Original Article
Turk J Endocrinol Metab. 2021;25:288-294

Comparison of Mental Health and Quality of Life in Euthyroid Patients Under Levothyroxine Mono-therapy Based on the Causes of Hypothyroidism

Levotiroksin Monoterapisi Alan Ötiroid Hastalarda Ruh Sağlığı ve Yaşam Kalitesinin Hipotiroidi Nedenlerine Göre Karşılaştırılması

Mahboobeh HEMMATABADI*, Nasrin Asgari-SORAN*, Fatemeh ESFAHANIAN*, Elham SHARAFI***, Mostafa QORBANI,**** Nooshin SHIRZA*,**

*Department of Endocrinology, Vali-Asr Hospital, Endocrinology and Metabolism Research Center, Imam Khomeini Complex Hospital, Tehran University of Medical Sciences, Tehran, IRAN
**Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, IRAN
***Department of Psychiatry, Psychosomatic Research Center, Tehran University of Medical Sciences, Tehran, IRAN
****Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, IRAN

Abstract

Objective: A controversy prevails regarding the adequacy of levothyroxine treatment in hypothyroid patients to reduce the risk of psychiatric illness, mood disorders and improve their quality of life. This study evaluated the relationship between different causes of hypothyroidism, mental health, and quality of life in patients treated with levothyroxine. **Material and Methods:** This cross-sectional study was performed on three groups of hypothyroid patients (Hashimoto thyroiditis, thyroidectomy, radioiodine therapy) treated with levothyroxine for at least six months, with the last thyroid-stimulating hormone within the normal range. After recording the demographic characteristics and thyroid hormone profiles, quality of life [12-item Short-Form Health Survey (SF-12)] and mental health [General Health Questionnaire 28 (GHQ-28)] were evaluated. **Results:** A total of 109 patients were evaluated in 3 groups of Hashimoto (48 patients), radioiodine therapy (15 patients), and thyroidectomy (46 patients). No significant difference was found between the 3 groups as evaluated by the total score of the SF-12 and GHQ-28 questionnaires. The FT3/FT4 ratio was significantly correlated with five variables related to mental health and quality of life. **Conclusion:** The study did not find any association between the cause of hypothyroidism and psychological symptoms. However, a possible association between psychological symptoms and thyroid function status is suggested.

Keywords: Hypothyroidism; thyroxine; mental health; quality of life

Özet

Amaç: Hipotiroid hastalarda levotiroksin tedavisinin psikiyatrik hastalık ve duygudurum bozuklukları riskini azaltmadaki ve yaşam kalitesini iyileştirmedeki yeterliliği konusunda bir tartışma söz konusudur. Bu çalışmada, levotiroksin ile tedavi edilen hastalarda hipotiroidizmin farklı nedenleri, ruh sağlığı ve yaşam kalitesi arasındaki ilişki değerlendirilmiştir. **Gereç ve Yöntemler:** Bu kesitsel çalışma, en az 6 ay boyunca levotiroksin ile tedavi edilen ve son tiroid uyarıcı hormon değeri normal aralıkta olan 3 grup hipotiroid hasta (Hashimoto tiroiditi, tiroidektomi, radyoiyot tedavisi) üzerinde yapıldı. Demografik özellikler ve tiroid hormon profilleri kaydedildikten sonra yaşam kalitesi [Kısa Form-12 (12-item Short-Form Health Survey "SF-12")] ve ruh sağlığı [Genel Sağlık Anketi-28 (General Health Questionnaire 28 "GHQ-28")] değerlendirildi. **Bulgular:** Hashimoto (48 hasta), radyoiyot tedavisi (15 hasta) ve tiroidektomi (46 hasta) olmak üzere 3 grupta toplam 109 hasta değerlendirildi. SF-12 ve GHQ-28 anketlerinin toplam puanı ile değerlendirilen 3 grup arasında anlamlı bir fark bulunmadı. FT3/FT4 oranı ise ruh sağlığı ve yaşam kalitesi ile ilişkili 5 değişkenle anlamlı şekilde korele idi. **Sonuç:** Çalışmada, hipotiroidizmin nedeniyle psikolojik belirtiler arasında herhangi bir ilişki bulunamamıştır. Bununla birlikte, psikolojik semptomlar ile tiroid fonksiyon durumu arasında bir ilişki söz konusu olabilir.

