Treating Hypothyroidism with Thyroxine/Triiodothyronine Combination Therapy in Denmark: Following Guidelines or Following Trends?

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Key Words

Hypothyroidism · Triiodothyronine · Thyroid ·
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Abstract

Background: Five to ten percent of patients with hypothyroidism describe persistent symptoms despite being biochemically well regulated on levothyroxine (L-T₄). Thyroxine (T₄)/triiodothyronine (T₃) combination therapy [L-T₄/liothyronine (L-T₃) or desiccated thyroid] are still regarded as experimental with no evidence of superior effect on persistent symptoms according to meta-analyses. However, some randomized controlled trials have demonstrated patients' preference for T₄/T₃ combination therapy as compared to L-T₄ monotherapy. In 2013, attention to combination therapy increased in Denmark after a patient published a book describing her experiences with hypothyroidism and treatment. **Objective:** To investigate current Danish trends in the use of T₄/T₃ combination therapy. **Methods:** We used an Internet-

based questionnaire, distributed as a link via two Danish patient fora. Further, information was obtained from the Division of Pharmacies and Reimbursement at the Danish Health and Medicines Authority and from the only pharmacy in Denmark producing desiccated thyroid and L-T₃ tablets. **Results:** A total of 384 patients answered the questionnaire, and 293 responders were included. Sixty-nine percent of the responders had six or more symptoms, and 84% reported a treatment effect. Forty-four percent of the responders received their prescriptions from general practitioners; 50% received desiccated thyroid and 28% reported that they adjust their dose themselves. Responders followed by general practitioners more frequently received desiccated thyroid and adjusted their dose themselves. **Conclusions:** Increased media focus has changed the prescription pattern of thyroid hormones; European guidelines on T₄/T₃ combination therapy are not always followed in Denmark and many patients adjust their medication themselves and may therefore be at risk of overtreatment.

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Introduction

To prescribe triiodothyronine (T_3) as an add-on to levothyroxine ($L-T_4$) treatment or not to prescribe T_3 is a question which is nowadays considered by many physicians. Patients are also seeking alternative treatments of hypothyroidism, and the Internet is a popular source for answers [1].

Hypothyroidism is common in Denmark with an incidence rate of 32.8 per 100,000 person-years [2]. In 2011, 118,000 patients (2% of the total Danish population) received medical treatment for hypothyroidism (data from The Danish Register of Medicinal Product Statistics).

The standard treatment of hypothyroidism is $L-T_4$. However, 5–10% of patients continue to have symptoms despite being biochemically well regulated on $L-T_4$ monotherapy. Some researchers suggest that T_3 – the biological active form of thyroid hormone – should be used in these cases [3]. It has also been suggested that some patients are not able to benefit from monotherapy due to defects in their deiodinase enzymes converting thyroxine (T_4) to T_3 , qualifying these patients for combination therapy [3].

T_4/T_3 combination therapy can be given as combination of $L-T_4$ /liothyronine ($L-T_3$) or as desiccated thyroid. The therapy is controversial: T_3 is easy to overdose, which can lead to suppressed thyroid-stimulating hormone (TSH), with an increased risk of complications such as heart disease [4], osteoporosis [5, 6] and potentially dementia [7]. A meta-analysis showed no evidence of effect of T_4/T_3 combination therapy compared to $L-T_4$ monotherapy on bodily pain, depression, anxiety, fatigue, quality of life or body weight [8]. However, four randomized controlled trials and one parallel study have demonstrated patients' preference for $L-T_4/L-T_3$ combination therapy compared to $L-T_4$ [3]. Indeed, one of these studies demonstrated significantly better scores in 7 of 11 tested quality of life and depression scores on $L-T_4/L-T_3$ combination therapy in a selected patient group with autoimmune thyroiditis and high baseline psychological discomfort [9].

This treatment has become a 'hot' topic on patient associations' websites [3] and the demand for it has been increasing. A Dutch population study from 2012 showed a rise in the use of T_4/T_3 combination therapy of more than 60% between 2005 and 2011 [10]. In May 2013, a Danish patient suffering from hypothyroidism published a book [11] telling her story of a miraculous recovery on $L-T_4/L-T_3$ combination therapy, encouraging other pa-

tients to follow her example. Shortly thereafter, many Danish clinicians reported an increased demand for T_4/T_3 combination therapy among patients, inspiring us to perform this study.

