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Factors Contributing to High Levothyroxine Doses in Primary Hypothyroidism: An Interventional Audit of a Large Community Database

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Background: While few hypothyroid patients require more than the expected weight-related dose of levothyroxine, the underlying causes of larger-than-expected dosing requirements have not been studied in a single cohort. Our aim was to determine and quantify the multiple factors contributing to high-dose levothyroxine requirements in a cohort of patients with hypothyroidism.
Methods: The Grampian Automated Follow-Up Register (GAFUR) monitors around 17,500 hypothyroid patients. In 2008, 190 (1%) patients took >225 μg of levothyroxine daily. A questionnaire was sent to 174 patients (16 were untraceable) to assess causes and to offer blood tests for endomysial, parietal cell (PCA), and thyroid peroxidase (TPO) autoantibodies. Primary care practices were contacted for medication details. All patients with positive endomysial autoantibodies were referred to a gastroenterologist. Thyroid function tests and levothyroxine doses were re-evaluated in 2011.
Results: A total of 125 questionnaires (72%) were returned. Mean levothyroxine dose was 248 μg daily. Twenty-six patients (20.8%) took medication known to interfere with levothyroxine absorption, and 21 patients (16.8%) admitted to compliance issues. Seven patients had positive anti-endomysial antibodies on initial screening, with four being new diagnoses of celiac disease, and PCA were positive in 27 (21.6%) patients. At follow-up in 2011, the mean levothyroxine dose had decreased in patients on interfering medications and in the four new cases of celiac disease.
Conclusions: Causes of patients needing high-dose levothyroxine replacement include poor compliance, medication interference, PCA (as a marker of atrophic/autoimmune gastritis), and celiac disease. Doses can be decreased following advice regarding medication or after management of underlying conditions.

Introduction

Hypothyroidism is common, with the incidence of primary hypothyroidism in the United Kingdom being 3.5 per 1000 in women and 0.6 per 1000 in men (1). In iodine-sufficient countries, most cases are due to autoimmune hypothyroidism. Undertreated patients can suffer from cardiac and neurological morbidity (2). Hypothyroidism is usually easily treatable, but some patients require atypically high doses of levothyroxine. Causes include poor compliance, excess body weight, and interferences due to food, drugs, or malabsorption (3). Most patients require 1.6–1.8 μg of levothyroxine per kilogram of body weight, although lean body mass is a better measure to use, with expected doses being 2–3 μg/kg (4–6).

Approximately 62–82% of orally administered levothyroxine is absorbed from the jejunum and ileum (7,8). Levothyroxine absorption is maximal when the stomach is empty, and bioavailability is lowered by several dietary factors (9,10) and medication (11,12). Surgical and autoimmune damage to the gut can impair levothyroxine absorption (13–17). In practice, poor medication compliance is the most common reason for a high levothyroxine requirement, but this is often difficult to prove. Levothyroxine dose requirement may be increased by drugs, which accelerate its metabolism. Additional factors (18,19) are described in Table 1.

Celiac disease and autoimmune gastritis are important conditions, as both commonly occur in association with autoimmune hypothyroidism. The incidence of celiac disease ranges from 2% to 5% in patients with autoimmune thyroid

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Table 1. Common Factors That Can Increase Levothyroxine Dose Requirement

Medical conditions	*Dietary factors*	*Medications interfering with absorption (11)*	*Medications increasing metabolism (11)*
Jejunoileal bypass surgery or other bowel resection* (13,14)	Dietary fibers (9)	Ferrous sulfate	Carbamazepine
Celiac disease (15,16)	Fruit juices	Calcium carbonate	Rifampicin
Autoimmune gastritis (17)	Dairy products	Proton pump Inhibitors	Phenytoin
Atrophic gastritis secondary to *Helicobacter pylori* (18)	Coffee (10) Meals	Cholestyramine Orlistat	Estrogen
Pancreatic insufficiency		Sucralfate	
Obstructive liver disease and cirrhosis of liver (19)		Aluminium hydroxide Sertraline (12)	

*Bypass surgery has a variable impact, and while it could be the cause of a high levothyroxine dose in a patient, other causes should also be considered.

disease, which is significantly higher than the general population incidence of 1% (13,14). Celiac disease mainly affects the jejunum and ileum, which are the main sites for levothyroxine absorption (20). As celiac disease can present in many different ways and is often asymptomatic, screening is recommended in patients with other autoimmune disorders and in patients with higher than expected doses of levothyroxine (13,21,22).