Anahtar kelimeler: Hipotiroidi; tiroksin; ruh sağlığı; yaşam kalitesi

Address for Correspondence: Nooshin SHIRZA, Department of Endocrinology, Vali-Asr Hospital, Endocrinology and Metabolism Research Center, Imam Khomeini Complex Hospital, Tehran University of Medical Sciences, Tehran, IRAN
Phone: +98-21-66911294 **E-mail:** nshirzad11@gmail.com

Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 16 Mar 2021 **Received in revised form:** 05 Jul 2021 **Accepted:** 05 Jul 2021 **Available online:** 20 Aug 2021

DOI: 10.25179/tjem.2021-83124

Introduction

Hypothyroidism is a syndrome caused by thyroid hormone deficiency (1). The annual incidence of primary hypothyroidism in the UK is 3.5 per 1,000 women and 0.6 per 1,000 men (2). In a study in the US, the prevalence of hypothyroidism was estimated to be 4.6% of the total population (3). In a study in Shiraz, Iran, 3.4% of the study population had low thyroid-stimulating hormone (TSH) levels (4). In another study in Iran, the prevalence of hypothyroidism in males and females was found to be 4.8% and 12.8%, respectively (5). Overall, the prevalence of hypothyroidism has been estimated at 5%, with a further estimation of 5% being undiagnosed (1).

Different studies prove that hypothyroidism is associated with anxiety disorders and depression (6). Although anxiety and depression were prevalent among hypothyroid patients, well-treated patients have been found to have the same depressive and cognitive dysfunction as healthy controls (7,8). Hypothyroidism can affect cognitive and mood function and mimic psychiatric disorders in severe cases like major depression (9). Symptoms such as depression, mood changes, and cognitive impairment can disrupt patients' daily activities and decrease their quality of life (10). The cause of psychiatric disorders in patients with hypothyroidism remains controversial. Factors like alterations in the cerebral circulation increased T3 production, decreased TSH response to thyrotropin-releasing hormone (TRH), changes in neurotransmitter metabolism, and environmental factors can all contribute to these disorders (11).

At present, the standard treatment for hypothyroidism is thyroid hormone replacement with levothyroxine. Some studies report that patients on levothyroxine monotherapy show persistent complaints and nonspecific symptoms, such as weight gain, poor performance of neurocognitive function, and fatigue-related symptoms (12,13). Besides, some other studies indicate that patients after thyroidectomy, who are on levothyroxine monotherapy, often state that their symptoms are not similar to those before surgery (14,15). This evidence has led to the hypothesis that the normal levels of TSH in patients treated with levothyroxine are not necessarily equal to the remission of all symptoms and other variables other than normal TSH levels.

However, the relationship between thyroid profiles and patients' mental health and the role of thyroid hormone replacement therapy remains unclear; further studies are needed to determine its proportions. Therefore, the current study assesses the relation of different causes of hypothyroidism to mental health and quality of life in patients on levothyroxine therapy.

Material and Methods

This study was conducted in a referral hospital clinic (Imam Khomeini Hospital) in Tehran, Iran. The study population comprised all hypothyroid patients referred to this clinic during 2018. The sample size was determined according to 2 mean comparison formulas, considering power 0.8 and alpha 0.05. The mean (standard deviation) of total quality life score in radioiodine therapy and Hashimoto thyroiditis was considered as 30.7 (7.5) and 36.8 (6.2), respectively. The sample size was estimated to be 22 subjects per group.

Inclusion criteria were: at least six months of monotherapy with levothyroxine, TSH within the therapeutic range, age over 20 years, and body mass index between 19-35. Patients with chronic cardiovascular or renal disease, diabetes, hypertension, pregnant women, those on treatment with psychiatric drugs, those taking drugs that influence thyroid hormones status (such as carbamazepine, amiodarone, phenytoin, and lithium), and those with thyroid cancer were excluded. From each patient, 10 cc blood samples were drawn for measuring FT3, FT4, and TSH. TSH was determined using the Padyabteb kit (Padyabteb Inc., Tehran, Iran), while FT3 and FT4 were assessed using the Monobind equipment (Monobind Inc., Lake Forest, CA, USA).

The Persian version of the 12-item Short-Form Health Survey (SF-12) questionnaire, whose validity and reliability had been previously confirmed across several chronic diseases and conditions (16-19), was used to assess the health-related quality of life. The instrument evaluates eight health domain categories. The physical health-related domains include role physical, physical func-

tioning, general health, and body pain. Mental health-related scales include social functioning, role emotional, vitality, and mental health.

