Drugs R D
DOI 10.1007/s40268-015-0116-6

ORIGINAL RESEARCH ARTICLE

Comorbidities, Concomitant Medications, and Diet as Factors Affecting Levothyroxine Therapy: Results of the CONTROL Surveillance Project

Marjorie McMillan[1] · Keith S. Rotenberg[2] · Kevin Vora[2] · Arnold B. Sterman[3] · Lionel Thevathasan[4,5] · Michael F. Ryan[6] · Munish Mehra[7] · Walter Sandulli[2]

Abstract

Background The CONTROL Surveillance Project was a comprehensive patient-based survey conducted among hypothyroid patients undergoing treatment. The primary objective of the study was to specifically quantify the prevalence of factors adversely affecting levothyroxine therapy.

Methods Participants were selected from a large proprietary database. Those eligible for the study completed a 21-question survey.

Results Of the eligible hypothyroid patients, 925 (92.5 %) were being treated with levothyroxine monotherapy. The mean age was 60.4 years; 755 (81.6 %) were female and 168 (18.2 %) were male. Almost half of those receiving levothyroxine (435, 47.0 %) had at least one comorbid condition that could adversely affect its absorption: gastroesophageal reflux disease (33.8 % of patients), irritable bowel syndrome (9.7 %), lactose intolerance (7.8 %), or a history of gastric bypass surgery or bowel resection (3.0 %). Other factors reported by many patients that could adversely affect levothyroxine absorption included use of prescription medications (20.6 %) and over-the-counter medications (34.3 %) used to treat comorbid gastrointestinal (GI) conditions; use of dietary supplements (51.8 %, primarily calcium and iron); and intake of foods/beverages high in fiber, iodine, or soy (68.0 %). Of the 13.4 % who reported difficulty controlling their hypothyroid symptoms, significantly more patients with comorbid GI conditions reported such difficulty (7.8 versus 5.6 %, $P < 0.01$). Frequent changes in levothyroxine dosing (two or more dose changes in the past year) were reported by 8.0 % of survey participants. Those with GI comorbidities were nearly twice as likely to have such changes (5.0 versus 3.0 %, $P < 0.01$).

Conclusion Better initial workup of patients, including identification of relevant GI comorbidities and allergies, may help in the early detection of factors that may affect the performance of levothyroxine.

M. McMillan, K. S. Rotenberg, and K. Vora contributed equally to this work.

✉ Marjorie McMillan
aci@wrte4u.com; margiesmc@aol.com

[1] McMillan Survey Research and Statistical Consulting, 8428 Arendal Cove, Memphis, TN, USA

[2] Akrimax Pharmaceuticals, LLC, Cranford, NJ, USA

[3] Morristown, NJ, USA

[4] LT Associates Ltd, Paris, France

[5] Department of Neuroscience, University of Oxford, Oxford, UK

[6] Medical/Marketing Decisions, LLC, Bridgewater, NJ, USA

[7] Quantum Change Group, LLC, Gaithersburg, MD, USA

Published online: 21 December 2015

Key Points

This study documented the prevalence in hypothyroid patients of factors known to affect levothyroxine efficacy and tolerability.

The results suggest that there is room for improved dialogue between physicians and patients regarding the proper administration of levothyroxine and the avoidance of foods and drugs that complicate its use.

For patients receiving higher-than-recommended doses of levothyroxine, a complete patient re-evaluation is recommended to determine the presence of factors that affect the ability of levothyroxine to achieve desired therapeutic results.

Adopting these steps may improve patients' quality of life and reduce the financial burden placed on the healthcare system, resulting from the frequent physician and pharmacy visits, medication adjustments, laboratory tests, and poor compliance associated with levothyroxine therapy.

1 Introduction

1.1 Background and Study Rationale

Hypothyroidism often results from autoimmune thyroid disease or thyroid resection [1, 2]. In the majority of cases, hypothyroidism can be treated effectively by oral thyroid hormone supplementation, most commonly with levothyroxine. Typically, patients require 1.6–1.8 μg of levothyroxine per kilogram of body weight, although lean body mass is a better criterion for dosing, with typical doses being 2–3 μg/kg [3–6].

Key factors adversely affecting levothyroxine performance have been widely reported in the clinical literature. They include comorbid conditions and their treatments, diet, tolerability of medication, and compliance with instructions for administration [7–18].

When levothyroxine is taken in a fasting state, up to 80 % of it can be absorbed [19].

However, the absorption of levothyroxine can be limited by a variety of diseases of the gastrointestinal (GI) tract, including inflammatory bowel disease (IBD), atrophic gastritis, celiac disease, *Helicobacter pylori* infection, gastroesophageal reflux disease (GERD), lactose intolerance, and gastroparesis, among others. The presence of these conditions may adversely affect levothyroxine absorption and thereby affect its dose requirements [7–12, 15–18, 20].

Additional factors that have been shown to affect levothyroxine absorption and performance—some of which may be related to the diseases of the GI tract noted above—include excess body weight; poor compliance with therapy; diet; gastric bypass surgery (reduced or delayed absorption); and use of certain nutritional supplements, vitamins, and medications, such as proton pump inhibitors, histamine receptor blockers, cholestyramine, and motility-modifying agents [7, 8, 12–17].

1.2 Study Objectives

The primary objective of the CONTROL Surveillance Project was to specifically quantify the prevalence of factors that are known to adversely affect levothyroxine performance, including:

- The prevalence of GI conditions known to affect drug absorption.
- Sensitivity to inactive ingredients contained in tablet drug formulations (i.e., excipients).
- Consumption of prescription and non-prescription medications, vitamins, foods, and beverages known to interfere with levothyroxine therapy.
- Patient understanding and compliance with levothyroxine administration guidelines (e.g., timing before and after meals).

2 Methods

2.1 Survey Development/Selection of Patients

The survey's content was developed as a cooperative effort between Akrimax Pharmaceuticals, LLC (Cranford, NJ, USA; the study sponsor) and Healthcare Research and Analytics, LLC (HRA; Parsippany, NJ, USA). HRA programmed the questionnaire into an online instrument via its Confirmit tool.

Prior to the full launch of the survey, it was tested to ensure that recording of data was consistent with the survey's questions and screening criteria. All survey responses were recorded confidentially, with the study sponsor being blinded to the responses of individual participants.

Participants were selected from a large proprietary database from Research Now®. Research Now® identified individuals with a self-reported diagnosis of primary hypothyroidism and recruited potential survey respondents for this online quantitative study via e-mail invitations from their proprietary "By-Invitation-Only®" panel. Each person contacted was assigned an individual ID for recording his or her entire survey participation history, including "Did not meet inclusion/exclusion criteria".

Those who accepted the invitation to take part in the survey were provided with a link to access the survey web page, where they were provided with information about the project, the anonymity of the survey's findings, an outline of what study subjects were required to do, and the time required. Subjects were informed that every attempt would be made to ensure the confidentiality of their data, and they were given a statement indicating that participation was voluntary and that withdrawal from the survey was possible at any stage.

