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

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Hypothyroidism · Triiodothyronine · Thyroid · Levothyroxine · Liothyronine

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 adjusted 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.
To prescribe triiodothyronine (T₃) as an add-on to levothyroxine (L-T₄) treatment or not to prescribe T₃ 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-T₄. However, 5–10% of patients continue to have symptoms despite being biochemically well regulated on L-T₄ monotherapy. Some researchers suggest that T₃ – 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 (T₄) to T₃, qualifying these patients for combination therapy [3].

T₄/T₃ combination therapy can be given as combination of L-T₄/liothyronine (L-T₃) or as desiccated thyroid. The therapy is controversial: T₃ 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 T₄/T₃ combination therapy compared to L-T₄ 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-T₄/L-T₃ combination therapy compared to L-T₄ [3]. Indeed, one of these studies demonstrated significantly better scores in 7 of 11 tested quality of life and depression scores on L-T₄/L-T₃ 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 T₄/T₃ 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-T₄/L-T₃ combination therapy, encouraging other patients to follow her example. Shortly thereafter, many Danish clinicians reported an increased demand for T₄/T₃ combination therapy among patients, inspiring us to perform this study.

Our aim was to look at Danish trends in prescribing T₄/T₃ 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 T₄/T₃ 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 desicated thyroid and L-T₃, 5-μg tablets (the most used L-T₃ preparation in Denmark).

**Questionnaire**

We used an Internet-based questionnaire via Survey Xact (Ramboll Management Consulting, © 2013–2014 Ramboll). 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.stophyroidmadness.com, and alternatives to the established societies). We asked the respondents about age, sex, education level, medication, symptoms, recent blood test results, which T₃ medication they received, the effect of T₄/T₃ combination therapy, and which physician prescribed and adjusted their medication. The inclusion criterion was: all patients on any kind of T₄/T₃ combination therapy who responded on the questionnaire. The exclusion criterion was: not answering the question about which T₄/T₃ combination therapy the responder was taking.

**Investigating Trends in T₄/T₃ 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 T₄/T₃ 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 χ² test for categorical data (IBM SPSS Statistics ver. 22). Selected answers in the questionnaire were dichotomized in order to perform statistical analysis (table 1).
Results

Patient Characteristics

There were 384 respondents 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.
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.

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.
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 (χ² test, p < 0.0001) and more of them adjusted their dose themselves (χ² 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 (χ² 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 2012–2013 from Glostrup Pharmacy, Denmark.

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<th>2012</th>
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<tr>
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<td>Quarters 1 2 3 4</td>
<td>Quarters 1 2 3 4</td>
</tr>
<tr>
<td>L-T3 tablets (5 μg)</td>
<td>– 10 79 150</td>
<td>171 513 900</td>
</tr>
<tr>
<td>Desiccated thyroid tablets (60 mg)</td>
<td>53 96 151 176</td>
<td>225 228 414 400</td>
</tr>
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It was not possible to extract exact data from 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-
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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 discussion 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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