Our aim was to look at Danish trends in prescribing T_4/T_3 combination therapy and to investigate whether the European guidelines [3] were being followed and how the therapy is monitored, prescribed and adjusted. Furthermore, we aimed at characterizing the patient group who receives T_4/T_3 combination therapy.

Materials and Methods

We had three different sources of information: (1) an Internet-based questionnaire conducted by the authors, (2) data from the Danish Register of Medicinal Product Statistics and Division of Pharmacies and Reimbursement at the Danish Health and Medicines Authority and (3) data from Glostrup Pharmacy, the only pharmacy in Denmark that produces desiccated thyroid and $L-T_3$ 5- μ g tablets (the most used $L-T_3$ preparation in Denmark).

Questionnaire

We used an Internet-based questionnaire via Survey Xact (Rambøll Management Consulting, © 2013–2014 Rambøll). The link to the questionnaire was open for patient replies from February 11, 2014 until April 2, 2014, and was distributed via two patient fora ('Thyreoida landsforeningen', a 10-year-old society for patients suffering from all thyroid diseases, and 'Stofskiftesupport', a new forum initiated by hypothyroid patients that is particularly based on people's interest in the book mentioned above [11] and pages like <http://www.stopthethyroidmadness.com>, and alternatives to the established societies). We asked the respondents about age, sex, education level, medication, symptoms, recent blood test results, which T_3 medication they received, the effect of T_4/T_3 combination therapy, and which physician prescribed and adjusted their medication. The inclusion criterion was: all patients on any kind of T_4/T_3 combination therapy who responded on the questionnaire. The exclusion criterion was: not answering the question about which T_4/T_3 combination therapy the responder was taking.

Investigating Trends in T_4/T_3 Combination Therapy

Through the Division of Pharmacies and Reimbursement at the Danish Health and Medicines Authority, we were able to quantify the number of applications for reimbursement of T_4/T_3 combination therapy from March 2012 to November 2014. Furthermore, Glostrup Pharmacy provided us with data on sales of these products during 2013.

Statistical Methods

Results from the questionnaire were analyzed with descriptive statistics and with subgroup analysis using a Mann-Whitney test for numerical data and a χ^2 test for categorical data (IBM SPSS Statistics ver. 22). Selected answers in the questionnaire were dichotomized in order to perform statistical analysis (table 1).

Table 1. Characteristics of respondents (n = 293) in a Danish Internet-based questionnaire study of T₄/T₃ combination therapy

	All responders (n = 293)	Responders treated by endocrinologists (n = 114)	Responders treated by general practitioners (n = 122)	Responders on L-T ₄ / L-T ₃ combination therapy (n = 110)	Responders on desiccated thyroid (n = 126)
Sex					
Female	275 (94)	107 (94)	117 (96)	105 (95)	119 (94)
Age					
≤40 years	58 (20)	29 (25)	19 (16)	23 (21)	25 (20)
41–60 years	186 (63)	71 (62)	82 (67)	73 (66)	80 (63)
≥61 years	49 (17)	14 (12)	21 (17)	14 (13)	21 (17)
Education					
Primary or secondary education	31 (11)	12 (11)	8 (7)	9 (8)	11 (9)
Vocational or short tertiary education <3 years	83 (28)	33 (29)	37 (30)	29 (26)	41 (33)
Tertiary education >3 years	175 (60)	67 (59)	75 (61)	70 (64)	72 (57)
No answer	4 (1)	2 (2)	2 (2)	2 (2)	2 (2)
Duration of hypothyroidism					
0–12 months	13 (4)	5 (4)	3 (2)	3 (3)	5 (4)
1–3 years	43 (15)	14 (12)	20 (16)	21 (19)	13 (10)
3–10 years	105 (36)	46 (40)	44 (36)	44 (40)	46 (37)
>10 years	132 (45)	49 (43)	55 (45)	42 (38)	62 (49)
TSH level at diagnosis					
Did not remember TSH at diagnosis	77 (26)	28 (25)	27 (22)	35 (32)	20 (16)
<4 mU/l	75 (26)	29 (25)	32 (26)	23 (21)	38 (30)
4–10 mU/l	53 (18)	26 (23)	20 (16)	28 (25)	18 (14)
10–20 mU/l	33 (11)	15 (13)	11 (9)	8 (7)	18 (14)
20–50 mU/l	19 (6)	8 (7)	9 (7)	6 (5)	11 (9)
>50 mU/l	36 (12)	8 (7)	23 (19)	10 (9)	21 (17)
TSH level at the most recent control					
<0.01 mU/l	41 (14)	9 (8)	23 (19)	9 (8)	23 (18)
0.01–1.0 mU/l	157 (54)	65 (57)	77 (63)	68 (62)	74 (59)
1.0–2.5 mU/l	42 (14)	18 (16)	14 (11)	17 (15)	15 (12)
2.5–4.0 mU/l	24 (8)	13 (11)	7 (6)	12 (11)	8 (6)
>4.0 mU/l	16 (5)	9 (8)	1 (1)	4 (4)	6 (5)
No answer	13 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Duration of T ₄ /T ₃ combination therapy					
<3 months	85 (29)	43 (38)	28 (23)	41 (37)	30 (24)
3–6 months	79 (27)	38 (33)	33 (27)	40 (36)	31 (25)
6–12 months	48 (16)	11 (10)	30 (25)	12 (11)	29 (23)
1–3 years	42 (14)	13 (11)	22 (18)	8 (7)	27 (21)
>3 years	28 (10)	9 (8)	9 (7)	9 (8)	9 (7)
No answer	11 (4)	0 (0)	0 (0)	0 (0)	0 (0)