The presence of autoimmune gastritis may also influence levothyroxine dose requirements. A screening study of 391 patients with autoimmune hypothyroidism found positive parietal cell antibodies (PCA) in 155 patients (39.6%). Levothyroxine requirement was significantly higher in these patients compared to PCA-negative patients (17).

The exact contribution of each of these factors to high levothyroxine requirements is unclear. Most previous studies that have examined levothyroxine requirements in patients with hypothyroidism have focused on a single element or have been isolated case reports. We aimed to determine and quantify the multiple factors contributing to high-dose levothyroxine requirements in a large cohort of patients with primary hypothyroidism being followed prospectively using a community-based thyroid register.

Methods

Patients

In September 2008, the Grampian Automated Follow-Up Register (GAFUR) had around 17,500 hypothyroid patients who were on levothyroxine therapy. GAFUR is a joint venture between the secondary care-based specialist thyroid service and primary care practices in the Grampian Health Board area of North East Scotland. Patients on treatment with levothyroxine except thyroid cancer patients, who are not included in the follow-up register, are recalled for thyroid function testing (TFTs) at preset follow-up intervals, typically 12–18 months. The results are reviewed centrally in secondary care, and if satisfactory, with thyrotropin (TSH) within the reference range (0.35–3.3 mU/L), an automatic routine recall is generated. If abnormal, the result is reviewed by a thyroid specialist who will make recommendations to the GP regarding dose change. The details of this comprehensive database have been previously described (23,24).

A search of GAFUR in 2008 revealed 190 (1%) adults who were taking $>225\,\mu$g of levothyroxine daily, predominantly in tablet form, which is twice the expected maximum daily requirements for a 70 kg individual.

Letters were sent to 174/190 patients (16 patients being untraceable) inviting them to attend their GP for further evaluation. A questionnaire addressing symptoms of malabsorption, symptoms of hypothyroidism, compliance with levothyroxine, and the most recent height and weight was sent to the GP and the healthcare professional, who took the blood sample, completing it at the patient's visit.

One hundred and twenty-five questionnaires were returned by the healthcare professional between September 2008 and September 2009. GP practices were contacted by telephone to confirm the patients' current medication details and medical problem list. After reviewing results, letters were sent to patients and GPs with results and recommendations. Depending on TSH results, levothyroxine dose adjustments were suggested. All patients with positive celiac serology were reviewed in the endocrine unit and referred to a gastroenterologist for distal duodenal biopsy and management, which included dietetic review and advice regarding a gluten-free diet (GFD). For patients with positive PCA, vitamin B12 levels were requested. All patients were advised to take levothyroxine on an empty stomach and avoid co-ingestion with food, coffee, and other medications known to interfere with levothyroxine absorption for at least one hour. The importance of regular tablet taking for people who admitted compliance issues was reiterated by letter, and GPs were requested to review these patients to reinforce this.

In 2011, TFTs and levothyroxine doses were collated from 119 patients (five had died and one had moved out the area) through GAFUR, electronic medical records, and direct contact with the GP practice.

Laboratory evaluations

Laboratory tests comprised biochemical analysis of serum samples for free thyroxine (fT4)/TSH (Siemens Advia Centaur) and immunoglobulin A (IgA; Dade Behring Prospec) along with indirect immunofluorescent testing for gastric PCA and endomysial antibodies (using rat stomach and primate distal oesophagus substrates respectively) and quantitative enzyme-linked immunosorbent assay (ELISA) detection

of thyroid peroxidase (TPO) antibodies. All laboratory tests were performed using standardized, commercial reagents and methodologies supported by robust internal quality control and external quality assurance processes. Serum IgA measurements were undertaken to validate the results of IgA isotype anti-endomysial antibody testing (as the then-standard methodology for celiac serological screening).

