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RESEARCH ARTICLE

THYROID HORMONE REPLACEMENT IN TOTAL THYROIDECTOMIZED PATIENTS: SYMPTOMATIC AND METABOLIC EFFECTS OF LEVOTHYROXINE MONOTHERAPY

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ABSTRACT

Purpose: In this study, we planned to investigate the effects of L-thyroxine monotherapy on total thyroidectomized patients. The main goal of our study is to evaluate if FT4 therapy is good enough not only to maintain euthyroidism but also to provide a good quality of life and a balance in their metabolism

Methods: In this study, we retrospectively evaluated 30 total thyroidectomized patients without malignancy. We compared their thyroid hormone levels, glucose metabolism, lipid metabolism, their body mass indexes, and their symptoms of thyroid problems before surgery and after one year of treatment of L-thyroxine monotherapy.

Results: the pre-op and post-op thyroid hormone levels were both in the normal range but the FT4 levels were significantly higher in the 1st year results than pre-op results (1,42 ± 0,18 vs 1,29 ± 0,49 respectively P=0,005*) The FT3 levels also were in the normal range in pre and 1st year post-op but post-op FT3 levels were significantly lower than pre-op levels (2,25 ± 0,27 vs 2,92 ± 0,49 retrospectively P<0,001*). The pre-op and postop TSH levels were euthyroid and not statistically significant. The patients tended to gain weight and it seems to be because of a tendency of being insulin resistant. (HOMA-IR pre-op and post-op were 2,2 ± 1,1 vs 2,6 ± 1,1 P<0,01 retrospectively; pre-op and post-op weights were 69,8 ± 9,5 vs 71,1 ± 10,3 P=0,006* respectively). Even all of them were euthyroid the patients tended to feel hypothyroidism symptoms.

Conclusion: This study demonstrates that even though they are euthyroid with FT4 treatment total thyroidectomized patients may suffer from hypothyroidism signs and symptoms and metabolic deterioration may occur in such patients. We recommend that we should aim not only to normalize s-TSH levels but also to normalize patients' metabolic parameters and improve the quality of daily life when regulating our treatments.

Keywords: "thyroid hormone replacement", L-thyroxine, euthyroidism, metabolism

INTRODUCTION

We can adequately correct biochemical euthyroidism in total thyroidectomized patients with levothyroxine (LT4) replacement therapy, but some of them still complain of disturbances in their psychological and physical well-being (1). The reason for this may be the absence of some T3 in their circulation (2). Our thyroid synthesizes 2 different thyroid hormones (TH): one of them is thyroxine (T4) which has 4 iodine atoms; the second one is its biologically active brother

with 3 iodine atoms called triiodothyronine (T3). In healthy adults, the thyroid gland secretes all of the T4 in circulation but only 1/5 of T3 is secreted by the gland. The rest of T3 comes from non-thyroidal peripheric cells. Most of our cells convert T4 to T3 and releases an iodine atom and nearly 4/5 of the T3 comes from this conversion (3). Patients who had total thyroidectomy are mostly being treated with T4 monotherapy. As there is no thyroid tissue left the %20 of the T3 is not supplied and a T3 deficiency may be present in these patients. There are studies in the literature comparing pre and postoperative T3 levels in these kinds of patients. Those studies showed that the patients who had total or near-total thyroidectomy had normal TSH levels when they were receiving T4-monotherapy and those levels were similar to their preoperative T4 levels. But they had mildly lower T3 levels. Some studies added T3 to their T4-monotherapy to make the same pattern of blood levels T3/T4 as they had before the surgery but this resulted in a suppressed TSH level. Because of these findings, the euthyroid status of patients who had total or near-total thyroidectomy needs to be determined (4-6). With this study, we aimed to evaluate thyroid functions of total-thyroidectomized patients pre and postoperatively when they were receiving T4-monotherapy. We selected patients who had total thyroidectomy diagnosis with a Fine Needle Aspiration Biopsy (FNA) as papillary carcinoma but an negative surgical pathology result.

MATERIALS AND METHODS

In this study, we retrospectively evaluated all patients between January 2015 to January 2020 who fulfill our inclusion criteria, and patients who accepted to participate recruited our study. The patients in our study were euthyroid patients who had total thyroidectomy because of a suspicious fine-needle aspiration biopsy (FNA) (suspicious for papillary or follicular thyroid carcinoma) and negative surgical pathological results.