Also, the Persian version of the General Health Questionnaire 28 (GHQ-28), whose validity and reliability had been previously confirmed (20), was used to assess mental health. This instrument assesses somatization, anxiety, social dysfunction, and depression. The maximum score for this instrument is 28.

All the collected data were analyzed using the IBM SPSS 20.0 software (IBM Corp, 2009). Continuous and categorical variables have been presented as median [inter quartile range (IQR)] for numerical data and percentages for categorical data. The chi-square test, Kruskal-Wallis, Mann-Whitney U, and Pearson correlation tests were used to compare the data of demographic variables, mental health, and quality of life in the three study groups. Bonferroni correction for comparison between the groups was done in post-hoc analysis after the Kruskal-Wallis test with Mann-Whitney U tests. A p value less than 0.018 was considered significant.

All participants gave informed consent before enrollment, and patient anonymity was preserved. The study was carried out as per the Helsinki Declaration Principles. The study was approved by the Ethics Committee of Tehran University of Medical Sciences (22.07.2018/IR.TUMS.IKHC.REC.1397. 081). In addition, not impose any additional cost to patients.

Results

One hundred and nine participants were eligible for inclusion in the study. Of these, 17 (15.6%) were men, and 92 (84.4%) were women. Patients were distributed into 3 groups according to the hypothyroidism causes: the Hashimoto group (48 patients), radioiodine therapy group (15 patients), and thyroidectomy group (46 patients). The mean age of patients was 49.72±11.37 years, with a range of 20-73 years. There was no significant difference in the distribution of sex, age, body mass index, and thyroid function tests between groups, except for serum T3, which was lower in the radioiodine therapy group than the Hashimoto group (p=0.003) (Table 1).

Of these, 54.2% of patients in the Hashimoto group, 39.1% patients in the thyroidectomy group, and 40% in the radioiodine therapy group had a good quality of life (score: 32-48), as assessed by a questionnaire (p=0.3). The median (IQR) total scores of the SF-12 questionnaire in the three groups were 37 (9), 34 (15), and 34 (10) in the Hashimoto, radioiodine therapy, and thyroidectomy groups, respectively (p=0.3). No statistically significant difference in the total SF-12 scores and each of the eight SF-12 scales was observed between the 3 groups (p>0.018) (Power=0.67) (Table 2).

The median (IQR) score of the GHQ-28 questionnaire in the three groups of Hashimoto, radioiodine therapy, and thy-

Table 1. Baseline characteristics and thyroid function tests in euthyroid patients with different causes for hypothyroidism.

Group Variable	Radioiodine therapy	Post thyroidectomy	Hashimoto thyroiditis	p value*
Gender (M/F)	11/4	37/9	44/4	0.144
Age, year, median (IQR)	58 (9)	52 (12)	46 (15)	0.17
BMI, kg/m^2, median (IQR)	26.67 (3.54)	27.84 (4.64)	27.55 (7.08)	0.5
Levothyroxine dose, mcg/week, median (IQR)	700 (200)	700 (300)	500 (350)	0.04
TSH, µIU/mL, median (IQR)	2.7 (3.6)	1.5 (1.75)	1.8 (1.9)	0.17
FT3, pg/mL, median (IQR)	2 (0.1)	2.25 (0.5)	2.3 (0.5)	0.003
FT4, pg/mL, median (IQR)	11.3 (2.9)	12.4 (2.93)	11.9 (3.1)	0.25
FT3/FT4, median (IQR)	0.18 (0.04)	0.17 (0.06)	0.19 (0.05)	0.14

*p value based on Kruskal-Wallis test; BMI: Body mass index; TSH: Thyroid-stimulating hormone; IQR: Inter quartile range.

Table 2. SF-12 scores in euthyroid patients with different causes for hypothyroidism.

