Elmer Press

Original Article

J Endocrinol Metab. 2016;6(4):109-115

Demographic and Clinical Factors Associated With the Appropriate Target Thyroid-Stimulating Hormone Values in Patients With Primary Hypothyroidism Treated With Levothyroxine

Lara Moreira Baptista de Sousa[a], Elisa Baranski Lamback[a], Thomaz Schroder Lameirinhas[b], Michelle Botelho Caarls[c, d], Leonardo Vieira Neto[a, e, f]

Abstract

Background: Hypothyroidism control is inadequate in up to 30-40% of patients. This study aimed to determine the control rate of primary hypothyroidism and the demographic and clinical factors associated with the hypothyroidism control.

Methods: An observational and retrospective study was conducted between January 2014 and October 2015. Data were obtained from 174 medical records. Regarding hypothyroidism control analysis, patients were subdivided into two groups: the appropriate control group and the inappropriate control group. Autoimmune and post-surgical hypothyroidism secondary to benign nodular thyroid disease (BNTD) was classified as of benign etiology, and differentiated thyroid carcinoma (DTC) as of malignant origin.

Results: The majority of patients consisted of women (93.68%), with a mean age of 55.53 ± 14.13 years old. The most common etiology was of autoimmune origin (41.95%). Adequate control of hypothyroidism was found in 55.17% of patients. Patients who had longer disease duration (P = 0.002), who kept using the same brand of levothyroxine (P = 0.001) and who were non-smokers (P = 0.004) had better control, and hypothyroidism from benign etiology also tended to be associated with better control (P = 0.08).

Conclusions: Primary hypothyroidism still has a high percentage of poor control seen worldwide, despite its relatively simple treatment. In this study, almost 50% of the patients had inadequate control of hypothyroidism. The factors associated with good control, both of benign and malignant origin, were related to the use of the same brand of levothyroxine and to not smoking, and the benign etiology group tended to correlate with better treatment control.

Keywords: Primary hypothyroidism; Thyroid cancer; Autoimmune hypothyroidism

Manuscript accepted for publication August 19, 2016

[a]Endocrinology Section, Hospital Federal da Lagoa, Rio de Janeiro, Brazil
[b]Endocrinology Section, Santa Casa de Misericordia de Juiz de Fora, Juiz de Fora, Brazil
[c]Institute of Biomedical Sciences, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
[d]Laboratorio de Inflamacao, Institute of Biophysics Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
[e]Department of Internal Medicine and Endocrine Section, Medical School and Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[f]Corresponding Author: Leonardo Vieira Neto, Endocrine Section, Ilha do Fundao, Rio de Janeiro, RJ 21941-913, Brazil. Email: netolv@gmail.com

doi: http://dx.doi.org/10.14740/jem367w

Introduction

Hypothyroidism is one of the most common endocrine disorders seen worldwide [1-5]. Its treatment aims to restore euthyroidism and to normalize metabolic alterations and risks associated with uncontrolled disease [6]. The treatments are based on thyroid-stimulating hormone (TSH) assessment, targeting the normal range in cases of benign disease, or TSH suppression for the treatment of differentiated thyroid carcinoma (DTC) [4, 7]. If under-treated, hypothyroidism may increase the risk of coronary artery disease and DTC relapse [7-9]. Additionally, if over-treated, there is an increased risk of atrial fibrillation, left ventricular hypertrophy, ischemic heart disease in adults over 65 years old and bone loss in postmenopausal women [10-13].

Despite it being theoretically simple to treat hypothyroidism with levothyroxine (LT-4), due to its convenient availability, low cost and simple dosage, hypothyroidism control is inadequate in up to 30-40% of patients [1, 2, 14, 15], of which 15-29% of cases may be due to under-treatment and 18-24% of cases due to over-treatment [1, 2]. The two major causes of poor control are non-adherence to treatment [4] and the presence of factors adversely affecting LT-4 therapy [16, 17]. In a Brazilian study by Bagattoli et al [18], 82% of patients failed to comply adequately to medical advice, losing follow-up in 36% of cases or not following medical prescription in 66% of cases, of which 28% ignored the need for the continued use of LT-4.