Qualified subjects then completed the 21-question survey online (see "Appendix"). Subjects received an honorarium or gratuity (as termed by Research Now®) of US$20, based on the length of time a subject took to complete the survey online and the sample type, in keeping with the panel membership policies of Research Now®. The honorarium or gratuity did not exceed the agreed-upon amount set by the study sponsor or exceed the industry standards for market research among this sample type. Respondents received their honoraria/gratuities upon completion of the survey.

The survey was initiated on March 27, 2015, and completed on April 8, 2015.

2.2 Sample Size and Inclusion/Exclusion Criteria

The study was designed to be exploratory, and all statistical tests were performed to provide hypotheses for future research. The primary intent of the study was to gather data through a patient survey for better understanding of the prevalence of factors that are known to affect the performance of levothyroxine therapy. A pre-survey power analysis determined that a sample size of 1000 subjects would be sufficient to obtain estimates of prevalence rates that reflect the prevalence of certain GI conditions in the target population, with a 95 % confidence interval. For conditions such as GERD and *H. pylori* infection, whose prevalence in the general population is relatively high (15–40 %) [9, 10, 13], a sample size of 1000 subjects would provide an estimated 95 % confidence interval of ±2–3 %. For conditions with a low prevalence (e.g., a condition with a 0.75 % prevalence reported in the literature), such as Crohn's disease or ulcerative colitis [13], a sample size of 1000 subjects would provide an estimated 95 % confidence interval of ±0.53 %.

2.2.1 *Inclusion Criteria*

Each subject was required to meet all of the following criteria:

- Being treated with prescription medication for hypothyroidism.
- At least 19 years of age.
- US resident.
- Voluntary agreement to provide informed consent.
- Able to read English.
- Willing and able to complete the survey.

2.2.2 *Exclusion Criteria*

Any subject who met the following criterion was excluded:

- Not taking prescription medication to treat hypothyroidism.

2.3 Survey Completion and Quality Assurance

Patients entered their answers online. If a patient did not complete the survey, i.e., did not progress to the last question and enter an answer, his or her survey was recorded as incomplete and the answers were not included in the results. Incomplete surveys were categorized separately from survey terminations (patients disqualified through screening questions). More information regarding the survey completion and quality assurance process is presented in Table 1.

2.4 Data Management, Tabulations, and Statistical Analyses

The survey questions incorporated multiple choice/closed-ended questions, either "single punch/single select" or "multiple punch/select all that apply". Some questions included an open-ended option, "Other (specify: …)". Coding of all answers, data checks, summary tabulations, and statistical analyses of the data, including tests of significance for hypothesis testing, were performed by HRA. All were exploratory in nature, and no adjustments for multiple comparisons were made. The Quantum software package (IBM, Armonk, NY, USA) was used for all phases of data processing, online data collection sources, and SPSS®-generated data.

Table 1 Survey completion and quality assurance features

Feature
Personal computers used by patients
Clicking on survey link = unique respondent
Answers required for each question before proceeding
Return to previous questions not allowed
Survey exit without completing all questions = incomplete
Following survey submission, return to survey not allowed
Assignment of unique ID plus RVID programming prevented further access from same computer

RVID relevant ID

For continuous data, the number of subjects, mean, standard deviation, median, minimum, and maximum were calculated. Where appropriate, statistical tests were performed for hypothesis-testing purposes. Demographic data for the sample are presented by age, gender, and race.

2.5 Study Ethics

The protocol and appropriate related documents were reviewed and approved by IntegReview IRB (Austin, TX, USA), constituted and functioning in accordance with US federal guidelines [21].

The study was conducted in accordance with the standard operating practices of the study sponsor, Akrimax, which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines [21].

Each subject was informed that participation in the study was voluntary and that he or she could withdraw from the study at any time. A waiver of informed consent was issued by IntegReview IRB, in accordance with US federal guidelines [22].

Research Now® and HRA followed all national, regional, and local laws with respect to privacy and data protection. Research Now® ensured that the survey complied with all applicable industry standards set by the Council of American Survey Research Organizations (USA) and the Market Research Association (USA).

Secure servers at Research Now® were used to carry out the collection of survey data. Personal information was fully protected. Sampling teams did not have direct access to the database that might have revealed the identity of users. The survey remained anonymous and linked to the subject database using numeric IDs to ensure protection of the identity of each subject, and, as discussed above, to prevent unauthorized access to the survey and multiple participations by individual subjects.

3 Results

3.1 Survey Completion Rates

Sixty-six percent of invited subjects (1000/1506) qualified for, and completed, the survey. Such a high percentage was most likely attributable to the ability of Research Now® to target subjects who had been previously self-identified as hypothyroid patients. There were 320 incomplete surveys and 186 survey terminations.

3.2 Demographics

Of the 1000 patients who completed the survey, 925 (92.5 %) were receiving levothyroxine monotherapy. Others were being treated either with a combination of levothyroxine and other hypothyroid medications or with non-levothyroxine therapies. The mean age of patients receiving levothyroxine monotherapy was 60.4 years (range 19 to >75 years; 8 % were aged ≥75 years, 30 % were aged 65–74 years, 37 % were aged 55–64 years, and 15 % were aged 45–54 years). Most respondents [755 (81.6 %)] were female; only 168 (18.2 %) were male (two respondents declined to specify gender). Over 90 % of respondents were Caucasian (Table 2). Nearly two-thirds (62.9 %) had been taking hypothyroid medication for more than 10 years.

3.3 Prevalence of Relevant Comorbid Diseases/ Conditions and Use of Concomitant Medications

The prevalence of comorbid diseases or conditions that could adversely affect the absorption of levothyroxine was substantial and generally consistent with that reported in the medical literature for the population at large [9–13, 16, 23] (Table 3).

A substantial number of hypothyroid patients reported taking medications for comorbid GI conditions—either prescription medications (20.6 %) or over-the-counter (OTC) medications (34.3 %)—that could also adversely affect the absorption of levothyroxine (Tables 4, 5).

3.4 Other Key Factors Affecting Levothyroxine Performance

Certain dietary supplements are known to cause malabsorption of levothyroxine [7, 8, 13, 15, 17]. Overall, 51.8 % of patients indicated that they frequently take one or more such dietary supplements, with calcium supplements (47.5 %) and iron supplements (11.9 %) being most frequently reported.

A majority (68.0 %) of patients indicated that they frequently (more than twice weekly) eat food or consume beverages that are known to cause malabsorption of levothyroxine. These include high-fiber foods (bran flakes, broccoli, fiber bars, fiber drinks), foods high in iodine (dried seaweed, cranberries, lobster, cod, plain yogurt), and soy-based foods.

More than 20 % of patients reported taking levothyroxine during breakfast or later in the day, including during lunch or dinner. Many patients (21.5 %) reported taking levothyroxine less than the recommended 30 min before eating.

