



Comparison of Triiodothyronine Level in Patients Treated with Levothyroxine for Different Causes of Hypothyroidism

Farklı Hipotiroidizm Nedenleri Dolayısıyla Levotiroksin ile Tedavi Edilen Hastalarda Triiyodotironin Seviyesinin Karşılaştırılması

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Abstract

Objective: Several lines of evidence suggest that the symptoms of hypothyroidism, including psychological symptoms and metabolic effects, persist in a significant percentage of patients treated with levothyroxine (L-T4). A hypothesis to explain this phenomenon is that the triiodothyronine (L-T3) serum levels may not be completely normalized. This study aimed to compare the level of serum free T3 (FT3) in patients who are biochemically euthyroid after L-T4 monotherapy with different underlying causes of hypothyroidism. **Material and Methods:** This cross-sectional study was conducted on patients with hypothyroidism who received L-T4 monotherapy and were biochemically euthyroid. The serum levels of thyroid-stimulating hormone (TSH), free T4 (FT4), FT3, and FT3/FT4 ratio were measured in these patients. Patients were divided into three groups based on the cause of hypothyroidism (radioiodine therapy, thyroidectomy and Hashimoto), and the results of biochemical tests of the thyroid were compared in three groups. **Results:** Of the 78 patients studied, 12 (15.4%) cases were male, and 66 (84.6%) cases were female. Among the variables studied, only the mean value of FT3 was significantly different in the three groups ($p=0.006$), where the highest mean value was seen in the Hashimoto group, and the lowest mean value was seen in the radioiodine therapy group. **Conclusion:** The results of this study showed that although hypothyroidism patients can be optimally treated with L-T4 alone, in many of these patients, the level of FT3 will not be in therapeutic range, and the mean serum FT3 levels in these patients could be related to their hypothyroidism causes.

Keywords: Hypothyroidism; triiodothyronine; Hashimoto disease; thyroxine

Özet

Amaç: Çeşitli kanıtlar, levotiroksin (L-T4) ile tedavi edilen hastaların önemli bir kısmında, psikolojik semptomlar ve metabolik etkiler dâhil olmak üzere hipotiroidizm semptomlarının sebat ettiğini göstermektedir. Bu fenomeni açıklamak üzere öne sürülen bir hipotez, triiyodotironin (L-T3) serum seviyelerinin tamamen normalleştirilememesidir. Bu çalışmada, altta yatan hipotiroidizm nedenleri farklı olup L-T4 monoterapisi sonrası biyokimyasal olarak ötiroid olan hastalarda serum serbest T3 (sT3) düzeylerini karşılaştırmak amaçlanmıştır. **Gereç ve Yöntemler:** Kesitsel tipteki bu çalışma, L-T4 monoterapisi alan ve biyokimyasal olarak ötiroid olan hipotiroidili hastalarda gerçekleştirildi. Bu hastalarda tiroid uyarıcı hormon (TSH), serbest T4 (sT4), sT3 serum düzeyleri ve sT3/sT4 oranı ölçüldü. Hastalar, hipotiroidizmin nedenine göre üç gruba ayrıldı (radyoyot tedavisi, tiroidektomi ve Hashimoto) ve tiroid biyokimyasal testlerinin sonuçları bu üç grupta karşılaştırıldı. **Bulgular:** Çalışmaya alınan 78 hastanın 12 (%15,4)'si erkek, 66 (%84,6)'sı kadındı. İncelenen değişkenler içinde, sadece ortalama sT3 değeri üç grup arasında anlamlı olarak farklıydı ($p=0,006$) ve en yüksek ortalama değer Hashimoto grubunda, en düşük ortalama değer ise radyoyot tedavisi grubunda görüldü. **Sonuç:** Bu çalışmanın sonuçları, hipotiroidizm hastaları tek başına L-T4 ile optimal şekilde tedavi edilebilmesine rağmen, bu hastaların çoğunda sT3 seviyesinin terapötik aralıkta olmayacağını göstermiştir ve bu hastalardaki ortalama serum sT3 düzeyleri hipotiroidizmin nedeni ile ilişkili olabilir.

Anahtar kelimeler: Hipotiroidizm; triiyodotironin; Hashimoto hastalığı; tiroksin

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Introduction

The most common thyroid dysfunction is hypothyroidism; the global prevalence of overt hypothyroidism in the general population varies between 0.2% and 5.3%[\(1,2\)](#).