Poor control predictors, studied in the population with

primary hypothyroidism regardless of its origin, are diverse, and include the use of fiber-rich diets, decreased gastric secretion and the use of medications such as calcium carbonate [19-22]. However, some recommendations are still controversial, such as the use of proton pump inhibitor drugs, the change in LT-4 formulations and the use of generic brands, since the bioequivalence of the different formulations of LT-4 is controversial [16, 23-29]. The use of LT-4 in a fasting state (30 - 60 min before breakfast), despite disagreement in the literature, is recommended by the Latin American Thyroid Society (LATS) Clinical Guidelines of 2013 and by the 2014 Guidelines of the American Thyroid Association (ATA) [6, 30-33].

Given the high prevalence of primary hypothyroidism, regardless of its etiology, its high rate of poor control and the potential risks of under- or over-treatment, it is important to know which predictors are associated with good control to ensure adequate treatment and to reduce the potential risks of overt hypothyroidism. Thus, the aim of this study was to evaluate the control rate of primary hypothyroidism and the demographic and clinical factors associated with hypothyroidism control in patients followed up in a Brazilian public tertiary hospital.

Materials and Methods

Study design and population

A retrospective study was conducted between January 2014 and October 2015, at the Endocrinology Section of Hospital Federal da Lagoa (HFL). All patients were seen by one of seven endocrinologists in this tertiary referral center. Inclusion criteria were predefined as follows: patients aged older than 18 years old; diagnosed with hypothyroidism of autoimmune origin, post-thyroidectomy secondary to DTC, or post-thyroidectomy due to benign nodular thyroid disease (BNTD); who were treated with LT-4 (for either clinical or subclinical hypothyroidism); and who had at least one TSH and a free thyroxin (FT4) assessment during the studied period. Exclusion criteria included the following: younger than 18 years old, pregnant women, use of amiodarone, ferrous sulfate, carbamazepine, phenytoin or rifampicin and those with unavailable TSH and FT4 measurement in the studied period.

Data collection

The following data were collected from data available in paper-based or electronic medical records: patient's age at the last consultation (in years), gender (male or female), ethnicity (Caucasians or non-Caucasians), education (illiterate; until fourth grade of elementary school; until the eighth grade of elementary school; high school; or superior diploma), the family's monthly income (up to two minimum wages; or more than two minimum wages), hypothyroidism's etiology (autoimmune; after thyroidectomy due to BNTD or after thyroidectomy by DTC), the disease duration (in months), the most recent TSH (mIU/L) and FT4 (ng/dL) values, the use of the same LT-4 brand for the last 3 months prior to laboratory testing, the use of LT-4's name-brand or generic brand, the presence of comorbidities (dyslipidemia (if lipids above the upper limit of normal range or the use of antilipemics drugs); type 2 diabetes mellitus (T2DM, if fasting plasma glucose levels $\geq$ 126 mg/dL in two distinct occasions; 2-h plasma glucose level $\geq$ 200 mg/dL during a 75-g oral glucose tolerance test; random plasma glucose $\geq$ 200 mg/dL in a patient with classic symptoms of hyperglycemia; or the use of anti-diabetic medication), obesity (if body mass index (BMI) $\geq$ 30 kg/m^2) or hypertension (whether systolic and/or diastolic blood pressure $\geq$ 140 and/or $\geq$ 90 mm Hg, respectively, or the use of antihypertensive medications)) and the presence of smoking ($\geq$ 1 cigarette/day) or current alcohol consumption (daily consumption reported in records) [34-36].