Of the 925 patients who were receiving levothyroxine, 112 (12.1 %) reported experiencing GI upset (nausea, stomach cramps, or diarrhea) when taking it.

Overall, 15.2 % of patients receiving levothyroxine reported allergies to one or more excipients that are known

Table 2 Racial and ethnic distribution of survey participants

	Total [*n* (%)]	Hypothyroidism w/o GI condition [*n* (%)]	Hypothyroidism w/GI condition [*n* (%)]
Total	925	490	435
Non-Hispanic White or Euro-American	867 (94)	454 (93)	413 (95)
Black, Afro-Caribbean, or African American	13 (1)	5 (1)	8 (2)
Latino or Hispanic American	17 (2)	8 (2)	9 (2)
East Asian or Asian American	13 (1)	11 (2)	2 (*)
South Asian or Indian American	4 (*)	3 (1)	1 (*)
Middle Eastern or Arab American	3 (*)	3 (1)	– (–)
Native American or Alaskan Native	5 (1)	2 (*)	3 (1)
Mixed race	2 (*)	2 (*)	– (–)
Prefer not to answer	9 (1)	6 (1)	3 (1)
Total mentions	933	494	439

Some respondents specified more than one category

w/GI with gastrointestinal, *w/o GI* without gastrointestinal

* <1 %

Table 3 Prevalence of relevant concomitant diseases/conditions in hypothyroid patient population receiving levothyroxine ($n = 925$)

Concomitant disease/condition	*n* (%)
Acid reflux or GERD	313 (33.8)
IBS	90 (9.7)
Food allergies	85 (9.2)
Lactose intolerance	72 (7.8)
Gastric bypass or bowel resection	28 (3.0)
H. pylori infection	19 (2.1)
Gastroparesis	15 (1.6)
Celiac disease	10 (1.1)
Ulcerative colitis	10 (1.1)
Crohn's disease	6 (0.6)
Atrophic gastritis	1 (0.0)
Other[a]	157 (17.0)
None of the above	488 (52.8)

Because patients could specify more than one concomitant disease or condition, the total for the last column exceeds 100 %

GERD gastroesophageal reflux disease, *IBS* irritable bowel syndrome

[a] Other = numerous gastrointestinal and non-gastrointestinal conditions

Table 4 Hypothyroid patients on levothyroxine ($n = 925$) receiving medication for relevant concomitant diseases/conditions

Concomitant disease/condition	*n* (%)
Acid reflux or GERD	246 (26.6)
IBS	28 (3.0)
Food allergies	11 (1.2)
Lactose intolerance	9 (1.0)
Gastric bypass or bowel resection	8 (0.9)
Gastroparesis	7 (0.8)
Ulcerative colitis	6 (0.6)
Crohn's disease	5 (0.5)
Atrophic gastritis	1 (0.1)
Celiac disease	1 (0.1)
H. pylori infection	1 (0.1)
Other[a]	139 (15.0)
None of the above	607 (65.6)

Because patients could specify medication for more than one concomitant disease or condition, the total for the last column exceeds 100 %

GERD gastroesophageal reflux disease, *IBS* irritable bowel syndrome

[a] Other = numerous gastrointestinal and non-gastrointestinal conditions

to be included in most tablet drug formulations. Those most frequently reported were allergies to lactose (11.9 %), gluten (3.78 %), and food dyes and sucrose (1–2 % each).

3.5 Control of Symptoms

Lack of hypothyroid symptom control was reported by survey respondents. Of the 124 patients (13.4 %) reporting difficulty controlling their hypothyroid symptoms, significantly more patients with comorbid GI conditions who were taking levothyroxine reported difficulty with symptom control, versus those without such conditions ($P < 0.01$) [Table 6].

3.6 Changes in Hypothyroid Medication/Changes in Levothyroxine Dose

More than 80 % of surveyed patients reported having had at least one change in their prescribed hypothyroid medication since beginning therapy. Many patients (16.0 %) reported 5–10 changes, and 6.1 % reported having >10

changes. As presented in Fig. 1, the overall number of self-reported changes in hypothyroid medication since the beginning of treatment with levothyroxine was comparable between those with and those without comorbid GI conditions.

While many participants in the CONTROL Surveillance Project had been on levothyroxine for several years, many (31.4 %) reported a change in levothyroxine dose within the past year. Among patients experiencing ≥2 levothyroxine dose changes during the past year, those with self-reported GI comorbidities had nearly twice the prevalence of the other patients ($P < 0.01$) [Fig. 2].

3.7 Quality-of-Life Factors and Self-Reported Patient Satisfaction

While the CONTROL Surveillance Project was not designed to measure quality of life, nearly 11 % of respondents indicated that their thyroid condition "reduced their quality of life" and "rendered them unable to do the things they used to do". Similarly, 28.4 % of all respondents indicated that their thyroid condition limited their ability to "take on any activity or task". Overall, 16.6 % of patients indicated that they have been "unable to live life normally since undergoing treatment for hypothyroidism".

A minority of respondents reported ever discussing with their physician topics such as the proper administration of hypothyroid medication (44.4 %), concomitant use of prescription medications (29.5 %), concomitant use of OTC medications (12.6 %), use of dietary or food supplements (10.9 %), or the presence of stomach or GI conditions (10.0 %) or food allergies (4.1 %) that may interfere with levothyroxine therapy.

Overall, 19.6 % of patients stated that they are not fully satisfied with their hypothyroid treatment. Significantly more patients with comorbid GI conditions reported dissatisfaction with their thyroid treatment, versus those without such conditions ($P < 0.05$) (Table 7).

Table 5 Numbers of hypothyroid patients on levothyroxine ($n = 925$) who were taking antacids or acid reducers >2 times/week

Antacid or acid reducer	*n* (%)
Prescription acid reducer	– (–)
Proton pump inhibitor[a]	180 (19.5)
Histamine (H_2)-receptor blocker[b]	0 (0.0)
Non-prescription acid reducer	– (–)
Proton pump inhibitor[a]	83 (9.0)
Histamine (H_2)-receptor blocker[b]	53 (5.7)
Non-prescription antacids[c]	168 (18.2)
Other non-prescription antacid or acid reducer[d]	13 (1.4)
Other prescription antacid or acid reducer[e]	11 (1.2)
None of the above	543 (58.7)

Because patients could specify more than one medication, the total for the last column exceeds 100 %

[a] Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

[b] Cimetidine, ranitidine

[c] Multiple brands

[d] Other non-prescription antacids or acid reducers = generics of multiple products

[e] Other prescription antacids or acid reducers = generics of multiple products

4 Discussion

Many factors contribute directly or indirectly to the failure of levothyroxine therapy. These can adversely affect treatment satisfaction and can lead to unnecessary consumption of healthcare resources in the form of increased physician and pharmacy visits, laboratory costs, and medication adjustments [24–33].