Hypothyroidism can be classified as primary (due to deficiency of thyroid hormone), secondary (due to deficiency of TSH), tertiary (due to deficiency of thyrotropin-releasing hormone), and peripheral (extra-thyroidal). One of the causes of primary hypothyroidism is the loss of functional thyroid tissue, which can be caused by chronic autoimmune thyroiditis (Hashimoto thyroiditis), other autoimmune thyroiditis, surgery (thyroidectomy), radioiodine therapy, infiltrative and infectious disease and congenital defects [\(2\)](#).

Thyroid hormone replacement therapy is the standard treatment of hypothyroidism. In the second half of the 20th century, the synthetically produced sodium salt of thyroxine (levothyroxine (L-T4)) became commercially available. Since then, levothyroxine has been the substance of choice for balancing thyroid hormone deficiency [\(1\)](#).

Previous studies showed that some patients on levothyroxine monotherapy continue to complain of persistent nonspecific symptoms, such as the poor performance of neurocognitive functioning, weight gain, and symptoms that are fatigue-related [\(3,4\)](#). Moreover, those patients who are on levothyroxine monotherapy after thyroidectomy will often state that they did not experience similar symptoms before surgery [\(5,6\)](#). This evidence has led to the hypothesis that in some patients, monotherapy with levothyroxine is unable to provide sufficient levels of T3 in target tissues. An experimental study conducted in rats showed that monotherapy with levothyroxine might provide insufficient intracellular levels of T3 [\(7\)](#). Few studies have demonstrated the benefit of liothyronine (L-T3)/L-T4 combination therapy in humans [\(8,9\)](#). On the other hand, some literature does not recommend the addition of treatment with L-T3 for treating hypothyroidism. Some studies have also shown that treatment with L-T3 can increase the risk of angina or myocardial infarction or cause unpleasant symptoms such as headaches, sweating, tremors, nervousness, irritability, and palpitations [\(10,11\)](#).

Purpose

According to the controversy regarding whether hypothyroid patients can be optimally treated with levothyroxine alone, a study to find patients benefiting from L-T3 treatment will be helpful. Therefore, in this study, we evaluated the impact of different causes of hypothyroidism on thyroid markers in patients treated with levothyroxine.

Material and Methods

A cross-sectional study was conducted on patients referring to Imam Khomeini Hospital in Tehran, Iran in 2018. The study population included patients with hypothyroidism who had been treated with levothyroxine for at least six months, and their last TSH was in a normal range (0.5-5 mIU/mL). All patients that met the inclusion criteria during one year entered the study.

The inclusion criteria included age over 20 years, body mass index between 19-35, history of hypothyroidism, and at least six months of monotherapy with levothyroxine. Pregnant women, people with chronic cardiovascular disease and chronic renal disease, as well as those treated with drugs that affect thyroid hormones metabolism (such as lithium, amiodarone, phenytoin, and carbamazepine), those taking psychiatric drugs, and those with thyroid cancer (except for medullary thyroid cancer), were not included. Hashimoto thyroiditis was diagnosed using anti-thyroid peroxidase and anti-thyroglobulin antibodies. Patients with a prior history of near-total or total thyroidectomy and radioiodine therapy for hyperthyroidism due to Graves disease or nodular goiter were enrolled in the study.

The age, sex, and the last serum TSH level of patients were entered into the checklist. Blood samples of about 10 cc were taken from each patient for measuring the levels of TSH, FT3, and FT4 by using Padyabteb kit (Padyabteb Inc., Tehran, Iran) and Monobind kit (Monobind Inc., Lake Forest, CA, USA), respectively. All the thyroid hormone measurements were performed in the same laboratory. The normal range of FT3 and FT4 were 2.3-4.2 pg/mL and 0.8-1.8 ng/dL, respectively.

Statistical analysis was performed by using the IBM SPSS 19.0 software (IBM Corp, 2009). A comparison of the results of the

thyroid function tests and demographic variables in three groups was performed using ANOVA and Chi-square test.

The project was approved by the Ethics Committee of Imam Khomeini Hospital Complex-Tehran University of Medical Sciences (Approval ID: IR.TUMS.IKHC.REC. 1397.241, Approval Date: 2018-11-21). Written informed consent was obtained from all patients, and no additional cost was imposed.