Patients were divided into separate groups to carry out two types of analysis. For the hypothyroidism control analysis, patients were subdivided into two groups: the appropriate control group and the inappropriate control group, based on the approach taken by the attending physician registered in medical records. Each of the seven endocrinologists used the latest guidelines prevailing during the studied period (which were ATA's hypothyroidism guideline from 2014 and ATA's DTC guideline from 2009) [33, 37]. Patients were included on the controlled group if no LT-4 dose adjustment was performed, during the entire studied period, after analyzing several TSH and FT4 values, while those in the uncontrolled group had their LT-4 dose adjusted taking into account the patient's age, weight and the hypothyroidism's etiology.

Briefly, for hypothyroidism of benign origin, adequate control was defined as a TSH value within the reference range (0.4 - 4.0 mIU/L) [33]. And for DTC, TSH-suppressive therapy was sought for patients with persistent disease, in the absence of specific contraindications or for high risk disease patients clinically and biochemically free of disease (serum TSH below 0.1 mIU/L indefinitely or of 0.1 - 0.5 mIU/L for 5 - 10 years, respectively). For patients with low risk for recurrence, the serum TSH was kept within the low normal range (0.3 - 2 mIU/L) [37].

In relation to disease duration, the estimated time of hypothyroidism from a benign origin was considered to start at diagnosis and from a malignant origin immediately after thyroidectomy was performed.

Regarding the etiology of primary hypothyroidism, those of benign etiology were included in a group that consisted of patients with autoimmune hypothyroidism or hypothyroidism from thyroidectomy for BNTD, while another group, of malignant origin, was composed of patients with hypothyroidism due to thyroidectomy for DTC. Patients were classified as having autoimmune hypothyroidism if elevated anti-thyroid peroxidase antibodies were present, and registered in medical records; as having benign hypothyroidism post-thyroidectomy if thyroidectomy was registered in health records for BNTD, and pathological examination confirmed its benign origin; or from malignant origin if thyroidectomy records were compatible with thyroid carcinoma, along with a pathological description confirming carcinoma.

Serum TSH and FT4 values were collected in HFL's laboratory and were determined in all participants by a chemiluminescent immune-metric assay (Diagnostic Products Corpora-

Table 1. Demographic and Clinical Data

Variables	Data*
Male/female, N (%)	11 (6.32%)/163 (93.68%)
Age (years)	55.53 ± 14.13
Disease duration (months)	48 (3 - 600)
TSH value (mIU/L)	2.09 (0.004 - 40.50)
Free T4 value (ng/dL)	1.19 (0.41 - 2.22)
Ethnicity (n = 173)	
Caucasians	112 (64.74%)
Non-Caucasians	61 (35.26%)
Education (n = 173)	
Illiterate	28 (16.18%)
Until fourth grade of elementary school	48 (27.75%)
Until eight grade of elementary school	38 (21.96%)
High school	43 (24.86%)
Superior diploma	16 (9.25%)
Monthly income (n = 168)	
< 2 minimum wages	99 (58.93%)
> 2 minimum wages	69 (41.07%)
Etiology (n = 174)	
Autoimmune	73 (41.95%)
Thyroidectomy due to cancer	51 (29.31%)
Thyroidectomy due to BNTD	50 (28.74%)
Overall etiology (n = 174)	
Benign	123 (70.69%)
Malignant	51 (29.31%)

*Data are presented as N (%), mean ± SD or median (min. - max.), according to the variable. "N" indicates the number of patients.

tion, Automatic Instrument Immulite 2000®), with reference values ranging from 0.4 to 4.0 mIU/L and 0.8 to 1.9 ng/dL, respectively.

Statistical analysis

The statistical analyses were performed using SPSS version 20.0 for MacOS (SPSS Inc., Chicago, IL). Most of the variables except age were not found to follow a normal distribution using the Kolmogorov-Smirnov test. For the descriptive analysis, categorical variables were expressed as the percentage and frequency, and numerical variables were expressed as mean ± SD or median (minimum - maximum) according to their distribution pattern. Student's *t*-test or the Mann-Whitney U tests were performed to compare the numerical variables between the two groups according to their distributions. Fisher's exact test and Chi-square test were used to compare categorical variables. A P-value < 0.05 was considered statistically significant. P-values ≥ 0.05 and ≤ 0.09 were considered to indicate a tendency towards statistical significance.