Values represent n (%). Excluded from subgroups: responders who answered 'other' to the question of which T₄/T₃ combination therapy used and/or those who answered 'purchase on the Internet' to the question 'who prescribed their medicine'. For subgroup analyses and p values see text in the Results section.

Results

Patient Characteristics

There were 384 responders to the survey, and 293 were included after excluding responders according to the exclusion criterion. Patient characteristics are summarized in table 1. Of those who received medical treatment for other conditions (n = 157), 111 respondents answered which other condition they were treated for: vitamin D

insufficiency (50%), depression or anxiety (9%), high blood pressure (8%), diabetes (3%), heart disease (3%), and others (28%).

As for the most recent TSH levels, 14% of respondents reported that their TSH level was less than 0.01 mU/l (totally suppressed). The TSH level at the time of diagnosis of hypothyroidism was reported being below 4 mU/l in 26%, i.e. below the recommended upper normal reference range in Denmark.

Table 2. Frequency of different symptoms before initiation of T₄/T₃ combination therapy (i.e. on L-T₄ monotherapy) among responders in a Danish Internet-based questionnaire study on T₄/T₃ combination therapy

	Main symptom		All symptoms	
	n	%	n	%
Being tired	78	27	267	91
Lack of energy	49	17	256	87
Cognitive problems	32	11	244	83
Musculoskeletal symptoms	30	10	222	76
Weight problems	23	8	220	75
Pain	12	4	145	49
Diffuse symptoms	13	4	142	48
Depression	7	2	114	39
Constipation	5	2	124	42
Sweating	1	0.3	92	31
Other	43	15	105	36
Total	293	100		

Responders were asked to select their symptoms from a list of 11 different symptoms, and to choose only one main symptom.

Fig. 1. Number of symptoms per participant.

Symptoms before Initiating T₄/T₃ Combination Therapy

When respondents were on T₄ monotherapy, before starting T₄/T₃ combination therapy, they had many different symptoms (fig. 1). As many as 69% of the patients had six or more different symptoms (median 7, IQR: 5–8). The frequency of the different symptoms can be seen in table 2.

Table 3. Who prescribes the medicine and who adjusts the dose?

	n	%
<i>Who prescribes?</i>		
General practitioner	130	44
Specialist	119	41
Bought on the Internet	13	4
No answer	31	11
Total	293	100
<i>Who adjusts?</i>		
Physician, on the basis of blood samples	129	44
Physician, on the basis of symptoms	51	17
I adjust myself on the basis of symptoms	82	28
No answer	31	11
Total	293	100

T₄/T₃ Combination Therapy

In total, 43% of the respondents used L-T₃: 28% used 5-μg tablets, 13% used 20-μg tablets and 1% did not answer which dose of L-T₃ tablets they took. Desiccated thyroid was used by 50% of the respondents: 39% used desiccated thyroid from Glostrup Pharmacy, whereas 11% answered that they used other kinds of desiccated thyroid purchased on the Internet. A minor percentage (7%) of respondents answered ‘other drug’ regarding their T₄/T₃ combination therapy, and 1% answered that they took both L-T₃ and desiccated thyroid. In 44% of the cases, general practitioners prescribed the medication, and 28% of respondents answered that they adjust their medicine themselves (table 3).