Ethics

The study protocol was discussed with the Grampian Research Ethics Committee who advised that formal ethical review was unnecessary and classed the study as a ''clinical service evaluation.'' Anonymity of all data was ensured in line with Caldicott principles.

Statistics

Data are presented as means except where otherwise specified. Normally distributed variables were compared with the Student's *t*-test. Nonparametric variables were compared with the Mann–Whitney test. Categorical data are presented as percentages and were analyzed with Fisher's exact test. Correlation coefficients were determined using Spearman's correlation test. Data were analyzed using the statistical software package SPSS for Windows v16.0 (SPSS, Inc.). The null hypothesis was rejected at the 5% significance level.

Results

Patient characteristics

There were 190 patients identified by the database as being on high-dose levothyroxine, but 16 patients were untraceable. Letters were sent to those 174 patients, with replies being received from 125 patients. There were more females (65.4%) than males (34.6%), but mean ages and body mass indexes (BMIs) were comparable (25) (Table 2).

Underlying diagnosis

The underlying thyroid diagnosis was unknown in 52 subjects (41.6%). Autoimmune hypothyroidism was documented in 47 individuals (37.6%), with 42 (34.4%) of the patients having positive TPO autoantibodies. Hypothyroidism was due to previous radioiodine in 16 (12.8%) patients and thyroid surgery in 10 (8%). Thyroid cancer patients are not included in the follow-up register.

Dose of levothyroxine and TSH levels

In 2009, 59 patients (46.5%) were on $>250\,\mu$g of levothyroxine, and this fell to 39 individuals (32.8%) in 2011. The average daily dose dropped by $>10\,\mu$g (p = n.s.; Table 3). Dose per kg was calculated, and lean body mass (25) was estimated at the start of the audit, but patient weight was not recorded at the end. The mean TSH levels also decreased from 4.5 mU/L to 3.5 mU/L (p = n.s.; normal 0.35–3.3 mU/L) with 41.6% of the whole group having a TSH within the reference range at baseline and increasing to 51.2% at the end of the audit period.

Causes of high-dose requirement

No cause for the high-dose requirement was found in the largest proportion of the group (46 patients, 36.8%). The presence of PCA was found in 27 patients (21.6%) of the cohort, and a similar proportion (25 patients, 20.8%) was on medication that can potentially interfere with levothyroxine absorption. Twenty-one patients (16.8%) admitted to compliance issues. Seven patients had positive anti-endomysial antibodies, with five patients (4%) having confirmed celiac disease, four of whom were new diagnoses. The greatest mean fall in levothyroxine dose (31 μg) was seen in the group who were on potentially interfering medication, with a maximum decrease of 150 μg in three patients. The group who had positive PCA also demonstrated a fall in mean levothyroxine dose (22 μg). By contrast, the group who admitted to poor compliance was found to have increased the

Table 2. Patient Characteristics at Start of Study

	Male	*Female*	*Whole group*
Number (%)	43 (34.4%)	82 (65.6%)	125
Mean age, years (range)	54.7 (22–85)	52.8 (26–96)	53.5 (22–96)
Mean weight, kg (range)	109 (73–180)	92.8 (54–152)	98.9 (54–180)
Mean estimated lean body mass, kg (range)	65.6 (47.7–92.3)	52.3 (34.1–73.6)	57.1 (34.1–92.3)
Mean height, m (range)	1.76 (1.57–1.93)	1.63 (1.4–1.84)	1.68 (1.4–1.93)
Mean BMI, kg/m^2 (range)	34.7 (20.8–53.9)	35.4 (20.3–65.3)	35.1 (20.3–65.3)
Dose levothyroxine, μg (range)	252 (200–350)	247 (150–350)	248
Dose levothyroxine per weight, μg/kg (normal 1.6–1.8 μg/kg)	2.4	2.8	2.6
Dose levothyroxine per estimated LBM, μg/kg (normal 2–3 μg/kg) (5)	3.9	4.8	4.5
TSH mU/L (normal 0.33–0.35 mU/L), baseline; final	3.72; 3.73	5.46; 3.29	4.46; 3.49

BMI, body mass index; LBM, estimated lean body mass based on Hume *et al.* (25); TSH, thyrotropin.