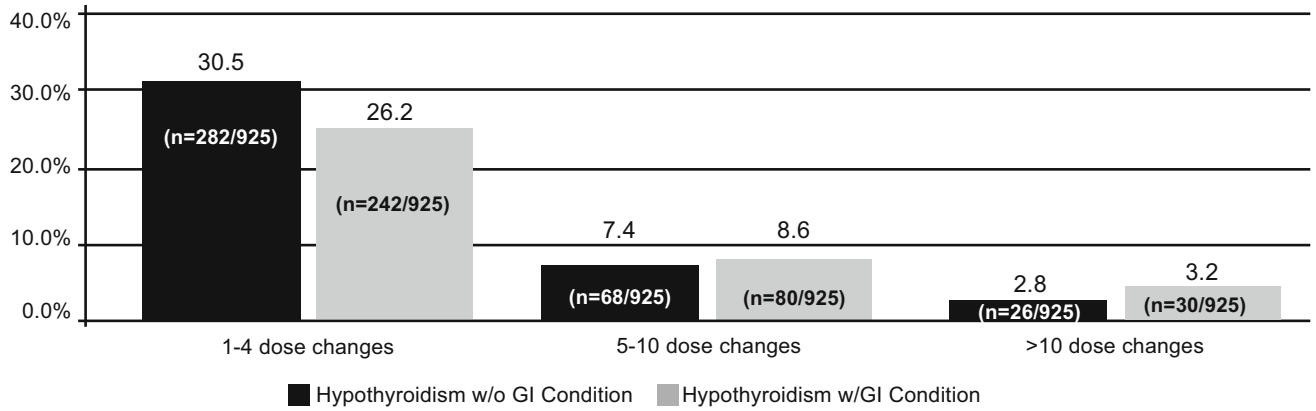
The CONTROL Surveillance Project is one of the most comprehensive patient-based surveys ever conducted among hypothyroid patients. It has helped to document the prevalence of factors that can complicate levothyroxine therapy. Unlike previous community-based surveys or retrospective analyses of patient medical records [3, 34, 35], CONTROL Surveillance attempted to measure the influences that diet, OTC medication use, and the degree of adherence to levothyroxine administration guidelines (before or after meals) may have on levothyroxine therapy. Such information is rarely, or only sporadically, recorded in patient records.

Table 6 Patients indicating their level of agreement with the statement "It's hard to control my hypothyroid symptoms"

	Hypothyroidism w/o GI condition [*n* (%)]	Hypothyroidism w/GI condition [*n* (%)]	Total [*n* (%)]
Completely or somewhat agree	52 (5.6)	72 (7.8)	124 (13.4)
Slightly agree or disagree	438 (47.4)	363 (39.2)	801 (86.6)
Total	490 (53.0)	435 (47.0)	925

Chi-square test *P* value: <0.01

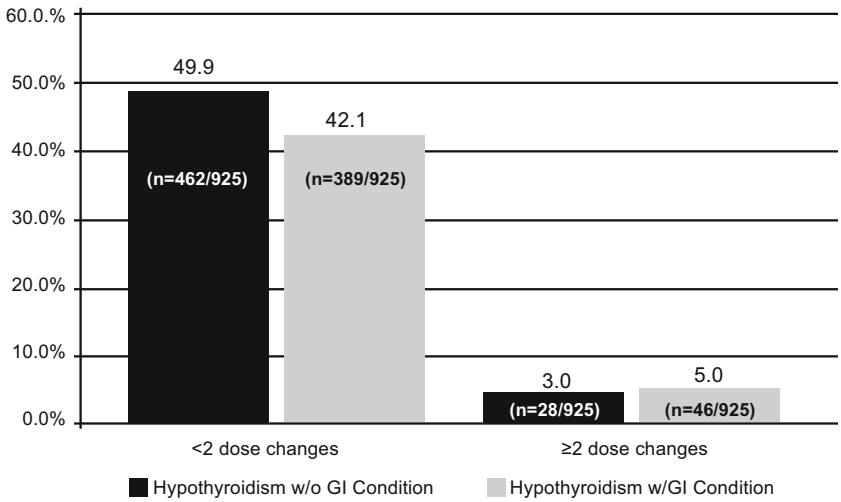
w/GI with gastrointestinal, *w/o GI* without gastrointestinal



Note: 88 (9.5%) of patients having hypothyroidism w/o GI conditions and 71 (7.7%) of patients w/GI conditions reported never having a change in their hypothyroid medication; 26 (2.8%) of patients having hypothyroidism w/o GI conditions and 12 (1.3%) of patients w/GI conditions did not know if they had ever had a change in their hypothyroid medication.w/GI with gastrointestinal, w/o GI without gastrointestinal

Fig. 1 Total number of changes in hypothyroid medication since initiation of therapy

Fig. 2 Number of changes in dose of levothyroxine in the past year



Chi-Square Test *P*-value: <0.01. w/GI with gastrointestinal, w/o GI without gastrointestinal

Table 7 Patients indicating their level of agreement with the statement "I am satisfied with my hypothyroid treatment"

	Hypothyroidism w/o GI condition [*n* (%)]	Hypothyroidism w/GI condition [*n* (%)]	Total [*n* (%)]
Completely or somewhat agree	407 (44.0)	337 (36.4)	744 (80.4)
Slightly agree or disagree	83 (9.0)	98 (10.6)	181 (19.6)
Total	490 (53.0)	435 (47.0)	925

Chi-square test *P* value: <0.05

w/GI with gastrointestinal, *w/o GI* without gastrointestinal

The results of the CONTROL Surveillance Project quantify the prevalence of GI disorders that can inhibit the absorption of levothyroxine and necessitate frequent levothyroxine dose adjustments. Of the 925 hypothyroid patients surveyed who were currently taking levothyroxine, 435 (47.0 %) had at least one commonly prevalent GI disease or condition. The prevalence rates of GERD, irritable bowel syndrome (IBS), gastroparesis, and a history of gastric bypass surgery or bowel resection were generally consistent between those found in the CONTROL

Surveillance Project and those reported in the literature for general patient populations [9–13, 16, 23]. It should be noted that the age range (from 19 to >75 years) and mean age (60.4 years) of the patient population in this survey mirror those of the hypothyroid population reported in the medical literature and in clinical practice [36], which would be expected with such a large sample of patients who self-identified as having this condition.

In comparison with all other patients in this study, significantly more of those who had such GI disorders reported difficulty achieving control of their hypothyroid symptoms ($P < 0.01$). Similarly, a relationship between these commonly prevalent GI conditions and the need for levothyroxine dose adjustment was noted. Participants experiencing ≥2 levothyroxine dose changes in the past year were more likely to have one or more of these conditions.

Hypothyroid patients requiring increased doses of levothyroxine have been well documented in the medical literature and in clinical practice [37]. Data from five different studies have shown that non-optimal levothyroxine therapy, resulting in thyroid-stimulating hormone (TSH) levels above (or below) the reference range, is common, ranging from 32 to 48 % of patients [38–42].