Results

A total of 90 patients were eligible for inclusion in the study, of which five were excluded due to a lack of appropriate blood samples. In the second test, the TSH level of seven patients did not lie in the therapeutic range, so they were excluded from the study. Finally, data of 78 patients were analyzed, of which 12 were men (15.4%), and 66 were women (84.6%).

The mean age of patients was 51.37 ± 10.02 years, with a minimum age of 32 years and a maximum age of 73 years.

Based on the cause of hypothyroidism, the patients were divided into three groups: the Hashimoto group (32 patients), the radioiodine therapy group (15 patients) and the thyroidectomy group (31 patients).

Distribution of age, sex, body mass index, and TSH levels were not significantly different in the three groups (Table 1).

The mean serum level of FT3 of participants was 2.27 ± 0.35 pg/mL, with a range of 1.4-3.2. The serum level of FT3 in all patients was in the normal range.

Just three of the patients (3.8%) had an FT3 in the upper half of the reference range, and all three patients were in the Hashimoto group.

Among the thyroid function tests that were evaluated in this study, only the level of FT3 was significantly different between the three groups. Hashimoto group had the highest mean value, and the radioiodine therapy group had the lowest mean value (Table 2).

The result of post-hoc test for comparison of the between-groups showed that only the Hashimoto group and radioiodine treatment group had statistically significant differences in the blood level of FT3 (Table 3).

Discussion

Based on the available evidence, the best treatment for hypothyroidism is still monotherapy with levothyroxine (12-14). In these patients, it is recommended to aim for a TSH in the lower half of the normal. Nevertheless, animal studies showed that normalization of serum TSH does not ensure normal T3 levels in all tissues (7). On the other hand, some patients treated with levothyroxine alone were dissatisfied with

Table 1. Comparison of baseline characteristics in patients treated with levothyroxine based on the causes of hypothyroidism.

Variable	Hashimoto group	Radioiodine therapy group	Thyroidectomy group	p-value*
Female/Male ratio	27/5	11/4	28/3	0.093
Age, year (Mean±SD)	48.26±10.3	53.29±9.89	53.97±9.21	0.066
TSH, μ IU/mL (Mean±SD)	2.11±1.13	2.9143±1.75	1.8±1.15	0.087
BMI, kg/m ² (Mean±SD)	27.78±4.31	27.71±2.6	28.35±4.34	0.845

*p-value based on one way ANOVA.

TSH: Thyroid-Stimulating Hormone; BMI: Body Mass Index; SD: Standard deviation.

Table 2. Comparison of thyroid function tests in patients treated with levothyroxine based on the causes of hypothyroidism.

Variable	Hashimoto group	Radioiodine therapy group	Thyroidectomy group	p-value*
FT3, pg/mL (Mean±SD)	2.39±0.349†	1.97±0.095†	2.2±0.34	0.006
FT4, ng/dL (Mean±SD)	12.06±2.34	10.84±1.43	12.25±2.094	0.299
FT3/FT4 (Mean±SD)	0.21±0.05	0.18±0.025	0.18±0.039	0.134

*p-value based on one way ANOVA

FT3: Free T3, FT4: Free T4, SD: Standard deviation.

Table 3. Post-hoc test results for the comparison of serum FT3 in patients treated with levothyroxine based on the causes of hypothyroidism.

Groups		Mean Difference of			95% Confidence	
		FT3, pg/mL	Std. Error	p-value*	Interval	
Radioiodine therapy group	Thyroidectomy group	-.23170	.13772	.219	-.5618	.0984
Radioiodine therapy group	Hashimoto group	-.41567	.13812	.010	-.7467	-.0846
Thyroidectomy group	Hashimoto group	-.18397	.08318	.076	-.3833	.0154

*p-value based on Tukey's post-hoc test.

their therapy (15). Therefore, this hypothesis has developed that this dissatisfaction could be due to the failure to replace the T3 that comes from the thyroid tissue. For this reason, some researchers have suggested that a percentage of patients with hypothyroidism may benefit from L-T4/L-T3 combination therapy.