A positive effect was described by 84% of respondents, and the effect was described as ‘miraculous’ (19%), ‘much better’ (43%), ‘better’ (22%), ‘no difference’ (6%) and ‘worsening’ (2%); 8% did not answer this question. Respondents were also asked if they wanted to continue the therapy: 81% answered ‘yes’, 2% answered ‘no’, 5% answered that they ‘have not decided yet’, and 12% did not answer this question.

Subgroup Analyses

We compared the following subgroups: (1) patients treated by general practitioners (n = 122) with patients treated by endocrinologists (n = 114), and (2) patients receiving desiccated thyroid (n = 126) with patients receiving L-T₄/L-T₃ combination therapy (n = 110). Patients who answered ‘purchase their medicine on Internet’ and those who answered ‘other’ T₃ treatment were excluded

Table 4. Number of sold packages of 100 tablets of L-T₃ and desiccated thyroid during 2012–2013 from Glostrup Pharmacy, Denmark

	Quarters	2012				2013			
		1	2	3	4	1	2	3	4
L-T ₃ tablets (5 µg)		–	–	10	79	150	171	513	900
Desiccated thyroid tablets (60 mg)		53	96	151	176	225	228	414	400

from all of these analyses. Furthermore, in analyses of TSH levels at the time of diagnosis, those who answered ‘do not remember TSH at diagnosis’ were excluded (table 1).

Comparing patients treated by endocrinologists versus general practitioners, we found no significant differences for the following variables: age, level of education, disease duration, TSH levels at diagnosis and number of symptoms. Patients treated by general practitioners had significantly lower ‘most recent’ TSH levels ($p < 0.0001$), had been relatively longer on T₄/T₃ combination therapy ($p = 0.004$), had better self-reported effect of the treatment ($p < 0.0001$), used more desiccated thyroid than L-T₃ (χ^2 test, $p < 0.0001$) and more of them adjusted their dose themselves (χ^2 test, $p < 0.0001$).

Compared to patients receiving L-T₄/L-T₃ combination therapy, patients receiving desiccated thyroid had been significantly longer on combination therapy ($p = 0.001$), had better self-reported effect of the treatment ($p < 0.0001$) and had lower ‘most recent’ TSH levels ($p = 0.047$). More of them adjusted their dose themselves (χ^2 test, $p < 0.0001$). When comparing age, level of education, disease duration, TSH levels at diagnosis and number of symptoms, no significant differences were found.

Amount of Prescribed T₃ Therapy

Glostrup Pharmacy started local Danish production of desiccated thyroid in 2011, and the production of L-T₃ 5-µg tablets was started in July 2012 – all sales were exclusively for Danish patients. Before July 2012 a small number of patients in Denmark were treated with L-T₃ 20-µg tablets, produced by Nycomed, Sweden. Some of these patients were changed from 20- to 5-µg tablets in 2012 (the exact number cannot be quantified). Table 4 describes the sale of L-T₃ and desiccated thyroid during 2012 and 2013. Sales of L-T₃ increased sixfold in less than a year: 150 packs of L-T₃ (100 tablets, each 5 µg) were sold in the first quarter of 2013 compared to 900 packs of L-T₃ during the last quarter of 2013. A smaller increase in sales

from 225 to 400 packs of desiccated thyroid (100 tablets, each 60 mg) was observed in the first quarter of 2013 and the last quarter of 2013, respectively.

It was not possible to extract exact data from the the Danish Register of Medicinal Product Statistics in order to determine how many patients were given a prescription for T₄/T₃ combination therapy. However, the Division of Pharmacies and Reimbursement at the Danish Health and Medicines Authority was able to provide us with data on the number of applications for reimbursement of T₄/T₃ combination therapy. This figure was used as a surrogate for the number of new patients starting T₄/T₃ combination therapy, assuming that nearly all of the physicians prescribing L-T₃ or desiccated thyroid also applied for individual reimbursement for their patients. We compared the number of applications from July 2012 to June 2013 with the number of applications from July 2013 to June 2014 and found a 3.8-fold increase. The increased number of applications seems to have stabilized for the rest of 2014 (fig. 2).

Discussion

To our knowledge, this is the first questionnaire-based study on patients receiving T₄/T₃ combination therapy. The main findings were: (1) patient demand for T₄/T₃ combination therapy in Denmark increased abruptly in 2013, probably due to increased focus in the media, (2) the European Guidelines were not followed consistently in Denmark and (3) many patients adjusted their medication themselves and may therefore be at risk of overtreatment.