A power calculator was used considering a local population of 6 million in Rio de Janeiro and an overall prevalence of 1.5-9% of primary hypothyroidism [4, 6].

Results

Out of 216 selected patients with primary hypothyroidism, 42 were excluded for not having available TSH and/or FT4 assessments, or for not having a well-defined hypothyroidism etiology. Clinical and demographic data of the 174 patients included in this study are shown in Table 1.

The majority of patients consisted of women (93.68%), with a mean age of 55.53 ± 14.13 years and of Caucasian ethnicity (64.74%). Most of the patients studied until fourth grade (27.74%), and a minority had a superior education diploma (9.25%). The median disease duration was 48 months (3 - 600), with a median TSH value of 2.09 mIU/L (0.004 - 40.50) and FT4 value of 1.19 ng/dL (0.41 - 2.22). The most common etiology was of autoimmune origin (41.95%), followed by post-thyroidectomy for DTC (29.31%) and post-thyroidectomy for

Table 2. Data According to Overall Etiology

	Benign	Malignant	P-value
Age (years)	57.37 ± 13.73	51.08 ± 14.22	0.008
Disease duration (months)	60 (3 - 600)	24 (3 - 288)	< 0.001
TSH value (mIU/L)	2.56 (0.004 - 40.50)	0.89 (0.004 - 36.29)	0.010
FT4 value (ng/dL)	1.17 (0.57 - 1.83)	1.36 (0.41 - 2.22)	0.018

BNTD (28.74%).

Taken together, benign etiologies were the most frequent hypothyroidism cause (70.69%), in which the mean age was higher in the benign group compared to the malignant etiology group (57.37 ± 13.73 vs. 51.08 ± 14.22, respectively; P = 0.008). The median disease duration was also higher in the benign group (60 (3 - 600) vs. 24 months (3 - 288); P < 0.001). The median TSH level in the benign group was higher (2.56 (0.004 - 40.50) vs. 0.89 mIU/L (0.004 - 36.29); P = 0.01), while the median FT4 value was lower in the benign etiology group (1.17 (0.57 - 1.18) vs. 1.36 ng/dL (0.41 - 2.22); P = 0.018) (Table 2).

Regarding hypothyroidism control rate, 55.17% of patients achieved adequate control. The median disease duration was higher in the controlled group compared to the uncontrolled group (48 (4 - 480) vs. 36 months (3 - 600), respectively; P = 0.02), as opposed to the median TSH values (1.60 (0.01-31.31) vs. 6.83 (0.004 - 40.50) mIU/L, respectively; P < 0.001). The mean age and median FT4 were not different between the groups according to hypothyroidism control rate.

Statistically significant differences were observed with the use of the same LT-4 brand, which was associated as a good control of hypothyroidism, compared to patients who changed the brand of LT-4 (P = 0.01). Additionally, smoking proved to be associated with poor control, with adequate control only observed in 0.01% of smokers (P = 0.04). A trend was observed regarding adequate control in the benign etiology group, which was higher, compared to the malignant etiology group (P = 0.08) (Table 3).

Current drinking, dyslipidemia, T2D, hypertension and obesity were not associated with hypothyroidism control.

Discussion

In this study, the control rate of primary hypothyroidism, of both benign (autoimmune and hypothyroidism from thyroidectomy for BNTD) and malignant origin (post-thyroidectomy due to DTC), was analyzed, as well as possible factors for good control. This study represents real life in the treatment and follow-up of patients with hypothyroidism. In the literature, data comparing control rate to hypothyroidism from malignant cases are scarce. Studies that determine hypothyroidism control rates do not mention hypothyroidism from malignant etiology, and only address cases of hypothyroidism from benign origin. As opposed to these studies available, in this series, every group was taken into account, and no significant difference was found in hypothyroidism control rate among different etiologies. Adequate control rates were observed in approximately 76% of patients in the benign origin group and in almost 24% in the malignant group (P = 0.08). According to the literature, the average control rate of primary hypothyroidism ranged from 60% to 70% [1, 2, 14, 15] and the main predictors studied were of poor and not good control.