The criteria for exclusion from our study were:
i) Patients using L-thyroxine (LT4) treatment before the thyroid operation
ii) Patients who had the diagnosis of any kind of thyroid carcinomas in the pathological examination of the surgical specimen.
iii) Patients who had accompanying thyroid problems to the thyroid nodules such as Graves' disease, Hashimoto's thyroiditis.
iv) Patients that under other medical therapies that may affect their thyroid function or the metabolism of the thyroid hormones (corticosteroid, estrogen, sucralfate, amiodarone, β-blocker, lithium)
v) Patients with chronic concomitant diseases (Diabetes, coronary heart disease, Chronic renal failure)
vi) Women who are pregnant and breastfeeding, or peri-menopausal women; vii) Obese patients (body mass index (BMI)>30 kg/m2).

This present study was approved by the ethics committee Of Bakırçay University, All the patients who fulfill these criteria gave written informed consent for our study.

The protocol of our study

There were 30 patients (age 27–71 years) who had total thyroidectomy with the diagnosis of a positive or suspected papillary or follicular thyroid carcinoma with FNA. Total thyroidectomy was always performed by extra-capsular dissection under the inferior and lateral traction of the upper pole by an Allis clamp. All terminal vessels were ligated or sealed close to the thyroid capsule. This maneuver helps the surgeon to identify and protect the superior laryngeal nerve and upper parathyroid gland. In the procedure for total thyroidectomy, upper-pole dissection was always terminated before reaching the lower edge of the cricothyroid muscle, because it is the entry area of the recurrent laryngeal nerve to the larynx. After the procedure on the upper pole, the attention was turned to the lower pole. Once again, all terminal vessels close to the thyroid capsule were ligated and sealed. During this part of the procedure, the second parathyroid gland was usually visualized and was preserved in situ with its blood supply. The thyroid was suspended from both upper and lower poles, using two Allis clamps, and the median thyroid vein was then ligated. Extra-capsular dissection was advanced down to the tracheoesophageal groove. Whenever RLN was exposed, it was dissected and protected until its entry point to the larynx. If the parathyroid glands were inadvertently damaged, they were implanted in the sternocleidomastoid muscle.
All of the patients were prescribed 1,5 µg/kg of LT4 daily as they didn't have any carcinoma diagnosis. The target for TSH was euthyroid levels (1- 2,5 µIU/mL). For achieving this goal, thyroid hormones were tested one month after the surgery and made dose adjustments if needed, and rechecked the

following month until a stable TSH was achieved. After the stabilization of the LT4 dose patients were followed every 6 months. All patients were followed by the same endocrinologist during this study and treatment period.

Laboratory tests

Preoperative thyroid hormone levels and metabolic parameters were evaluated 2 days before surgery. The postoperative thyroid profiles were evaluated following the hormonal stabilization and on the first year of the operation. The venous blood samples were collected early in the morning following an overnight fast and before ingestion of LT4. Plasma glucose was measured by the glucose oxidase technique (Biobak Lab Sup. Ankara). Insulin levels were measured by micro-particle enzyme immunoassay (Abbot, Germany). Serum high-density lipoprotein (HDL), total cholesterol, and triglyceride (TG) were measured by enzymatic assay (Boehringer-Mannheim, Germany). The low-density lipoprotein level was calculated using the Friedwald equation. (7) HOMA-IR and body mass index (BMI) levels were calculated

Free T3 (normal range 1.8–4.2 pg/mL) and free T4 (normal range 0.8–1.9 ng/dL) levels were measured using a radioimmunoassay; and serum TSH levels were measured using solid-phase chemiluminescent immunometric assay (Immulite 2000, Diagnostic Products Corporation)

Symptoms to evaluate thyroid function

We asked our patients to answer the questions of our questionnaires on the same day of the blood sample tests prior to the operation and after five years follow-up. As seasons seem to affect the feelings about thyroidal dysfunctions the postoperative questionnaires were obtained in the 1st years after thyroidectomy and on the same season of the operation. We used the scores developed by Billewicz et al (8) and Zulewski et al. (9) for hypothyroidism, by Klein et al. for hyperthyroidism (10).

There were 8 questions in the questionnaire and they were based on included based on the most common symptoms that seem to be affected by the thyroid functions: (i) sweating; (ii) intolerance to cold or heat; (iii) energy feeling daily activities; (iv) bowel activities; (v) appetite; (vi) moistness of the skin; (vii) temperature of extremities; (viii) tremor of hands ix) palpitation of the hearth. The answers to the questionnaires were recorded on the Likert scale from –2 to +2. Items regarding tremor and palpitation symptoms were recorded on a Likert scale from 0 to +2.