Group		Radioiodine therapy	Post thyroidectomy	Hashimoto thyroiditis	
Variable		(n=15)	(n=46)	(n=48)	p value*
Physical	PF	5 (1)	5 (2)	5 (2)	0.83
	RP	4 (2)	4 (2)	4 (1)	0.37
	BP	4 (1)	4 (1)	4 (2)	0.3
	GH	3 (1)	3 (1)	3 (0)	0.09
Mental	VT	3 (1)	3.5 (1)	3 (2)	0.87
	SF	4 (2)	5 (1)	5 (2)	0.09
	RE	4 (2)	4 (1)	4 (1)	0.82
	MH	8 (3)	8 (2)	9 (3)	0.39
Summary	PCS	15 (5)	14 (5)	15.5 (5)	0.29
	MCS	20 (7)	19 (5)	21 (6)	0.37
Total		34 (15)	34 (10)	37 (9)	0.3

*p value based on Kruskal-Wallis test; Variables as obtained by Median [inter quartile range (IQR)]; PF: Physical functioning; RP: Role physical; BP: Body pain; GH: General health; VT: Vitality; SF: Social functioning; RE: Role emotional; MH: Mental health; PCS: Physical composite scores; MCS: Mental composite scores.

roidectomy was 18 (15), 17 (22), and 17.5 (17), respectively (p=0.8). No statistically significant differences in the total GHQ-28 scores and each of the four domains were observed between the three groups (p>0.05) (Power=0.51) (Table 3).

Table 4 represents the correlations of the total SF-12 scores, each of the eight SF-12 scales, and GHQ-28 scores with thyroid function tests of the participants. Serum levels of FT3, TSH, and FT3/FT4 ratio correlated with social dysfunction score, physical functioning, and vitality, respectively. Other thyroid function tests were not significantly associated with variables related to mental health and quality of life according to the Bonferroni correction in the three study groups.

Discussion

The study compared the quality of life and mental health of three hypothyroid patient groups (radioiodine therapy, thyroidectomy, Hashimoto thyroiditis) after levothyroxine treatment and achieving euthyroid status. No statistically significant differences were observed in patients' quality of life and mental health between the three groups. Accordingly, these patients' quality of life and mental health appears to be independent of their cause of hypothyroidism. To the authors' best knowledge, this is the first study to investigate the quality of life and mental health after euthyroidism with levothyroxine treatment, based on the underlying causes for hypothyroidism.

Table 3. GHQ-28 scores in euthyroid patients with different causes for hypothyroidism.

Group	Radioiodine therapy	Post thyroidectomy	Hashimoto thyroiditis	
Variable	(n=15)	(n=46)	(n=48)	p value*
Somatization	6 (9)	5 (6)	5 (3)	0.64
Anxiety	5 (6)	5 (6)	6 (7)	0.89
Social Dysfunction	7 (2)	7 (4)	6 (3)	0.23
Depression	1 (3)	0 (2)	0 (3)	0.63
Total	17 (22)	17.5 (17)	18 (15)	0.8

*p value based on Kruskal-Wallis test; Variables were presented by Median [inter quartile range (IQR)]; GHQ-28: General Health Questionnaire 28.

Table 4. Correlation of GHQ-28 scores and SF-12 scores with thyroid function tests in patients on levothyroxine therapy.

Variable		TSH	FT3	FT4	FT3/FT4
		r (p value)	r (p value)	r (p value)	r (p value)
SF-12 Questionnaire	GH	-0.014 (0.908)	0.123 (0.312)	-0.131 (0.280)	0.218 (0.070)
	PF	-0.327 (0.006)	-0.022 (0.854)	-0.144 (0.235)	0.138 (0.253)
	RP	0.002 (0.986)	0.113 (0.354)	-0.102 (0.399)	0.181 (0.134)
	RE	-0.112 (0.356)	0.083 (0.493)	-0.032 (0.793)	0.107 (0.380)
	BP	-0.163 (0.177)	0.014 (0.907)	-0.111 (0.361)	0.128 (0.292)
	SF	-0.191 (0.112)	0.074 (0.543)	-0.094 (0.439)	0.124 (0.307)
	VT	0.049 (0.688)	0.222 (0.064)	-0.217 (0.071)	0.346 (0.003)
	MH	-0.179 (0.138)	0.192 (0.111)	-0.007 (0.952)	0.154 (0.204)
	PCS	-0.177 (0.143)	0.061 (0.617)	-0.153 (0.207)	0.201 (0.094)
	MCS	-0.153 (0.205)	0.199 (0.099)	-0.103 (0.398)	0.236 (0.049)
	Total	-0.174 (0.149)	0.147 (0.225)	-0.133 (0.273)	0.235 (0.049)
GHQ-28 Questionnaire	Somatization	-0.027 (0.824)	-0.074 (0.541)	-0.024 (0.846)	-0.054 (0.657)
	Anxiety	0.050 (0.683)	-0.049 (0.686)	0.023 (0.849)	-0.081 (0.502)
	Social Dysfunction	0.115 (0.342)	-0.281 (0.017)	0.076 (0.531)	-0.278 (0.020)
	Depression	-0.037 (0.762)	-0.181 (0.135)	0.151 (0.212)	-0.253 (0.035)
	Total	0.024 (0.841)	-0.159 (0.190)	0.049 (0.686)	-0.172 (0.154)