In a study by Vaisman et al. [42], questionnaires were used to evaluate levothyroxine replacement treatment in patients with primary hypothyroidism being followed in referral centers in Brazil. Among all patients taking thyroid medication, 42.7 % had an abnormal serum TSH level (28.3 % were undertreated and 14.4 % were overtreated). The investigators concluded that a significant number of patients taking thyroid hormones are not in the therapeutic range, on the basis of TSH assays. Clinicians should, therefore, consider monitoring patients on thyroid replacement more frequently and provide patients with more precise recommendations about proper use of levothyroxine.

Vigário et al. [43] performed a cross-sectional study involving 2057 patients receiving levothyroxine replacement for primary hypothyroidism at four referral centers in Brazil. The results showed that a total of 14.4 % of patients were overtreated (13.0 % with subclinical hyperthyroidism and 1.4 % with overt hyperthyroidism). The prevalence of undertreatment was 25.9 % (21.5 % with subclinical hypothyroidism and 4.4 % overt hypothyroidism). The investigators concluded that undertreatment of hypothyroidism is associated with poor patient health-related quality of life (especially physical and emotional aspects), and adequate levothyroxine therapy should always be given to maintain serum TSH levels within the reference range.

It is also interesting to note that more than 20 % of patients in our survey reported taking levothyroxine during breakfast or later in the day, including during lunch or dinner. Many patients (21.5 %) reported taking levothyroxine less than the recommended 30 min before eating. Inappropriate timing of ingestion may have contributed to less-than-optimal levothyroxine performance in these patients.

In a randomized, double-blind, crossover trial involving 90 patients, however, Bolk et al. [44] found that levothyroxine taken at bedtime rather than in the morning significantly improved thyroid hormone levels. These investigators recommended that clinicians consider prescribing levothyroxine intake at bedtime.

Regarding gastric bypass surgery, its impact on the absorption of levothyroxine can vary, depending on the procedure [23]. Rubio et al. [45] evaluated the absorption of levothyroxine in morbidly obese patients before ($n = 15$) and after ($n = 15$) a Roux-en-Y surgical procedure. Although bypass surgery did not diminish the absorption of levothyroxine in this study, a small but significant delay in the absorption of levothyroxine was observed in patients following surgery.

4.1 Comparisons with Prior Patient Surveys

The CONTROL Surveillance Project extends the findings of two earlier, more limited, surveys among treated hypothyroid patients [34, 35]. In 1977, the Whickham Survey [34] determined the prevalence of overt hypothyroidism to be 1.4–1.9 % in females and 0.1 % in males in a general population of 2779 (mean age 47 years) in County Durham, England. In 2006, Wilson et al. [35] conducted another community-based, cross-sectional survey in the UK, involving 5690 subjects aged 65 years and older—the Birmingham Elderly Survey. The investigators reported prevalence rates of 0.4 % for overt hypothyroidism and 2.9 % for subclinical hypothyroidism. In obtaining subject demographic information, the investigators reported the overall prevalence rates of GI diseases to be 0 % in subjects with overt hypothyroidism and 1.8 % in subjects with subclinical hypothyroidism. However, the sample sizes of the two groups were small ($n = 23$ and $n = 168$, respectively), and the GI diseases were not categorized systematically. In both surveys, there was no attempt to document the prevalence of factors [such as diet, medication consumption (prescription and non-prescription), and patient behaviors] that are known to affect the performance of levothyroxine.

4.2 Study Limitations

The CONTROL Surveillance Project was controlled and powered to determine statistically meaningful results and to provide key insights into important issues surrounding

levothyroxine treatment in hypothyroid patients. But, given the lack of control over patient inclusion by race, among other reasons, its findings should be considered more hypothesis generating than conclusive. Because this was a patient survey with no access to patient records, certain data, such as thyroid hormone levels, were not available to assist in interpretation of the results. The high percentage of Caucasian respondents in CONTROL Surveillance is not consistent with the racial mix of the hypothyroid population at large reported in the published literature [46]. However, the overrepresentation of Caucasians is consistent with the results reported in other patient survey panels. Knapton and Myers [46] have reported the tendency of many non-Caucasians to have lower response rates to online surveys; the reasons for it are unclear.

5 Conclusion

Levothyroxine has been the "gold standard" treatment for hypothyroidism for over 60 years. It is one of the most frequently used medications in the USA, with over 115 million prescriptions dispensed in 2013 [47]. Notwithstanding the ubiquitous use of levothyroxine, there have been few surveys that address the prevalence of commonly cited reasons for its frequently suboptimal performance.

The CONTROL Surveillance Project documents the prevalence of factors that are well known to affect levothyroxine efficacy and tolerability. GI comorbidities, concomitant drug use, and dietary habits that complicate levothyroxine therapy may be more prevalent among treated hypothyroid patients than is generally understood. Similarly, allergies to excipient ingredients found in most tablet drug formulations may also be more common than is generally perceived. The frequency of levothyroxine dose changes, the need for unexpectedly high doses, and the inability of levothyroxine to control the symptoms of hypothyroidism have been shown to correlate with the presence of these factors [48].

The results of the CONTROL Surveillance Project suggest that there is room for improved dialogue between physicians and patients regarding the proper administration of levothyroxine and the avoidance of foods and drugs that complicate its use. In particular, better initial workup of patients (including identification of relevant comorbidities and allergies) may help to detect factors that can lead to suboptimal efficacy or tolerability of levothyroxine. For patients already on levothyroxine therapy who are receiving doses that are higher than those recommended by current treatment guidelines [49], a complete patient re-evaluation is recommended to determine the presence of factors that affect the ability of levothyroxine to achieve desired therapeutic results [50–52]. Adopting these additional steps may improve the quality of life for patients and reduce the financial burden placed on the healthcare system that results from the frequent physician and pharmacy visits, medication adjustments, laboratory tests, and poor compliance associated with levothyroxine therapy.

Acknowledgments The authors would like to thank Lisa Rowe and Brenda Kiminyo-Bode at Healthcare Research and Analytics, LLC (Parsippany, NJ, USA) and Aesculapius Consulting, Inc. (East Brunswick, NJ, USA) for their editorial support.

Compliance with Ethical Standards

Conflicts of interest All potential conflicts of interest and financial considerations are provided in the "Disclosures" section below.

Author participation Each of the authors participated in the data collection, data organization, and/or writing of this manuscript.

Disclosures This study was funded by Akrimax Pharmaceuticals, LLC (Cranford, NJ, USA). Marjorie McMillan, MPH (McMillan Survey Research and Statistical Consulting, Memphis, TN, USA) was contracted by Akrimax for survey research consulting services. Keith S. Rotenberg, PhD, Kevin Vora, RPh, and Walter Sandulli, MBA, are employees of Akrimax. Arnold B. Sterman, MD, has been a consultant for Akrimax and Newron Sweden. Lionel Thevathasan, MD, owner of LT Associates Ltd (Paris, France), has been a consultant for Akrimax, AstraZeneca, Bayer, Daiichi-Sankyo, Medscape, Roche, and Sanofi. Michael F. Ryan, PhD (Medical/Marketing Decisions, LLC, Bridgewater, NJ, USA) was contracted by Akrimax for survey research and writing services. Munish Mehra, PhD (Quantum Change Group, LLC, Gaithersburg, MD, USA) was contracted by Akrimax for statistical services.