A recent population-based case-control study on newly diagnosed and untreated hypothyroid patients reported a median of 5 symptoms (IQR: 3–7) [12]. We found an even higher number of symptoms in our patients when only receiving L-T₄ monotherapy (median 7; IQR: 5–8). Frequent symptoms in our patients on L-T₄ monothera-

Fig. 2. Number of applications for reimbursement of T₄/T₃ treatment.

py, before initiating T₄/T₃ combination therapy, were 'being tired' (in 91% of respondents), 'constipation' (42%) and 'pain' (49%). Carle et al. [12] reported appearance of these symptoms in untreated hypothyroid patients/healthy controls: 'tiredness' in 81/41%, 'constipation' in 39/17% and 'generalized pain' in 47/39%. This seems to indicate that when our patient group were on L-T₄ monotherapy, they had symptoms alike or even more severe than *untreated* hypothyroid patients. Otherwise, the characteristics of sex, age and education were similar to the typical Danish hypothyroid patient [2], i.e. a middle-aged woman with a middle or high level of education.

The rather diffuse symptoms reported as most frequent in our study have previously been explained by the inability of coping with the chronic nature of the disease [3], or by the hypothesis that some patients blame hypothyroidism for any symptoms. Another possible hypothesis is that some hypothyroid patients are more vulnerable compared to the basic population [9]. The latter hypothesis is in accordance with recent studies describing increased psychiatric morbidity as well as risk of disability pension in hypothyroid patients before as well as after L-T₄ therapy [13, 14].

With regard to the form of hypothyroidism designated subclinical hypothyroidism, there is an ongoing discus-

sion of when to treat and at what level the cutoff for the upper reference limit of TSH should be. In a very recent cohort study of 52,298 individuals in the UK, a falling threshold of TSH for initiating treatment of subclinical hypothyroidism was demonstrated, with the median TSH at the initiation of L-T₄ therapy decreasing from 8.7 in 2001 to 7.9 mU/l in 2009 [15]. Further, this study demonstrated a high risk of overtreatment since 10% had reduced TSH [15]. A register study in Denmark describes an increase of prescriptions of L-T₄, with an incidence rate increase of 81% over 9 years from 1997 to 2008 [16]. These changes could partly be due to the iodine fortification or a higher diagnostic activity with regard to thyroid dysfunction, but could also be due to an intensified treatment of subclinical hypothyroidism [16]. In the context of overtreatment, it was striking that we found 28% of the respondents adjust their medicine themselves (probably due to changes in the pattern of symptoms) and 14% of all respondents reported a suppressed TSH <0.01 mU/l. This indicates a high level of autonomy in this respondent group and that a portion of the respondents were potentially overtreated. Thus, the guidelines, including those from the European Thyroid Association, that propose a rather stringent dosage ratio between T₄ and T₃, might in general be read by doctors, but not by patients. The European Thyroid Association recommends that T₄/T₃ combination therapy should be given by experts in the field, and in this context it is interesting that patients treated by general practitioners as compared to those treated by endocrinologists had significantly lower 'most recent' TSH levels, used more desiccated thyroid and more often adjusted their dose themselves. It might be assumed that there are differences between general practitioners and expert endocrinologists with regards to how to handle nonscientific information on a special topic like T₄/T₃ combination therapy when brought by their patient from the Internet or as in the 'Danish case' supplemented by a nonscientific book. Similarly, there might be differences between these two groups of therapists with regards to following specific guidelines in endocrinology, including those provided by the European Thyroid Association [3].

Internet-based questionnaires have obvious flaws, the major one being selection bias. We expect that the patients who experienced a positive effect of the combination treatment were overrepresented. Further, 56% of the patients answering the questionnaire had been treated for a period of less than 6 months, which might increase the probability of a positive response, which is often seen during the initial treatment of a disease. Nevertheless, this

questionnaire gives us systematic insight into the patient experience, the same experience that is shared on patient sites on the Internet and read by numerous other patients.

Conclusions

The demand for T₄/T₃ combination therapy in Denmark increased dramatically in 2013. The European guidelines of hypothyroidism are not followed consistently in Denmark. Furthermore, many respondents report that they adjust their medication themselves. More evidence-based information on the effect and potential

side effects of this treatment modality is clearly needed for both endocrinologists, general practitioners and, most importantly, for the patients.

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Disclosure Statement

None of the authors have any conflict of interest.

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