*p-value based on Kruskal-Wallis test; r: Pearson correlation; GHQ-28: General Health Questionnaire 28; SF-12: 12-item Short-Form Health Survey; GH: General health; PF: Physical functioning; RP: Role physical; BP: Body pain; VT: Vitality; SF: Social functioning; RE: Role emotional; MH: Mental health; PCS: Physical composite scores; MCS: Mental composite scores.

Numerous studies have investigated the relationship between thyroid autoimmunity and psychiatric illness and have established conflicting results. Ott et al. reported that in euthyroid females undergoing thyroid surgery for benign thyroid disease, factors like chronic nervousness, chronic fatigue, chronic irritability, and lower quality of life were significantly associated with anti-thyroid peroxidase (TPO) levels. Ott et al. concluded that in Hashimoto's thyroiditis, higher anti-TPO antibody levels are associated with increased symptom load and decreased quality of life in female euthyroid patients and associated with Hashimoto's symptoms of thyroiditis are not merely due to overt hypothyroidism (21). Three other studies also found this association (22-24). On the other hand, Engum et al., in a large population-based study, found no relation between antithyroid antibodies and depression or anxiety (25). The differences between the present study results and those of the other studies might be due to the small number of patients included in the current study. Besides, most other studies have compared hypothyroid patients with healthy euthyroid people. In contrast, the present study was conducted on three groups of hypothyroid patients (radioiodine therapy, thyroidectomy, Hashimoto thyroiditis) treated with levothyroxine.

Another study represented a significant negative correlation between anti-TPO antibody levels and quality of life in patients with Hashimoto thyroiditis on long-standing levothyroxine therapy (26). In this study, patients were euthyroid for at least six months, and the difference in euthyroidism duration between the three groups was not considered.

In the present study, the FT3/FT4 ratio, FT3, and TSH levels were significantly correlated with some variables related to mental health and quality of life (vitality, social dysfunction score, and physical functioning). However, the degree of correlation was weak.

Kritz-Silverstein et al. found that TSH level was unrelated to cognitive function in a community-based sample and was inversely associated with depressed mood in men (27).

Contrary to the present study results, Saltevo et al., in a random, population-

based sample of 4,500 subjects, did not find any relation between depressive symptoms and thyroid function tests (28). In the other study by Samuels et al., subjects on levothyroxine therapy with suppressive and replacement doses of levothyroxine did not differ in cognitive function and mood, and there were no correlations between thyroid function tests and health status, mood, and cognition (29).

Future studies to evaluate the factors affecting the quality of life and mental health of hypothyroid patients treated with levothyroxine are warranted.

The limitation of this study was the small sample size in each studied group, especially in the radioiodine subgroup, because of the limited cases that are treated with radioiodine in the study center, which could affect the results of this study. Furthermore, assessment before and after initiation of levothyroxine and considering other potential connections, such as smoking with mental health, could have been informative on the treatment effects. Future studies with larger sample sizes, assessment at the initiation of treatment, and longer follow-ups are recommended.

Conclusion

The relationship between thyroid function status and patients' mental health and the role of thyroid hormone replacement therapy remains unclear and controversial. The study could not find any association between the cause of hypothyroidism and psychological symptoms. However, a possible association between psychological symptoms and thyroid function tests is suggested.

Acknowledgments

We would like to thank the Deputy of research at Tehran University of Medical Sciences, Tehran, Iran.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instru ments and materials which may negatively affect the evaluation process of this study.

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.

Authorship Contributions

Idea/Concept: Nooshin Shirzad; Design: Mahboobeh Hemmatabadi; Control/Supervision: Fatemeh Esfahanian; Data Collection and/or Processing: Nasrin Asgari-soran; Analysis and/or Interpretation: Mostafa Qorbani; Literature Review: Mahboobeh Hemmatabadi; Writing the Article: Mahboobeh Hemmatabadi; Critical Review: Elham Sharafi; References and Fundings: Nooshin Shirzad; Materials: Nooshin Shirzad.

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