Appendix

Hypothyroid Patient Survey

CB12-X438
SURVEY LENGTH: 10-15 MINUTES (21 QUESTIONS)
QUOTA: 1000 PATIENTS

SCREENER

S1. Please indicate which of the following, if any, medical conditions you have been diagnosed with and/or procedures you have had. (Select all that apply.)

a. Acid reflux or GERD
b. Atrophic gastritis
c. Celiac disease
d. Crohn's disease (inflammation affecting the entire digestive tract)
e. Food allergies
f. Gastric bypass or bowel resection
g. Gastroparesis (slows/stops the movement of food from the stomach)
h. H. pylori infection (a bacteria that infects the stomach)
i. Hypothyroidism (underactive thyroid) **TERMINATE IF NOT SELECTED**
j. Hyperthyroidism (overactive thyroid) **I & J ARE MUTUALLY EXCLUSIVE**
k. IBS (irritable bowel syndrome)
l. Lactose intolerance
m. Ulcerative colitis (inflammation affecting the colon/large bowel)
n. Other (specify:_____)
o. None of the above **MUTUALLY EXCLUSIVE**

SHOW ONLY OPTIONS SELECTED IN S1

S2. For which of the following, if any, are you currently taking medication(s) prescribed by your doctor? (Select all that apply.)

a. Acid reflux or GERD
b. Atrophic gastritis
c. Celiac disease
d. Crohn's disease (inflammation affecting the entire digestive tract)
e. Food allergies
f. Gastric bypass or bowel resection
g. Gastroparesis (slows/stops the movement of food from the stomach)
h. H. pylori infection (a bacteria that infects the stomach)
i. Hypothyroidism (underactive thyroid) **TERMINATE IF NOT SELECTED**
j. Hyperthyroidism (overactive thyroid) **I & J ARE MUTUALLY EXCLUSIVE**
k. IBS (irritable bowel syndrome)
l. Lactose intolerance
m. Ulcerative colitis (inflammation affecting the colon/large bowel)
n. **<<S1 OTHER>>**
o. None of the above **MUTUALLY EXCLUSIVE**

S3. Which of the following thyroid medications are you currently taking? (Select all that apply.)

a. Armour® Thyroid
b. Cytomel®
c. Levothroid®
d. Levoxyl®
e. Nature-Throid®
f. Synthroid®
g. Unithroid®
h. Tirosint®
i. WP Thyroid®
j. Generic levothyroxine
k. Other (specify:_____) **TERMINATE IF ONLY OTHER IS SELECTED**

S4. What is your age?
_____years **(OE – number range 1-99 – MUST BE 19 OR OLDER OTHERWISE TERMINATE)**

MAIN QUESTIONNAIRE

1. Since you were first diagnosed with hypothyroidism, how long have you been taking hypothyroid prescription medication(s) to treat the condition? (Select one.)
   a. Less than 6 months
   b. About 6-12 months
   c. About 1-2 years
   d. About 3-5 years
   e. About 6-10 years
   f. More than 10 years

2. Since you first started taking hypothyroid prescription medication(s), how many times has your prescribed hypothyroid medication been changed? (Select one.)
   a. Never
   b. 1 time
   c. 2 times
   d. 3 times
   e. 4 times
   f. 5-10 times
   g. >10 times
   h. I don't know

3. Have you ever stopped taking your prescribed hypothyroid medication for more than one month (past or present prescription)?
   a. Yes
   b. No

ASK IF Q3 = Yes

4. When you re-started your hypothyroid medication which one of the following were you prescribed? (Select one)
   a. The same dose of the same brand of hypothyroid medication you were taking before
   b. A different dose of the same brand of hypothyroid medication you were taking before
   c. A different brand of hypothyroid medication than you were taking before

ASK IF Q3 = Yes

5. Which of the following were reason(s) you stopped taking your hypothyroid medication for more than one month? (Select all that apply.)

RANDOMIZE

   a. Felt better, no need to take medicine
   b. Medication too expensive
   c. My brand was not available at pharmacy
   d. Insurance company wouldn't cover
   e. Prefer a non-drug remedy
   f. Medicine made me feel worse
   g. Other

6. Have you ever, past or present, experienced upset stomach or gastrointestinal (GI) upset (i.e. experienced symptoms like nausea, stomach cramps, diarrhea) when taking your hypothyroid medication? (Select one.)

Never	Rarely	Sometimes	Often	Always
○	○	○	○	○

TO BE CORRELATED WITH TREATMENT AND PHYSICIAN DISCUSSION

7. What type of doctor currently prescribes your hypothyroid medication? (Select one.)
   a. Primary Care Physician
   b. Endocrinologist
   c. Thyroid Specialist
   d. Other (specify:_____)

8. How many times in the past year, has your current doctor changed the dose of your **current** hypothyroid medication since you started taking it? (Select one.)
   a. Never
   b. 1 time
   c. 2 times
   d. 3 times
   e. 4 times
   f. 5-10 times
   g. >10 times

9. When do you typically take your hypothyroid medication?
   ALLOW RESPONDENT TO SELECT AT ANY TICK MARK; ALLOW UP TO TWO SELECTIONS

10. When you take your hypothyroid medication, do you typically take it **before** eating or **after** eating? (Select one.)
    a. Before eating
    b. After eating

ASK IF Q10 = Before eating

11. How much time, before eating, do you typically take your hypothyroid medication? (Select one.)
    a. Less than 10 minutes before eating
    b. 10-19 minutes before eating
    c. 20-29 minutes before eating
    d. 30-39 minutes before eating
    e. 40-49 minutes before eating
    f. 50-59 minutes before eating
    g. 1-2 hours before eating
    h. More than 2 hours before eating

ASK IF Q10 = After eating

12. How much time, after eating, do you typically take your hypothyroid medication? (Select one.)
    a. Less than 10 minutes after eating
    b. 10-19 minutes after eating
    c. 20-29 minutes after eating
    d. 30-39 minutes after eating
    e. 40-49 minutes after eating
    f. 50-59 minutes after eating
    g. 1-2 hours after eating
    h. More than 2 hours after eating

13. With regard to hypothyroid treatment, which of the following, if any, have you ever discussed with the doctor who currently prescribes your hypothyroid medication? (Please check all that apply.)