Table 3. Doses of Levothyroxine at the Start and End of the Study

	Start of study, n = *125*		*End of study,* n = *119*	
Dose of levothyroxine	*Number(%)*	*Mean dose (total weight)*	*Number (%)*	*Mean dose*
< 250 μg	44 (35.2)		62 (52.1%)	
250 or 275 μg	59 (47.2)	248μg (2.65μg/kg)	39 (32.8%)	235 μg
≥ 300 μg	22 (17.6)		18 (15.1%)	

dose ($M = 16$ μg), with the maximum dose increase being 75 μg in three patients (Table 4). None of these dose changes was statistically significant.

There was no significant difference in baseline BMI, height, or weight between the patients who had no cause found for their high-dose requirement and those who did, indicating that high doses of levothyroxine could not be attributable to weight *per se*.

Anti-endomysial antibodies

On initial screening, seven patients had positive anti-endomysial antibodies. The results of two patients were designated as transient, unexplained false positives with normal duodenal biopsy and with subsequent antibody testing being negative. In both cases, further investigation demonstrated that the false positivity arose from either point sampling or laboratory handling errors rather than from inherent suboptimal test performance characteristics of the endomysial antibody assay methodology or reagents. There were five patients (4%) with celiac disease, four diagnosed as a result of this audit and one diagnosed prior to the audit. One patient had a negative duodenal biopsy but remains positive for endomysial (and subsequently also antitissue transglutaminase) antibodies (presumably latent celiac disease). In this case, the levothyroxine dose increased by 25 μg, but a GFD was not advised at this time due to the absence of a positive biopsy. Two of the celiac patients were able to reduce their daily dose of levothyroxine by 50 μg, one of whom was also on carbamazepine, which can increase the levothyroxine dose requirement, and one patient continued on the same dose of levothyroxine. One patient was noted to have short-term memory loss, which may affect their compliance with a GFD. As only one patient had symptoms of celiac disease, there was possibly less incentive to follow a GFD, and while being advised to follow a GFD, actual compliance with this is beyond the scope of this audit.

PCA

PCA were found to be positive in 27 patients (21.6%) of the cohort. Seven patients were known to have pernicious anemia at the start of the audit period (Table 5). In the group who had PCA, there was a statistically significant negative correlation between the dose of levothyroxine per kg and the vitamin B12 level ($p = 0.04$, $r = -0.239$). There was no correlation between the absolute dose of levothyroxine and the B12 level.

Those who had positive endomysial or positive PCA took slightly higher doses of levothyroxine per kg (Table 4) than the other subgroups.

Autoimmune associations

Evidence of concurrent autoimmune disease was identified by the questionnaire in 14 patients (11.1%) in the cohort, with the greatest proportion of these having pernicious anemia. Other conditions included type 1 diabetes ($n = 2$, 1.6%), inflammatory bowel disease ($n = 2$, 1.6%), Addison's disease ($n = 1$, 0.8%), and vitiligo ($n = 1$, 0.8%).

Discussion

We have audited a large database of 17,500 patients on levothyroxine replacement therapy. Approximately 1% of

Table 4. Change in Dose According to Cause of High Levothyroxine Dose Requirement