Statistical analysis

IBM SPSS Statistics 27 was used for statistical analyses. Results are reported as the mean ± SD. Treatment effects (as pre-op levels for before T4 treatment) and 1st-year stable result (for after T4 treatment) were analyzed by paired t-test for normally disturbing values and by Wilcoxon signed-rank test for nonparametric disturbances. Significance was defined as a p-value < 0.001.

Table 1. Demographic Profile, Metabolic and Thyroid Function Test Results

	Pre-op	1st year	P
Weight	69,8 ± 9,5	71,1 ± 10,3	P=0,006*
BMI	25,2 ± 1,8	25,6 ± 2,0	P=0,007*
Blood Sugar	93,5 ± 4,5	95,4 ± 4,8	P<0,001*
Insulin	9,5 ± 4,5	10,9 ± 4,3	P<0,01*
HOMA-IR	2,2 ± 1,1	2,6 ± 1,1	P<0,01
T Cholesterol	227,6 ± 55,6	227,43 ± 43,27	P=0,94
TG	219,6 ± 79	223,8 ± 78	P=0,12
HDL	46,4 ± 14,8	46,9 ± 13,9	P=0,25
LDL	137,4 ± 50	135 ± 37,9	P=0,61
TSH	2,27 ± 0,79	2,15 ± 0,30	P=0,31
FT4	1,29 ± 0,49	1,42 ± 0,18	P=0,005*
FT3	2,92 ± 0,49	2,25 ± 0,27	P<0,001*

RESULTS

The demographic profile, metabolic and thyroid function test results are summarized in Table-1

The preoperative TSH, FT4, and FT3 were within the normal range; also in the first year results all TSH, FT3, and FT4 levels were within normal limits. There was no significant change in the TSH levels of patients during the 1 year follow-up period. The FT4 levels were also within normal ranges but 1st year

results were significantly higher than the preoperative results (p<0,05) The FT3 levels of pre-op and 1st year FT3 levels were also within the normal range but the 1st year FT3 results were significantly lower than pre-op FT3 results. (P<0,01).

When we evaluate the metabolic parameters there was a significant weight gain when we compare the patients 1 year "Tanita" results. Also, there was an increase in HOMA-IR due to both insulin level elevations and blood sugar elevations. There was a significant negative correlation between FT3 levels and HOMA-IR (r=-0,57 P<0,01). Two of our patients had impaired fasting glucose diagnosis (one had a BMI>30kg/m2 in the 1st year visit), none of them had diabetes diagnosis within the follow-up period.

The changes in the answers questionnaire are summarized in Table- 2: even though all were euthyroid according to their thyroid function tests there was a tendency of feeling to hypothyroidism pattern.

Table 2. Number of Patients Who Had Chances of Thyroid Function Symptoms Scale

	Increase	Decrease
Sweating	0	3
Intolerance to heat/cold	1	4
Daily Activity	0	4
Bowel Activity	1	3
Appetite	3	2
Moistness of the skin	0	1
Temperature of extremities	1	1
Tremor of hands	0	0
Palpitation of the hearth.	2	3

DISCUSSION

In our study, we demonstrated significantly lower serum FT3 levels in the 1st year of the surgery compared to preoperative results. All patients were euthyroid preoperative and also 1 year after the surgery. We also demonstrated significantly higher FT4 levels in the first year blood tests of our patients but all of them were within normal limits. These changes may be due to a lack of intra-thyroidal T3 production and higher levels of FT4 need for keeping the TSH levels in the same euthyroid range.

In daily clinic practice, endocrinologists face the problem of solving the problems of their patients who are still having hypothyroidism signs and symptoms despite they have adequate L-thyroxine treatment to keep their TSH levels within normal ranges (11). In the 1950s doctors used to treat their patients according to the signs of them as there were no available TSH assay and thyroid extracts from animals were the treatment they used. The peripheral conversion of T4 to T3 was demonstrated just after LT4 became commercially available. This made LT4 a gold standard therapy for hypothyroidism (12-13). By the early 1980s, it was widely recognized that LT4 doses in the 100-200 µg range (or even lover) were needed to normalize TSH levels 14)

As the sensitive TSH (s-TSH) assays became globally available, it is accepted as the main target to get euthyroid s-TSH levels for the treatment of hypothyroid patients. But these changes in the therapy caused another question: "Is monotherapy with LT4 enough to maintain serum T3 levels especially in total thyroidectomized patients?" Multiple cross-sectional studies are evaluating this question (5). Some of them found low levels of T3 (15, 16) but there are also studies demonstrated normal t3 levels in a patient who are on LT4 therapy (17,18). case There are two studies in the literature that describe opposite results. Ito et all studied 135 patients' T3 levels before and after total thyroidectomy and found similar results as our result (5). They indicated that TSH-suppressive doses of levothyroxine are needed to be able to accomplish the natural T3 levels that they had preoperatively. As our goal was to achieve euthyroid TSH levels we didn't elevate LT4 doses that much but even in normal levels the FT4 levels of patients were higher than their preoperative values and they had lower FT3 levels after the operation.