Our data revealed a good control rate of primary hypothyroidism regardless of origin (55.17%) under international studies' average (60-70%), but similar to a Brazilian study conducted by Vaisman et al (57.3%) [38]. One of the most common causes of inadequate control is associated to poor treatment adherence, with up to 28% of patients ignoring the need for the continued use of LT-4 [4, 16].

The female population was more prevalent among patients (93.67%) and also in the benign etiology group (72.39%), as observed globally in which hypothyroidism is more common in women, both of autoimmune etiology (6.2% in women and 1.2% men) and due to cancer (carcinoma is 2.5 times more prevalent in women) [39]. Although some patients' characteristics, such as Caucasian ethnicity or education, were not associated with control of hypothyroidism in our study, similar findings regarding adequate treatment were observed in ELSA-Brazil's study [5], in which female and Caucasian patients were the most adherent to treatment. Unlike this study, which showed a higher prevalence of treatment in patients with higher income, in our study, the majority of patients had an income of less than two minimum wages (58.92%), probably because our hospital is a public institution whose attended population has lower economic and social status.

In addition to the median disease duration (60 months), the patient's age was higher in the benign group, which is not surprising since there is more urgency to perform thyroidectomy in DTC compared with those undergoing surgery for benign disease, although no generalization can be made regarding age at diagnosis and, therefore, no comparison to data found in the literature can be established. Furthermore, the TSH value was higher and FT4 lower in the benign group, compatible with the treatment's objective for hypothyroidism of benign origin: TSH and FT4 within normal range [6]; unlike suppressed TSH sought in most treatments for DTC [7].

A statistical trend of adequate control was observed in the benign etiology group compared to the malignant group, which can be explained by the fact that since these patients have presented greater disease duration, they could have had more medical visits and LT-4 dose adjustments than in the other group. Another explanation would be that the TSH treatment target in this population is higher with a wider acceptable range. No data were found comparing these findings in the literature. Regardless of hypothyroidism's etiology, the disease duration was a factor for good control, supporting the hypothe-

Table 3. Patients Profile Based on Hypothyroidism Control and the Demographic and Clinical Factors Associated With Hypothyroidism Control

	Adequate	Inadequate	P-value
Etiology			0.08
Benign	73 (76.04%)	50 (64.10%)	
Malignant	23 (23.96%)	28 (35.90%)	
Sex			0.96
Male	6 (6.25%)	5 (6.41%)	
Female	90 (93.75%)	73 (93.59%)	
Ethnicity			0.78
Caucasians	63 (65.63%)	49 (63.64%)	
Non-Caucasians	33 (34.37%)	28 (36.36%)	
Education			0.99
Illiterate	16 (16.84%)	12 (15.38%)	
Up to fourth grade of elementary school	26 (27.37%)	22 (28.21%)	
Up to eighth grade of elementary school	20 (21.05%)	18 (23.08%)	
High school	24 (25.26%)	19 (24.36%)	
Superior diploma	9 (9.48%)	7 (8.97%)	
Monthly income			0.28
< 2 minimum wages	52 (55.32%)	47 (63.51%)	
> 2 minimum wages	42 (44.68%)	27 (36.49%)	
Use of the same LT-4 brand			0.01
Yes	87 (90.63%)	59 (76.62%)	
No	9 (9.37%)	18 (23.38%)	
LT-4 brand			0.55
Generic	13 (14.94%)	11 (18.64%)	
Name-brand	74 (85.06%)	48 (81.36%)	
Fasting			0.22
Yes	92 (95.83%)	71 (91.03%)	
No	4 (4.17%)	7 (8.97%)	
Current smoking			0.04
Yes	1 (0.01%)	6 (7.69%)	
No	95 (99.99%)	72 (92.31%)	

sis already demonstrated that longer disease duration is a good control factor in both malignant and benign etiology groups.