	Number (% of whole group); male (% of subgroup)	*Mean dose levothyroxine start of study, kg = total weight*	*Mean dose levothyroxine end of study*	*Mean change in dose (range of dose change)*
No cause found	46 (36.8%); M = 14 (31.1%)	241 μg ($n = 44$) 2.63 μg/kg ($n = 40$)*	232 μg ($n = 41$)	− 13 μg (–5.4%) (–150 to 100 μg)
Gastric parietal cell antibody positive	27 (21.6%); M = 7 (25.9%)	241 μg ($n = 27$) 2.73 μg/kg ($n = 23$)*	220 μg ($n = 26$)	− 22 μg (–9.1%) (–150 to 75 μg)
Medication Interference	26 (20.8%); M = 12 (46.2%)	250 μg ($n = 26$) 2.62 μg/kg ($n = 23$)*	219 μg ($n = 25$)	− 31 μg (–12.4%) (− 150 to 25 μg)
Compliance	21 (16.8%); M = 10 (47.6%)	255 μg ($n = 21$) 2.57 μg/kg ($n = 19$)*	272 μg ($n = 20$)	16 μg (6.3%) (− 25 to 75 μg)
Endomysial antibody positive	5 (4.0%); M = 2 (40%)	270 μg ($n = 5$) 3.25 μ/kg ($n = 4$)*	250 μg ($n = 5$)	− 20 μg (− 7.4%) (− 50 to 25 μg)

*Weight not available for some patients.

Table 5. Frequency of Parietal Cell Antibody Positivity and Vitamin B12 Deficiency

Condition	n *(% of cohort)*	*Initial levothyroxine dose*	*Final levothyroxine dose*	*Change in dose (range of dose change, p=n.s.)*
Gastric parietal cell antibody positive	27 (21.6%)	241 μg ($n=27$)	220 μg ($n=26$)*	−21 μg (−150 to 75 μg)
Vitamin B12 deficiency	7 (5.5%)	257 μg ($n=7$)	235 μg ($n=7$)	−22 μg (−75 to 0 μg)

*One patient died.

patients were taking at least 225 μg of levothyroxine per day. We quantified underlying causes and established the impact of simple intervention, which included written and verbal advice, medication review, and implementation of a GFD when applicable.

Underlying causes

PCA. The presence of PCA was found in 27 patients (21.6%) of the cohort (the largest single identifiable association with high levothyroxine dose requirement), many of whom had normal vitamin B12 levels. This is slightly less than the prevalence of approximately 30% reported by Checchi *et al*. (26), but is significantly higher than the baseline population of 2.5–9% (7). The likely mechanism of reduced levothyroxine absorption in PCA positive patients is impaired hydrochloric acid secretion as a result of chronic oxyntic cell damage (17). Atrophic gastritis severe enough to cause impaired levothyroxine absorption was first described more than 100 years ago, and could potentially occur before pernicious anemia or biochemical vitamin B12 deficiency become apparent (27). The interval between development of PCA and subsequent pernicious anemia can be as much as two or three decades (28).

In our PCA-positive cohort, the dose/kg of levothyroxine negatively correlated with the level of serum vitamin B12 ($p=0.04$, $r=-0.239$) in those with vitamin B12 deficiency. This concurs with the data described by Checci *et al.* (17) where the degree of gastric wall damage was in proportion to the dose of levothyroxine per kg.

Medication interference. We enquired about commonly used medications such as iron supplements, calcium supplements, anticonvulsants, and proton pump inhibitors, which can interfere with levothyroxine dissolution and absorption. In the case of enzyme-inducing anticonvulsants, levothyroxine metabolism is increased, leading to higher dose requirements. A simple medication review revealed these factors, and if their other medications interfere with levothyroxine absorption, patients can be advised to take levothyroxine at bedtime, several hours after eating (29) and at least one hour before their other medications or a meal.

Endomysial antibody positivity. Endomysial antibodies were found in seven patients (5.6%) of our cohort with four (3.2%) being new diagnoses of celiac disease, one having previously diagnosed celiac disease, and two being false positive results. This equates to 4% of our population having a diagnosis of celiac disease, which is substantially higher than the background prevalence of 1% of the general population in the United Kingdom (NICE Guidelines) (30). Only one of the newly diagnosed patients had typical symptoms of celiac disease, which can include gastrointestinal symptoms, weight loss, anemia, and vitamin D deficiency (16). It is also recognized that a high levothyroxine dose requirement can be the only initial manifestation of celiac disease (3,20,22,31,32). Treating celiac disease, and hence optimizing absorption, can decrease the levothyroxine requirement as well as having a beneficial effect on general health and preventing other complications of celiac disease (31).

