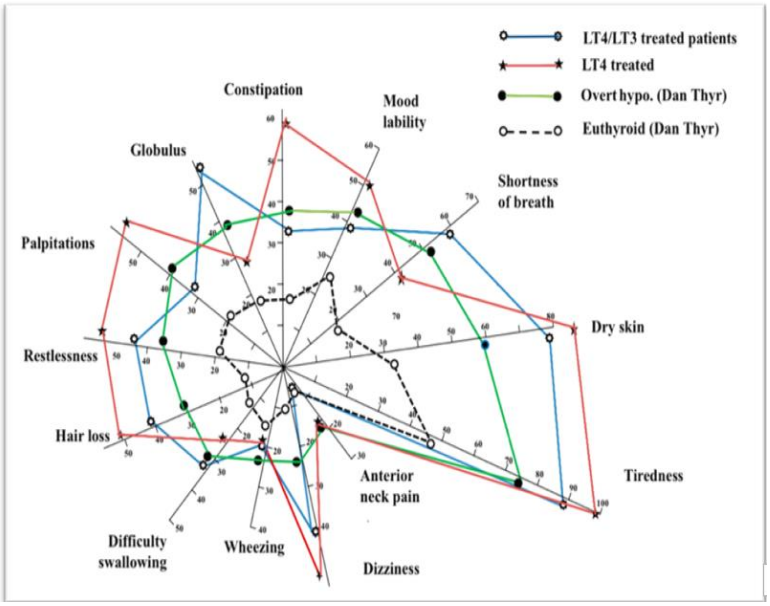

Figure 3 : Over-treatment, defined as TSH levels below 0.4 mU/L Of the patients included in this trial, 38% (n = 25 of 66) were over-treated, defined as having a blood TSH level below 0.4 mU/L. Serum TSH levels were less than 0.1 mU/L in 24% (n = 16) of individuals.

Score for symptoms: T3 responders (n = 54, blue line) and T3 non-responders (discontinuing LT3 treatment due to lack of effect) (n = 12, red line) compared to untreated clinical hypothyroidism (TSH >10 mU/L) (n = 108) in a matched patient's group (green line) and euthyroid controls (n = 216) from the Dan Thyr (dotted line) (19, 20, 21).

Adverse consequences

During the study visit, one patient showed previously unidentified atrial fibrillation, and two patients had prior diagnoses of osteoporosis. None of the T3 respondents reported experiencing any heart, gastrointestinal, weight, sleep, or mental health negative effects from LT3 treatment. None of the individuals in the T3 non-responder group had discontinued their medication because of adverse effects.

DISCUSSION

Eighty-two percent of hypothyroid patients with chronic symptoms who had previously switched from LT4 mono-therapy to combined LT4/LT3 therapy remained on combination medication after starting it, according to the current cross-sectional study. 38 percent were over-treated. The responders had a high quality of life, but they still had a lot of symptoms, and the treatment was well tolerated with no negative side effects. LT4/LT3 therapy is utilized by endocrinologists worldwide and sought by patients, despite the lack of concrete proof of improved quality of life associated with it (2). Data from 28 nations and 17,247 physicians who treat hypothyroid patients were included in the Thesis study's online European questionnaires. Forty percent of them said they would think about treating patients with chronic symptoms with a combination of LT4 and LT3. Significant variations existed between nations, and physicians in high-BNP nations were more likely than those in low-GNI nations to employ LTL4/LT3 therapy (23). Therapy is frequently started in response to patient requests for LT4/LT3 combined treatment. A qualitative study from the USA among ATA members describes the contradiction between guidelines and patient demands, revealing that patients' preferences were reported as a barrier to therapy following guidelines recommending against the use of LT4/LT3 combination treatment (24). In a prior study, our team discovered that the likelihood of receiving LT3 or desiccated thyroid extract treatment nearly quadrupled for those with the highest educational attainment relative to those with the lowest (25). T3 respondents in our study had QoL scores that were comparable to those of the general population at the same age (see Fig. 2). Another surprising finding was that both T3 non-responders and T3 responders exhibited high hypothyroidism symptom scores. Comorbidity was previously proven to be a strong predictor of which subclinical hypothyroid patients experienced symptoms (21). Patients with subclinical hypothyroidism did not experience a greater burden of symptoms than euthyroid patients in the absence of comorbidity. The patients in this study reported a significant burden of symptoms, likely due to subclinical hypothyroidism, and may be strongly self-selected for combination therapy because of other conditions (greater comorbidity). The addition of LT3 to LT4 therapy may not ameliorate other disorders.

It appears that the symptoms in both responders and non-responders are unrelated to LT3 treatment because the symptom scores were comparable to those of untreated, overtly hypothyroid women in the same age range. Only around 60% of hypothyroid individuals (26) have normal TSH following medication, according to numerous research. Under-treatment is typically the main issue, however in this study, 38% of patients received excessive treatment. Despite the goal of adhering to European criteria (1), patients are frequently over-treated. The patient health questionnaire-15 (PHQ-15) was used in a recent study to assess an online, worldwide cross-sectional survey of people with self-reported, treated hypothyroidism (n = 3516). They evaluated the prevalence of somatisation, which was once classified as somatic symptom disorder (SSD) and was linked to distress and excessive healthcare resource utilization.