The use of the same LT-4 brand during treatment was associated with adequate hypothyroidism control. These results are in agreement with current recommendations for hypothyroidism treatment, which suggest that, due to studies showing the lack of bioequivalence between different LT-4 preparations, it is more prudent to use the same brand during the entire treatment [6, 33]. There was no difference between generic LT-4 brands and name brands regarding control rate, also observed in studies conducted by Bagattoli et al [18] and Dong et al [29]. Contrary to LATS and ATA's latest recommendations on the use of LT-4 in a fasting state (30 - 60 min before breakfast), in our study no statistically significant difference was observed in the administration of LT-4 with or without fasting.

Only few studies available in the literature compared smoking to thyroid function modifications. The majority shows that smoking decreases TSH levels [40, 41]. Only one study revealed increased TSH value in smoking women who used LT-4, compared to smoking women who did not use LT-4 [42], which corroborates with our data showing that smoking is associated to poor control. Although low serum TSH also reflects poor control, interestingly, 100% of smokers belonged to the benign group.

Our study has some limitations. Since this study mirrors real life, the groups analyzed were very heterogeneous. And because this is a retrospective study, the assessment on proper treatment was impaired, and the patient's age at diagnosis was

not analyzed. As well as disease duration from autoimmune origin was not precise and could only be estimated at diagnosis.

In conclusion, primary hypothyroidism is a very common disease with a high percentage of poor control seen worldwide, despite its relatively simple treatment. In this study, only 55.17% of the patients achieved adequate control of hypothyroidism. Factors associated with good control were longer disease duration, the continued use of the same LT-4 brand and not smoking, findings still not robustly reported in the literature. Prospective and controlled studies are needed to better analyze these factors so that, in the future, poor control rates can be lowered globally.

Acknowledgments

We would like to thank the Endocrinology Section at HFL (Amanda Torres, Andrea Ferreira, Andreia Buzza, Carmine Osso, Daniel Bulzico, Deborah Livi, Eline Romagna, Fabiana Melnik, Fernanda Junqueira, Helena Bandeira, Julia Souza, Natasha Lozovey, Raissa Mota, Roberto Zagury, Ronaldo Sinay, Samira Oliveira, Silvio Voscaboinik and Yasmine Ddine).

Conflicts of Interest

The authors have nothing to declare.

Author Contributions

Study design: Leonardo Vieira Neto; study conduct: Leonardo Vieira Neto and Lara Moreira Baptista de Sousa; literature review: Leonardo Vieira Neto, Lara Moreira Baptista de Sousa, Elisa Baranski Lamback, Thomaz Schroder Lameirinhas and Michelle Botelho Caarls; data collection: Lara Moreira Baptista de Sousa; data analysis: Leonardo Vieira Neto and Lara Moreira Baptista de Sousa; data interpretation: Leonardo Vieira Neto, Lara Moreira Baptista de Sousa, Elisa Baranski Lamback, Thomaz Schroder Lameirinhas and Michelle Botelho Caarls; drafting manuscript: Lara Moreira Baptista de Sousa, Elisa Baranski Lamback and Thomaz Schroder Lameirinhas; revising manuscript content: Leonardo Vieira Neto and Michelle Botelho Caarls; approving final version of manuscript: Leonardo Vieira Neto, Lara Moreira Baptista de Sousa, Elisa Baranski Lamback, Thomaz Schroder Lameirinhas and Michelle Botelho Caarls. Leonardo Vieira Neto takes responsibility for the integrity of the data analysis.

Abbreviations

ATA: American Thyroid Association; BNTD: benign nodular thyroid disease; DTC: differentiated thyroid carcinoma; FT4: free thyroxin; HFL: Hospital Federal da Lagoa; LATS: Latin American Thyroid Society; LT-4: levothyroxine; T2D: type 2 diabetes mellitus; T4: thyroxin; TSH: thyroid-stimulating hormone.