Jonklaas et all concluded just the opposite, they studied 50 patients and indicated treatment with LT4 that normalizes serum TSH also restores serum T3 to pre-surgical levels But this study also accepts that relatively higher FT4 levels are needed to get euthyroid TSH levels which is the same finding in our study.

Ridgway et al studied 10 patients and evaluated their metabolic parameters when treated LT4 monotherapy and after 50 micrograms T3 added to the treatment (20). They found out that their basal metabolism rate (BMR) was slower when they were treated with LT4 even they were euthyroid and when they added T3 to the treatment the BMR is elevated. This may be the explanation of the weight gain of our patients in our study. They demonstrated an increase in the lipid parameters of their patients when treated with LT4 but we didn't demonstrate that kind of effect.

In our study, we showed that our patients had a significant deterioration in their insulin sensitivity within one year of postoperative LT4 treatment. The explanation for this comes from the study of Štěpánek L et all. They studied 1425 middle-aged individuals and indicated that insulin sensitivity is strongly correlated with T3/T4 levels. They suggested using the FT3/FT4 ratio in both the diagnosis and treatment of thyroid disorders. We demonstrated a strong negative correlation between HOMA-IR and FT3 levels (r=-0,57 P<0,01). Two of our patients had impaired fasting glucose diagnosis but none of them had diabetes diagnosis within the 1 year follow-up period. If we could continue with the follow-up process, there could be patients diagnosed with diabetes. Further studies are needed on insulin sensitivity in this LT4 monotherapy treatment model.

There are only a few studies evaluating signs and symptoms of thyroid functions in total thyroidectomized patients who were using LT4 monotherapy. Larisch et al. retrospectively investigated 319 patients with the diagnosis of differentiated thyroid carcinoma. Among those 319 patients 26% of them complained about hypothyroidism symptoms and 9,7% complained of hyperthyroidism symptoms but their THS levels were similar (median TSH=0,07 mIU/L). they indicated that FT3 levels can be in a normal range and the hypothyroidism symptoms were associated with FT3/FT4 ratios (22) Hirata et al. studied T4 treated hypothyroid patients and indicated an association with FT3 and body temperature especially in patients with total thyroidectomy or pituitary hypothyroidism.

In our study, we demonstrated significant complaints of hypothyroidism in our patients even though they were biochemically euthyroid.

In recent years new studies from functional and integrative medicine specialist suggest combined FT3 and FT4 therapy for the treatment of hypothyroidism (24, 25)

The shortcomings of our study were the small study group size and the absence of a group of patients who were treated with combination treatment of T3/T4 to compare the effects of both treatments. We will be planning a prospective study to evaluate the effects of different treatment models.

In conclusion, this study demonstrates that even though they are euthyroid with FT4 treatment total thyroidectomized patients may suffer from hypothyroidism signs and symptoms and metabolic deterioration may occur in such patients. We recommend that we should aim not only to normalize s-TSH levels but also to normalize patients' metabolic parameters and improve the quality of daily life when regulating our treatments.

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REFERENCES

1. Perros P, Van Der Feltz-Cornelis C, Papini E, Nagy EV, Weetman AP, Hegedüs L. The Enigma Of Persistent Symptoms In Hypothyroid Patients Treated With Levothyroxine: A Narrative Review. Clin Endocrinol (Oxf) 2021; Mar: 30.
2. Jonklaas J, Bianco AC, Cappola AR, Celi FS, Fliers E, Heuer H, et al. Evidence-Based Use of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism: A Consensus Document. Eur Thyroid J. 2021 Mar; 10(1):10-38
3. Pirahanchi Y, Tariq MA, Jialal I. Physiology, Thyroid. 2021; Feb 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.
4. Ito M., Miyauchi A., Hisakado M, Yoshioka W, Kudo T., Nishihara E, et al. Thyroid function related symptoms during levothyroxine monotherapy in athyreotic patients. Endocr J. 2019; Nov 28; 66(11):953-960.
5. Ito M, Miyauchi A, Hisakado M, Yoshioka W, Ide A, Kudo T, et al. Biochemical Markers Reflecting Thyroid Function in Athyreotic Patients on Levothyroxine Monotherapy. Thyroid 2017; Apr; 27(4):484-490.
6. Jonklaas J, Davidson B, Bhagat S, Soldin SJ. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy. JAMA 2008; 20;299(7):769-77.
7. Wolska A, Remaley AT. Measuring LDL-cholesterol: what is the best way to do it? Curr Opin Cardiol. 2020; 35(4):405-411.
8. Billewicz WZ, Chapman RS, Crooks J, Day ME, Gossage J, et al. Statistical methods applied to the diagnosis of hypothyroidism. Q J Med 1969; 38: 255–266.
9. Zulewski H, Müller B, Exer P, Miserez AR, Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J Clin Endocrinol Metab 1997; 82: 771–776.