They discovered that the prevalence of pSSD, which is defined as a score of >10 on the PHQ-15, was 58.6% in this community as opposed to 4–25% in reference populations (27). The high frequency of symptoms may be explained by this. Comparing the research is challenging, though, because our patient group had a high prevalence of comorbidities, particularly stress, which may possibly have an impact. Increased awareness of hypothyroid symptoms in this cohort may potentially be a contributing factor to the high prevalence of these symptoms without decreased QoL. The adverse effects of LT3 therapy have not been thoroughly studied. 11,147 LT3 users (9614 on LT4 and LT3) and 564,314 LT4-only users were compared in a large Swedish register-based study. The median LT3 dose was 17 μg (range: 3–26). The study's limitations include the relatively youthful patients in the LT3 usage group (median age of 46) and a 3-year follow-up (12). No changes were observed in cancer or all-cause mortality. According to a retrospective Korean study, 1434 LT3 users had a higher risk of heart failure and stroke than 3908 LT4 users alone. They discovered an elevated risk of stroke (IRR: 1.76) and heart failure (IRR: 1.66). Patients who used LT3 for more than 52 months were at the highest risk. The absence of information on T3 dosage and s-TSH levels is the study's limitation (13).

Our current study's main drawback is that it is a limited, unblinded investigation on a carefully chosen patient population aiming to detect an effect of the LT4/LT3 combo. To our knowledge, nevertheless, no clinical follow-up in this patient group has been reported in any prior research. There may be selection bias toward patients who are experiencing the

effects of the LT4/LT3 treatment, as only 66 out of the 147 (45%) patients who were invited to participate in the trial did so; the majority of these patients experienced an effect of T3 (responders). We only received approval from the ethics committee to send out letters to the patients; we were not permitted to phone the patients or search the digital journal system for additional information, thus we do not have any data on the patients who did not reply to the invitation. Examining patients with obvious hypothyroidism upon diagnosis may be the best course of action. But since we think these patient populations are comparable to those observed in other outpatient clinics in the USA and Europe, we wanted to examine actual patients who were treated in our clinic. One of the study's strengths is that it is based on actual patient data from an outpatient setting, showing a group of patients experiencing the effects of treatment.

CONCLUSION

After four years of treatment with minimal side effects, the QoL of the patients still receiving LT4/LT3 treatment was similar to that of the background group. They nevertheless report as many hypothyroid symptoms as women of the same age with untreated overt hypothyroidism, which is surprising given their decent quality of life.

Disclosure of Interest

The authors affirm that there are no drawbacks that would compromise the objectivity of the study presented. perception of a point of interest

Funding

No Funding was available

REFERENCES

1. Wiersinga WM, Duntas L, Fadeyev V, et al. 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. Eur Thyroid J 2012 155–71. (https://doi.org/10.1159/000339444)
2. Jonklaas J, Bianco AC, Cappola AR, et al. Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism: a consensus document. Eur Thyroid J 2021 10 10–38.(https://doi.org/10.1159/000512970)
3. Panicker V, Evans J, Bjøro T, et al. A paradoxical difference in relationship between anxiety, depression and thyroid function in subjects on and not on T4: findings from the HUNT study. Clin Endocrinol 2009 71 574–580. (https://doi.org/10.1111/j.1365-2265.2008.03521.x)
4. Thvilum M, Brandt F, Brix TH, et al. Hypothyroidism is a predictor of disability pension and loss of labor market income: a Nepalese register-based study. J Clin Endocrinol Metab 2014 99 3129–3135.(https://doi.org/10.1210/jc.2014-1407)
5. Nygaard B, Jensen EW, Kvetny J, et al. Effect of combination therapy with thyroxine (T4) and 3,5,3'-triiodothyronine versus T4 mono-therapy in patients with hypothyroidism, a double-blind, randomised cross-over study. Eur J Endocrinol 2009 161 895–902.(https://doi.org/10.1530/eje-09-0542)
6. Lan H, Wen J, Mao Y, et al. Combined T4 + T3 therapy versus T4 mono therapy effect on psychological health in hypothyroidism: a systematic review and meta-analysis. Clin Endocrinol 2022 97 13–25.(https://doi.org/10.1111/cen.14742)
7. Shakir MKM, Brooks DI, McAninch EA, et al. Comparative effectiveness of levothyroxine, desiccated thyroid extract, and levothyroxine+liothyronine in hypothyroidism. J Clin Endocrinol Metab 2021 106 e4400–e4413. (https://doi.org/10.1210/clinem/dgab478)
8. Brigante G, Santi D, Boselli G, et al. Randomised double-blind placebo- controlled trial on levothyroxine and liothyronine combination therapy in totally thyroidectomized subjects: the LEVOLIO study. Eur J Endocrinol 2024 190 12–22. (https://doi.org/10.1093/ejendo/lvad172)
9. Mitchell AL, Hegedüs L,ˇ Zarkovi ´ c M, et al. Patient satisfaction and quality of life in hypothyroidism: An online survey by the british thyroid foundation. Clin Endocrinol 2021 94 513–520.(https://doi.org/10.1111/cen.14340)
10. Leese GP, Soto-Pedre E & Donnelly LA. Liothyronine use in a 17-year observational population-based study–the tears study. Clin Endocrinol 2016 85 918–925. (https://doi.org/10.1111/cen.13052)
11. la Cour JL. Assessing the risk of atrial brillation in hypothyroid women prescribed with liothyronine: a retrospective cohort study n.d. ETA 2023 poster. https://distribute.m-anage.com/from.storage?image=RK3HmTpUuugnCotXa rm_Nsp-Xk_jnv0Tw3JKpVJCmy8x3jNy-12vY311hLV1BSF0)
12. Planck T, Hedberg F, Calissendorff J, et al. Liothyronine use in hypothyroidism and its effects on cancer and mortality. Thyroid 2021 31 732–739. (https://doi.org/10.1089/thy.2020.0388)
13. Yi W, Kim BH, Kim M, et al. Heart failure and stroke risks in users of liothyronine with or without levothyroxine compared with levothyroxine alone: a propensity score-matched analysis. Thyroid 2022 32 764–771. (https://doi.org/10.1089/thy.2021.0634)