RANDOMIZE

a. Dietary/food supplements
b. Food allergies
c. Nutrition
d. Use of OTC medications
e. Use of other prescription medications
f. Stomach or gastrointestinal conditions
g. Thyroid medication use (i.e., the proper way to take the medication, limitations, etc.)
h. None of the above **MUTUALLY EXCLUSIVE**

14. With regard to hypothyroid treatment, which of the doctor-provided resources are most important to you? (Please rank in order of importance, where 1 = The most important resource, 2 = Second most important, and so on.) **[PN – INSERT RANKING BOX TO ALLOW RANKING OF ALL RESOURCES LISTED]**

RANDOMIZE

a. Product samples
b. Product literature
c. Product coupons/vouchers
d. Disease state information
e. Information about support groups
f. Information about online resources

15. Thinking of your **overall** experience of being treated for hypothyroidism, please indicate your level of agreement with the following statements:

DO NOT RANDOMIZE

I am being treated for hypothyroidism and……	Disagree	Slightly agree	Somewhat agree	Completely agree
1. Nobody seems to understand or care about how I feel	❍	❍	❍	❍
2. I don't know where to get reliable information about my thyroid condition	❍	❍	❍	❍
3. It's hard to control my hypothyroid symptoms	❍	❍	❍	❍
4. My thyroid condition reduces my quality of life causing me not to be able to do the things I used to do	❍	❍	❍	❍
5. I am able to take on anything without being limited by my thyroid condition	❍	❍	❍	❍
6. I am satisfied with my hypothyroid treatment	❍	❍	❍	❍
7. I can live life normally	❍	❍	❍	❍

16. Please indicate which of the following antacid or acid reducers, if any, you take on a frequent basis **(more than 2 times per week)**. (Select all that apply.)

NOTE: PRODUCTS ARE TO BE GROUPED ON THE BACKEND UNDER NON-PRESCRIPTION ANTACIDS, PRESCRIPTION ANTACIDS, AND PRESCRIPTION ACID REDUCERS. DO NOT SHOW THESE GROUPS, RED TEXT, TO RESPONDENT.

a. AcipHex® **PRESCRIPTION ACID REDUCERS**
b. Alka-Seltzer® **NON-PRESCRIPTION ANTACIDS**
c. Gaviscon® **NON-PRESCRIPTION ANTACIDS**
d. Maalox® **NON-PRESCRIPTION ANTACIDS**
e. Nexium®, non-prescription **NON-PRESCRIPTION ACID REDUCERS**
f. Nexium®, prescription **PRESCRIPTION ACID REDUCERS**
g. Pepto-Bismol® **NON-PRESCRIPTION ANTACIDS**
h. Prevacid®, non-prescription **NON-PRESCRIPTION ACID REDUCERS**
i. Prevacid®, prescription **PRESCRIPTION ACID REDUCERS**

j. Prilosec®, non-prescription **NON-PRESCRIPTION ACID REDUCERS**
k. Prilosec®, prescription **PRESCRIPTION ACID REDUCERS**
l. Protonix® **PRESCRIPTION ACID REDUCERS**
m. Rolaids® **NON-PRESCRIPTION ANTACIDS**
n. Tagamet HB 200® **NON-PRESCRIPTION ACID REDUCERS**
o. Tums® **NON-PRESCRIPTION ANTACIDS**
p. Zantac® **NON-PRESCRIPTION ACID REDUCERS**
q. Other non-prescription antacid or acid reducers (specify:_____) **TBD, POST CODING**
r. Other prescription antacid or acid reducers (specify:_____) **TBD, POST CODING**
s. I do not take any antacid or acid reducers on a frequent basis **MUTUALLY EXCLUSIVE**

17. Which of the following dietary supplements, if any, do you take on a frequent basis **(more than 2 times per week)**? (Select all that apply.)
    a. Calcium
    b. Chromium picolinate
    c. Iron
    d. None of the above **MUTUALLY EXCLUSIVE**

18. Which of the following, if any, do you eat/drink **more than 2 times per week**? (Select all that apply.)
    a. Soy-based foods (i.e., soy beans, soy milk, tofu, etc.)
    b. Grapefruit / grapefruit juice
    c. Foods high in fiber (i.e. bran flakes, broccoli, fiber bars, fiber drinks, etc.)
    d. Foods high in iodine (i.e. dried seaweed, cranberries, lobster, cod, plain yogurt etc.)
    e. None of the above **MUTUALLY EXCLUSIVE**

19. Which of the following foods or food ingredients, if any, trigger an allergic reaction in you? (Select all that apply.)
    a. Food dyes
    b. Gluten
    c. Nuts
    d. Lactose (dairy)
    e. Sucrose (sugar)
    f. Other (specify:_____**[OE - text]**
    g. I do not suffer from any food allergies **HIDE IF S1_D IS SELECTED; MUTUALLY EXCLUSIVE**

20. What is your gender?
    a. Male
    b. Female
    c. Prefer not to answer

21. Which of the following best represents your racial or ethnic heritage? (Select all that apply)
    a. Non-Hispanic White or Euro-American
    b. Black, Afro-Caribbean, or African American
    c. Latino or Hispanic American
    d. East Asian or Asian American
    e. South Asian or Indian American
    f. Middle Eastern or Arab American
    g. Native American or Alaskan Native
    h. Other (please specify)_____ **(OE – text)**
    i. Prefer not to answer

[END SURVEY]

Thank you for your participation in this survey!