References

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160(4):526-534.
2. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. 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(2):489-499.
3. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995;43(1):55-68.
4. Wiersinga WM. Adult Hypothyroidism. In: De Groot LJ, Beck-Peccoz P, Chrousos G et al. (eds) Endotext. South Dartmouth (MA), 2000.
5. Schmidt MI, Duncan BB, Mill JG, Lotufo PA, Chor D, Barreto SM, Aquino EM, et al. Cohort Profile: Longitudinal Study of Adult Health (ELSA-Brasil). Int J Epidemiol. 2015;44(1):68-75.
6. Brenta G, Vaisman M, Sgarbi JA, Bergoglio LM, Andrada NC, Bravo PP, Orlandi AM, et al. Clinical practice guidelines for the management of hypothyroidism. Arq Bras Endocrinol Metabol. 2013;57(4):265-291.
7. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
8. Roberts CG, Ladenson PW. Hypothyroidism. Lancet. 2004;363(9411):793-803.
9. Gonzalez Vilchez F, Castillo L, Pi J, Ruiz E. [Cardiac manifestations of primary hypothyroidism. Determinant factors and treatment response]. Rev Esp Cardiol. 1998;51(11):893-900.
10. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med. 1994;331(19):1249-1252.
11. Biondi B, Fazio S, Carella C, Amato G, Cittadini A, Lupoli G, Sacca L, et al. Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. J Clin Endocrinol Metab. 1993;77(2):334-338.
12. Leese GP, Jung RT, Guthrie C, Waugh N, Browning MC. Morbidity in patients on L-thyroxine: a comparison of those with a normal TSH to those with a suppressed TSH. Clin Endocrinol (Oxf). 1992;37(6):500-503.
13. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY. Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. J Clin Endocrinol Metab. 1996;81(12):4278-4289.
14. Hannemann A, Friedrich N, Haring R, Krebs A, Volzke H, Alte D, Nauck M, et al. Thyroid function tests in patients