Poor compliance. Twenty-one patients (16.8%) admitted to compliance issues of missing a dose at least once/week. This increases the dose that is perceived to be required. For example, if a patient was prescribed 250 μg/day but missed only one dose per week, the actual dose taken would equate to 214 μg/day (14% dose reduction). Reasons for poor compliance may include the lack of symptoms if the patients miss a dose due to the long half-life of levothyroxine or the need to take levothyroxine on an empty stomach, particularly if they take other medications with a meal. It is important to address this in a nonaccusatory manner and give patient-centered advice to optimize compliance. Helpful suggestions include setting a reminder alarm or using a dosette box.

Patient weight. As there was no difference in weight between the groups with a specific cause of high dose requirement identified and those with no cause identified, it is unlikely that weight *per se* was a cause for high dose requirement.

Effects of intervention

After identifying the described causes of high levothyroxine dose requirement, interventions included verbal and written advice to patients and their family doctor, medication review, and referral to gastroenterologist for biopsy and management of celiac disease.

The biggest drop in levothyroxine dose was seen in the group who were on medication that could interfere with levothyroxine absorption, with a mean decrease of 31 μg and maximum decrease of 150 μg in three patients. Following recognition of the polypharmacy, a letter was sent to the patients and their GPs informing the patients to take their tablets on an empty stomach allowing at least one hour before eating or taking any more tablets. In those with a new diagnosis of celiac disease, there was a maximum dose decrease of 50 μg in two patients. Once the finding of positive endomysial antibodies was established, the patients were then referred to the GI team where they underwent a duodenal biopsy and appropriate dietary counselling. With the removal of gluten from their diets, it is likely that the duodenum repaired itself and absorption optimized (32).

While we are unclear about the reasons why the levothyroxine requirements fell in those with PCA, we speculate that providing general advice regarding medication ingestion and avoidance of intake with other medication, along with involvement in a clinical audit, may have contributed to an increased awareness and self-education regarding the levothyroxine dose and its intake.

We had hoped patients who admitted to poor compliance might change their habits and reduce their levothyroxine requirements. However, this group in our cohort had a mean increase in levothyroxine dose of 16 μg. Changing levothyroxine to once weekly dosing is an option (33). The weekly dose can be given with supervision from a family member or healthcare professional. Further studies on once weekly levothyroxine administration in poorly compliant patients are required to validate this method.

Limitations of the audit

This was an interventional audit, with the intervention being further evaluation, diagnosis, and advice to patients and referral to specialist teams, as appropriate. It is clinically relevant, as patients often have multiple factors that contribute to their high levothyroxine dose requirement. Dose reductions can be individually significant when causes, including autoimmune conditions or medication administration problems, are identified and dealt with. In 2011, following the intervention, the dose/kg was not available, as the GAFUR does not record weight. This, along with the small subcohorts, may contribute to the data not reaching statistical significance.

No cause for a high dose requirement was found in a third of the cohort. Possible reasons for this include data collection, with patients potentially overestimating their compliance, or other causes of impaired absorption such as the presence of *Helicobacter pylori*, which can affect gastric pH (18), lactose intolerance (34), over-the-counter medications (35), and dietary factors not accounted for (9,10).

Clinical practice points

There are limited published data from a single cohort of patients on high doses of levothyroxine, and this study addresses this by:

1. Describing characteristics and causes in patients needing high-dose levothyroxine replacement in a large population database.
2. Illustrating that medication that interferes with levothyroxine absorption accounts for 21% of patients on high-dose levothyroxine, and doses can be lowered after appropriate counselling.
3. Demonstrating that patients frequently miss doses of their levothyroxine, and reasons for this need to be addressed in order to assist patients achieve optimum compliance.
4. Suggesting that weight *per se* is not an adequate explanation for high-dose levothyroxine requirement.

This study also demonstrates the prevalence of previously unrecognized celiac disease (3.2%), gastric parietal cell antibodies (21.6%), and vitamin B12 deficiency (5.5%) in patients on high-dose levothyroxine, and that PCA-positive patients with low serum B12 levels can require a higher dose/kg of levothyroxine.

Author Disclosure Statement

No competing financial interests exist.

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