References

1. Dar RA, Chowdri NA, Parray FQ, Wani SH. An unusual case of Hashimoto's thyroiditis with four lobed thyroid gland. N Am J Med Sci. 2012;4:151–3.
2. Yaturu S, Fontinot J, Rowland T. Mixed medullary thyroid cancer and follicular cancer. Am J Case Rep. 2011;12:1–4.
3. Robertson HM, Narayanaswamy AK, Pereira O, et al. Factors contributing to high levothyroxine doses in primary hypothyroidism: an interventional audit of a large community database. Thyroid. 2014;24:1765–71.
4. Santini F, Pinchera A, Marsili A, et al. Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid disease. J Clin Endocrinol Metab. 2005;90:124–7.
5. Roos A, Linn-Rasker SP, van Domburg RT, Tijssen JP, Berghout S. The starting dose of levothyroxine in primary hypothyroidism treatment: a prospective, randomized, double-blind trial. Arch Intern Med. 2005;165:1714–20.
6. Mandel SJ, Brent GA, Larscn PR. Levothyroxine therapy in patients with thyroid disease. Ann Intern Med. 1993;119:492–502.
7. Khandelwal D, Tandon N. Overt and subclinical hypothyroidism: who to treat and how. Drugs. 2012;72:17–33.
8. Liwanpo L, Hershman JM. Conditions and drugs interfering with thyroxine absorption. Best Pract Res Clin Endocrinol Metab. 2009;23:781–92.
9. Badillo R, Francis D. Diagnosis and treatment of gastroesophageal reflux disease. World J Gastrointest Pharmacol Ther. 2014;5:105–12.
10. Cohen E, Bolus R, Khanna D, et al. GERD symptoms in the general population: prevalence and severity versus care-seeking patients. Dig Dis Sci. 2014;59:2488–96.
11. Fasano A, Catassi C. Clinical practice: celiac disease. N Engl J Med. 2012;367:2419–26.
12. Miller AD, Smith KM. Medication and nutrient administration considerations after bariatric surgery. Am J Health Syst Pharm. 2006;63:1852–7.
13. Ward LS. The difficult patient: drug interaction and the influence of concomitant diseases on the treatment of hypothyroidism. Arq Bras Endocrinol Metabol. 2010;54:435–42.
14. Groener JB, Lehnhoff D, Piel D, et al. Subcutaneous application of levothyroxine as successful treatment option in a patient with malabsorption. Am J Case Rep. 2013;14:48–51.
15. Gaitonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86:244–51.
16. Cellini M, Santaguida MG, Gatto I, et al. Systematic appraisal of lactose intolerance as cause of increased need for oral thyroxine. J Clin Endocrinol Metab. 2014;99:E1454–8.
17. Ianiro G, Mangiola F, Di Rienzo TA, et al. Levothyroxine absorption in health and disease, and new therapeutic perspectives. Eur Rev Med Pharmacol Sci. 2014;18:451–6.
18. Benvenga S. When thyroid hormone replacement is ineffective? Curr Opin Endocrinol Diabetes Obes. 2013;20:467–77.
19. Hasselström K, Siersbaek-Nielsen K, Lumholtz IB, Faber J, Kirkegaard C, Friis T. The bioavailability of thyroxine and 3,5,3′-triiodothyronine in normal subjects and in hyper- and hypothyroid patients. Acta Endocrinol (Copenh). 1985;110:483–6.
20. Checchi S, Montanaro A, Pasqui L, et al. L-Thyroxine requirement in patients with autoimmune hypothyroidism and parietal cell antibodies. J Clin Endocrinol Metab. 2008;93:465–9.
21. US Food and Drug Administration. International Conference on Harmonisation; good clinical practice: consolidated guideline; availability. Federal Register. 1997;62:25692–709.
22. US Department of Health and Human Services. Code of Federal Regulations. Title 45 Public Welfare. Section 46.116.7–8. US Department of Health and Human Services. 2009. http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf. Accessed 10 Dec 2015.
23. Padwal R, Brocks D, Sharma AM. A systematic review of drug absorption following bariatric surgery and its theoretical implications. Obes Rev. 2010;11:41–50.
24. McMillan C, Bradley C, Razvi S, Weaver J. Psychometric evaluation of a new questionnaire measuring treatment satisfaction in hypothyroidism: the ThyTSQ. Value Health. 2006;9:132–9.
25. Quinque EM, Villringer A, Kratzsch J, Karger S. Patient-reported outcomes in adequately treated hypothyroidism—insights from the German versions of ThyDQoL, ThySRQ and ThyTSQ. Health Qual Life Outcomes. 2013;11:68.
26. Virili C, Santaguida MG, Cellini M, Del Duca SC, Gargano L, Centanni M. Pilot study with softgel thyroxine preparation in the treatment of patients with T4 malabsorption due to gastric disorders. Endocr Rev. 2013;34:Abstract OR50-4.
27. Collins D, Wilcox R, Nathan M, Zubarik R. Celiac disease and hypothyroidism. Am J Med. 2012;125:278–82.
28. Centanni M. Thyroxine treatment: absorption, malabsorption, and novel therapeutic approaches. Endocrine. 2013;43:8–9.
29. Dorval E, Rey JF, Soufflet C, Halling K, Barthélemy P. Perspectives on gastroesophageal reflux disease in primary care: the REFLEX study of patient–physician agreement. BMC Gastroenterol. 2011;11:25.
30. Walker JN, Shillo P, Ibbotson V, et al. A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non-adherence to treatment. Eur J Endocrinol. 2013;168:913–7.
31. Vinagre AL, Souza MV. Levothyroxine absorption and difficult management of hypothyroid patients in the intensive care unit: two case reports and a literature review. Rev Bras Ter Intensiva. 2011;23:242–8.
32. Centanni M, Gargano L, Canettieri G, et al. Thyroxine in goiter, *Helicobacter pylori* infection, and chronic gastritis. N Engl J Med. 2006;354:1787–95.
33. Lahner E, Virili C, Santaguida MG, Annibale B, Centanni M. *Helicobacter pylori* infection and drugs malabsorption. World J Gastroenterol. 2014;20:10331–7.
34. Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham Survey. Clin Endocrinol (Oxf). 1977;7:481–93.
35. Wilson S, Parle JV, Roberts LM, et al. Prevalence of subclinical thyroid dysfunction and its relation to socioeconomic deprivation in the elderly: a community-based cross-sectional survey. J Clin Endocrinol Metab. 2006;91:4809–16.
36. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99:39–51.
37. Ramadhan A, Tamilia M. Treatment-refractory hypothyroidism. CMAJ. 2012;184:205–9.
38. Ross DS, Daniels GH, Gouveia D. The use and limitations of a chemiluminescent thyrotropin assay as a single thyroid function test in an out-patient endocrine clinic. J Clin Endocrinol Metab. 1990;71:764–9.
39. Parle JV, Franklyn JA, Cross KW, Jones SR, Sheppard MC. Thyroxine prescription in the community: serum thyroid stimulating hormone level assays as an indicator of undertreatment or overtreatment. Br J Gen Pract. 1993;43:107–9.
40. Cararis GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–34.
41. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489–99.

42. Vaisman F, Coeli CM, Ward LS, et al. How good is the levothyroxine replacement in primary hypothyroidism patients in Brazil? Data of a multicentre study. J Endocrinol Invest. 2013;36:485–8.
43. Vigário Pdos S, Vaisman F, Coeli CM, et al. Inadequate levothyroxine replacement for primary hypothyroidism is associated with poor health-related quality of life—a Brazilian multicentre study. Endocrine. 2013;44:434–40.
44. Bolk N, Visser TJ, Nijman J, et al. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. Arch Intern Med. 2010;170:1996–2003.
45. Rubio IG, Galrão AL, Santo MA, Zanini AC, Medeiros-Neto G. Levothyroxine absorption in morbidly obese patients before and after Roux-En-Y gastric bypass (RYGB) surgery. Obes Surg. 2012;22:253–8.
46. Knapton K, Myers S. A study of non-response patterns. Quirks Marketing Research Media. 2005. http://www.quirks.com/articles/a2005/20050106.aspx. Accessed 10 Dec 2015.
47. IMS Institute for Healthcare Informatics. Medicine use and shifting costs of healthcare. Danbury: IMS Health; 2014.
48. Ruchala M, Szczepanek-Parulska E, Zybek A. The influence of lactose intolerance and other gastro-intestinal tract disorders on L-thyroxine absorption. Endokrynol Pol. 2012;63:318–23.
49. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract. 2012;18:988–1028.
50. Bevan JS, Munro JF. Thyroxine malabsorption following intestinal bypass surgery. Int J Obes (Lond). 1986;10:245–6.
51. Network Scottish Intercollegiate Guideline. Management of diabetes: a national clinical guideline 116. Edinburgh: Healthcare Improvement Scotland; 2010.
52. Green PHR, Cellier C. Celiac disease. N Engl J Med. 2007;357:1731–43.