taking thyroid medication in Germany: Results from the population-based Study of Health in Pomerania (SHIP). BMC Res Notes. 2010;3:227.
15. Okosieme OE, Belludi G, Spittle K, Kadiyala R, Richards J. Adequacy of thyroid hormone replacement in a general population. QJM. 2011;104(5):395-401.
16. Liwanpo L, Hershman JM. Conditions and drugs interfering with thyroxine absorption. Best Pract Res Clin Endocrinol Metab. 2009;23(6):781-792.
17. McMillan M, Rotenberg KS, Vora K, Sterman AB, Thevathasan L, Ryan MF, Mehra M, et al. Comorbidities, Concomitant Medications, and Diet as Factors Affecting Levothyroxine Therapy: Results of the CONTROL Surveillance Project. Drugs R D. 2016;16(1):53-68.
18. Bagattoli RM, Vaisman M, Lima JS, Ward LS. Estudo de adesao ao tratamento do hipotiroidismo. Arquivos Brasileiros de Endocrinologia & Metabologia. 2000;44(6):483-487.
19. Liel Y, Harman-Boehm I, Shany S. Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult hypothyroid patients. J Clin Endocrinol Metab. 1996;81(2):857-859.
20. Centanni M, Gargano L, Canettieri G, Viceconti N, Franchi A, Delle Fave G, Annibale B. Thyroxine in goiter, Helicobacter pylori infection, and chronic gastritis. N Engl J Med. 2006;354(17):1787-1795.
21. Singh N, Singh PN, Hershman JM. Effect of calcium carbonate on the absorption of levothyroxine. JAMA. 2000;283(21):2822-2825.
22. Singh N, Weisler SL, Hershman JM. The acute effect of calcium carbonate on the intestinal absorption of levothyroxine. Thyroid. 2001;11(10):967-971.
23. Sachmechi I, Reich DM, Aninyei M, Wibowo F, Gupta G, Kim PJ. Effect of proton pump inhibitors on serum thyroid-stimulating hormone level in euthyroid patients treated with levothyroxine for hypothyroidism. Endocr Pract. 2007;13(4):345-349.
24. Dietrich JW, Gieselbrecht K, Holl RW, Boehm BO. Absorption kinetics of levothyroxine is not altered by proton-pump inhibitor therapy. Horm Metab Res. 2006;38(1):57-59.
25. Ananthakrishnan S, Braverman LE, Levin RM, Magnani B, Pearce EN. The effect of famotidine, esomeprazole, and ezetimibe on levothyroxine absorption. Thyroid. 2008;18(5):493-498.
26. Bolton S. Bioequivalence studies for levothyroxine. AAPS J. 2005;7(1):E47-53.
27. Joint statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. Thyroid. 2004;14(7):486.
28. Olveira G, Almaraz MC, Soriguer F, Garriga MJ, Gonzalez-Romero S, Tinahones F, Ruiz de Adana MS. Altered bioavailability due to changes in the formulation of a commercial preparation of levothyroxine in patients with differentiated thyroid carcinoma. Clin Endocrinol (Oxf). 1997;46(6):707-711.
29. Dong BJ, Hauck WW, Gambertoglio JG, Gee L, White JR, Bubp JL, Greenspan FS. Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. JAMA. 1997;277(15):1205-1213.
30. Bach-Huynh TG, Nayak B, Loh J, Soldin S, Jonklaas J. Timing of levothyroxine administration affects serum thyrotropin concentration. J Clin Endocrinol Metab. 2009;94(10):3905-3912.
31. Bolk N, Visser TJ, Nijman J, Jongste IJ, Tijssen JG, Berghout A. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. Arch Intern Med. 2010;170(22):1996-2003.
32. Rajput R, Chatterjee S, Rajput M. Can Levothyroxine Be Taken as Evening Dose? Comparative Evaluation of Morning versus Evening Dose of Levothyroxine in Treatment of Hypothyroidism. J Thyroid Res. 2011;2011:505239.
33. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid. 2014;24(12):1670-1751.
34. Diretrizes da Sociedade Brasileira de Diabetes, 2015-2016 (Accessed July 5, 2016 at site http://www.diabetes.org.br/sbdonline/images/docs/DIRETRIZES-SBD-2015-2016.pdf).
35. Gualandro DM, Azevedo FR, Calderaro D, Marcondes-Braga FG, Caramelli B, Schaan BD. I Diretriz de sobre Aspectos Especificos de Diabetes Melito (tipo 2) Relacionados a Cardiologia. Arq Bras Cardiol. 2014;102(5Supl.1):1-30.
36. Atualizacao das Diretrizes Para o Tratamento FarmacolOgico da Obesidade e do Sobrepeso, 2010. (Accessed July, 5, 2016 at site < http://www.abeso.org.br/uploads/downloads/2/5521af637d07c.pdf>).
37. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214.
38. Vaisman F, Coeli CM, Ward LS, Graf H, Carvalho G, Montenegro R, Jr., Vaisman M. How good is the levothyroxine replacement in primary hypothyroidism patients in Brazil? Data of a multicentre study. J Endocrinol Invest. 2013;36(7):485-488.
39. Moazezi Z, Mahmoudi M, Yahyahpour Y, Alaleh A. Risk factors of thyroid cancer in Babol, Northern Iran. Caspian J Intern Med. 2011;2(1):171-177.
40. Soldin OP, Goughenour BE, Gilbert SZ, Landy HJ, Soldin SJ. Thyroid hormone levels associated with active and passive cigarette smoking. Thyroid. 2009;19(8):817-823.
41. Meral I, Arslan A, Him A, Arslan H. Smoking-related Alterations in Serum Levels of Thyroid Hormones and Insulin in Female and Male Students. Altern Ther Health Med. 2015;21(5):24-29.
42. Jorde R, Sundsfjord J. Serum TSH levels in smokers and non-smokers. The 5th Tromso study. Exp Clin Endocrinol Diabetes. 2006;114(7):343-347.