10. Klein I, Trzepacz PT, Roberts M, Levey GS Symptom rating scale for assessing hyperthyroidism. Arch Intern Med 1988; 148:387–390.
11. Ettleson MD, Bianco AC. Individualized Therapy for Hypothyroidism: Is T4 Enough for Everyone? J Clin Endocrinol Metab. 2020; 105(9) :3090– 104.
12. Ross JS, Rohde S, Sangaralingham L, Brito JP, Choi L, Dutcher SK, et all. Generic and Brand-Name Thyroid Hormone Drug Use Among Commercially Insured and Medicare Beneficiaries, 2007 Through 2016. J. Clin. Endocrinol. Metab. 2019; 104(6):2305–2314.
13. Mitchell AL, Hickey B, Hickey JL, Pearce SHS. Trends in thyroid hormone prescribing and consumption in the UK. BMC Public Health 2009; 9 :132.
14. Sawin CT, Herman T, Molitch ME, London MH,Kramer SM. Aging and the thyroid. Decreased requirement for thyroid hormone in older hypothyroid patients. Am. J. Med.1983; 75 (2): 206–209.
15. Kahn A. Serum triiodothyronine levels in patients receiving L-thyroxine. Clinical Pharmacology & Therapeutics 1976; 19(part1): 523–530.
16. Gullo D, Latina A, Frasca F, Le Moli R, Pellegriti G, Vigneri R. Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. PLoS One 2011; 6(8): 225-52.
17. Jennings PE, O'Malley BP, Griffin KE, Northover B, Rosenthal FD. Relevance of increased serum thyroxine concentrations associated with normal serum triiodothyronine values in hypothyroid patients receiving thyroxine: a case for "tissue thyrotoxicosis." BMJ 1984; 289 (6459): 1645-1647.
18. Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health status, psychological symptoms, mood, and cognition in L-thyroxine-treated hypothyroid subjects. Thyroid 2007; 17(3): 249–258.
19. Jonklaas J, Davidson B, Bhagat S, Soldin SJ. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy. JAMA 2008; 299(7):769–777.
20. Ridgway EC, Cooper DS, Walker H, Daniels GH, Chin WW, Myers G, Maloof F. Therapy of primary hypothyroidism with l-triiodothyronine: Discordant cardiac and pituitary responses. Clinical endocrinology 1980; 13(5): 479–488.
21. Štěpánek L, Horáková D, Štěpánek L, Janout V, Janoutová J, Bouchalová K, et al. Free triiodothyronine/free thyroxine (FT3/FT4) ratio is strongly associated with insulin resistance in euthyroid and hypothyroid adults: a cross-sectional study. Endokrynol Pol. 2021; 72(1): 8-13.
22. Larisch R, Midgley JEM, Dietrich JW, Hoermann R. Symptomatic relief is related to serum free triiodothyronine concentrations during follow-up in levothyroxine-treated patients with differentiated thyroid cancer. Exp Clin Endocrinol. Diabetes 2018; 126: 546–552.
23. Hirata Y, Fukuoka H, Iguchi G, Iwahashi Y, Fujita Y, et al. Median-lower normal levels of serum thyroxine are associated with low triiodothyronine levels and body temperature in patients with central hypothyroidism. Eur J Endocrinol 2015; 173: 247–256.
24. Wellwood C, Rardin S. Adrenal and Thyroid Supplementation Outperforms Nutritional Supplementation and Medications for Autoimmune Thyroiditis. Integr Med 2014 Jun;13(3): 41-7.
25. Borson-Chazot F, Terra JL, Goichot B, Caron P. What Is the Quality of Life in Patients Treated with Levothyroxine for Hypothyroidism and How Are We Measuring It? A Critical Narrative Review. J Clin Med. 2021 Mar 30; 10(7): 1386.