To the best of the author's knowledge, no study has been conducted to investigate the status of thyroid hormones after treatment with levothyroxine, based on the causes of hypothyroidism. Therefore, for better identifying those patients who benefit from combined therapy, the present study was conducted to evaluate the impact of different causes of hypothyroidism on triiodothyronine levels in patients treated with levothyroxine.

Our results showed that the serum level of FT3 in all patients was in the normal range, but only 3.8% of the patients had an FT3 in the upper half of the reference range.

Previous studies have also shown that patients under levothyroxine monotherapy with a normal serum TSH, in comparison to euthyroid individuals not taking levothyroxine, exhibited relatively lower FT3 and lower T3/T4 ratios (16-19). However, some studies showed that serum T3 levels can be normal in patients under levothyroxine monotherapy with a normal serum TSH (20,21). These observations can be attributed to the smaller sample size of these studies.

Our results suggest that patients, in which the cause of hypothyroidism is radioiodine therapy, have the least amount of serum FT3. Thyroidectomy patients also had a low level of FT3, but there was no statistically significant difference. However, owing to the small sample size in the thyroidectomy group, the present study does not have

enough power to comment on this group. Nevertheless, the commonality of these two groups is the deficiency of thyroid tissue. Since 20% of the circulating T3 originates from the thyroid tissue, therefore, it was absent in this group of patients (22).

Furthermore, plasma T3 levels do not reflect upon the intracellular T3 stores nor on the intracellular T3 deficiency (23). Previous studies also suggested that hypothyroid post-thyroidectomy patients, when being replaced with levothyroxine alone, might require higher serum T4 levels. In these patients, the serum T3 levels will be lower than in the preoperative state (19,21,24). On the contrary, the results of animal and human studies on the L-T3/L-T4 combination therapy are very different. The results from studies conducted in animals mostly suggested combined therapy (7,25). However, outcomes of the human studies did not suggest the same (10,11). The reason for this difference may be due to the selection of thyroidectomized animals in these studies.

We did not evaluate the clinical manifestations of hypothyroidism in euthyroid L-T4-treated participants. Still, some studies have addressed this aspect and possible explanations for unresolved symptoms such as physical factors, psychological factors, social factors, economic factors, disease symptoms, cultural set-up, activities of the daily role, and treatment have been raised (26,27).

In summary, evidence of human studies does not support combination therapy for all patients with hypothyroidism. A meta-analysis of randomized controlled trials with 1,216 patients showed that there is no evidence supporting the superiority of L-T4/L-T3 combination therapy regarding improvements in blood lipids, body weight, quality of life, fatigue, or mood (28). It seems that among hypothyroid patients,

some might benefit from L-T4/L-T3 combination therapy. The results of this study showed that one of the factors that can be effective in determining the type of treatment (monotherapy or combination therapy) is the cause of hypothyroidism. However, previous studies have also considered the genetic background of the individual to be useful in determining the treatment modality. Panicker, et al., in a study, showed that patients with deiodinase-2 polymorphisms could benefit from L-T4/L-T3 combination therapy (29). Another study showed that the D2 gene polymorphism is associated with reduced T4 to T3 activation in thyroid and skeletal muscle (4). Future studies are needed to evaluate the factors affecting the response to the combination L-T4/L-T3 treatment.

Study Limitations

The main limitations of this study were its low sample size in radioiodine group, cross-sectional design, and a single measurement of TSH (Serum thyroid hormone levels can change, although very little, in repeated measures). Another limitation of this study was that the clinical manifestations of hypothyroidism were not evaluated in euthyroid L-T4-treated participants.

Conclusion

The results of this study showed that although hypothyroid patients can be optimally treated by levothyroxine monotherapy, in some of these patients, the level of FT3 will not be normal, and the mean serum FT3 levels in these patients could be related to their hypothyroidism causes.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of

the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Author Contributions

Study concept and design: Mahboobeh Hemmatbadi, and Nooshin Shirzad. Analysis and interpretation of data: Samaneh Azizimanesh, Fatemeh Esfahanian, and Mohammad Reza Mohajeri Tehrani. Drafting of the manuscript: Mahboobeh Hemmatbadi. Critical revision of the manuscript for important intellectual content: Samaneh Azizimanesh, Fatemeh Esfahanian, Mohammad Reza Mohajeri Tehrani, Nooshin Shirzad.

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