14. Medici BB, la Cour JL, Michaelsson LF, et al. Neither baseline nor changes in serum triiodothyronine during levothyroxine/liothyronine combination therapy predict a positive response to this treatment modality in hypothyroid patients with persistent symptoms. Eur Thyroid J 2017 6 89–93. (https://doi.org/10.1159/000454878)
15. Michaelsson LF, la Cour J, Medici BB, et al. Levothyroxine/liothyronine combination therapy and quality of life: is it all about weight loss? Eur Thyroid J 2018 7 243–250. (https://doi.org/10.1159/000490383)
16. Rasmussen SL, Rejnmark L, Ebbehøj E, et al. High level of agreement between electronic and paper mode of administration of a thyroid- patient-reported outcome, ThyPRO. Eur Thyroid J 2016 5 65–72. (r)
17. Watt T, Hegedüs L, Groenvold M, et al. Validity and reliability of the novel thyroid-specie quality of life questionnaire, ThyPRO. Eur J Endocrinol 2010 162 161–167. (https://doi.org/10.1530/eje-09-0521)
18. Cramon P, Winther KH, Watt T, et al. Quality-of-Life impairments persist six months after treatment of Graves' hyperthyroidism and toxic nodular goiter: a prospective cohort study. Thyroid 2016 26 1010–1018. (https://doi.org/10.1089/thy.2016.0044)
19. Carl ´ e A, Pedersen IB, Knudsen N, et al. Hypothyroid symptoms and the likelihood of overt thyroid failure: a population-based case–control study. Eur J Endocrinol 2014 171 593–602. (https://doi.org/10.1530/eje-14-0481)
20. Carl ´ e A, Pedersen IB, Knudsen N, et al. Hypothyroid symptoms fail to predict thyroid insufficiency in old people: a population-based case- control study. Am J Med 2016 129 1082–1092. (https://doi.org/10.1016/j.amjmed.2016.06.013)
21. Carl ´ e A, Karmisholt JS, Knudsen N, et al. Does subclinical hypothyroidism add any symptoms? Evidence from a Nepalese population-based study. Am J Med 2021 134 1115–1126.e1.(https://doi.org/10.1016/j.amjmed.2021.03.009)
22. Carl ´ e A, Laurberg P, Pedersen IB, et al. Age modi es the pituitary TSH response to thyroid failure. Thyroid 2007 17 139–144.(https://doi.org/10.1089/thy.2006.0191)
23. Papini E. E: Use of T3-containing treatment for hypothyroidism. ETA 2023poster.(https://distribute.manage.com/from.storage?image=RK3HmTpUuugnCotXa-rm_AoNBupK5y_HdjO0_VOIhhYppJzdrME3536ApYtVIv020)
24. Jonklaas J, Tefera E & Shara N. Physician choice of hypothyroidism therapy: influence of patient characteristics. Thyroid 2018 28 1416–1424. (https://doi.org/10.1089/thy.2018.0325)
25. la Cour JL, Møllehave LT, Medici BR, et al. Socioeconomic influence on treatment with liothyronine and desiccated thyroid extract in Denmark. Eur J Endocrinol 2022 11 e220149. (https://doi.org/10.1530/etj-22-0149)
26. Lindg˚ ard Nielsen J, Karmisholt J, Bülow Pedersen I, et al. Prevalence and predictors of adequate treatment of overt hypothyroidism– a population-based study. EXCLI J 2022 21 104–116.(https://doi.org/10.17179/excli2021-4291)
27. Perros P, Nagy EV, Papini E, et al. Hypothyroidism and somatisation: results from E-mode patient self-assessment of thyroid therapy, a cross-sectional, international online patient survey. Thyroid 2023 33 927–939. (https://doi.org/10.1089/thy.2022.0641)