Thyroid Function and Ultrasonography Abnormalities in Lithium-Treated Bipolar Patients: A Cross-sectional Study with Healthy Controls

Özlem KUMAN TUNÇEL¹, Fisun AKDENİZ², Süha Süreyya ÖZBEK³, Gülgün KAVUKÇU³, Gökçen ÜNAL KOCABAŞ⁴

¹Department of Psychiatry, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey

²Psychiatrist, Private Practice, İzmir, Turkey

³Department of Radiology, Ege University School of Medicine, İzmir, Turkey

⁴Department of Endocrinology, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey

ABSTRACT

Introduction: Lithium has many effects on thyroid physiology. Although these side effects have been known for a long time, large sample studies of lithium-treated patients using ultrasonography are lacking. The aim of this study is to investigate the detailed thyroid morphologies, hormone levels, and antibodies of lithium-treated patients compared with healthy controls.

Methods: This cross-sectional study involved 84 lithium-treated patients with bipolar disorder and 65 gender and age similar controls who had never been exposed to lithium. Subjects between 18 and 65 years of age were eligible for the study. Venous blood samples were acquired to determine the levels of free thyroxine (fT4), thyroid stimulating hormone (TSH), and thyroid antibodies; also, ultrasonographic examinations of the patients' thyroid glands were performed.

Results: There were no statistically significant differences in smoking habits, known thyroid disease, thyroid medication use, familial thyroid disease, fT4 level, autoimmunity, thyroid nodule presence, or Hashimoto's thyroiditis between the lithium and control groups. The median TSH level and thyroid volume were significantly higher in the

lithium group. In the lithium group, 14 cases (16.7%) of hypothyroidism, seven cases (8.3%) of subclinical hypothyroidism, and one case (1.2%) of subclinical hyperthyroidism were defined; in the control group, seven cases (10.8%) of hypothyroidism and two cases (3.1%) of subclinical hyperthyroidism were defined. Thyroid dysfunction, goiter, parenchymal abnormality, ultrasonographically defined thyroid abnormality, and thyroid disorder were found to be more prevalent in the lithium group. 90% of patients with goiter and 74.3% of patients with ultrasonographic pathologies were euthyroid.

Conclusion: It is important to note that 90% of the patients with goiter were euthyroid. This indicates that monitoring by blood test alone is insufficient. The prevalence rates of 47.6% for goiter and 83.3% for ultrasonographic pathology demonstrate that ultrasonographic follow-up may be useful in lithium-treated patients. To determine whether routine ultrasonographic examination is necessary, large sample prospective studies are necessary due to the limitations of this study.

Keywords: Goiter, hypothyroidism, lithium, thyroid gland, ultrasonography

INTRODUCTION

Lithium has several effects on thyroid physiology; its potential side effects have been known since its introduction for the treatment of bipolar disorder (1). Although lithium treatment frequently leads to hypothyroidism, it may also cause hyperthyroidism on rare occasions (2).

Lithium is concentrated in the thyroid gland at levels three to four times greater than in plasma (3). It interferes with various steps in the production of thyroid hormones. Influence on the hypothalamic-pituitary-thyroid axis has also been observed (2,3). Normally, thyroid stimulating hormone (TSH) stimulates a cAMP mechanism to increase the synthesis and release of triiodothyronine (T3) and thyroxine (T4). Lithium inhibits cAMP activity, resulting in decreased T3 and T4 levels. To maintain homeostasis, TSH hypersecretion occurs. This indicates the onset of hypothyroidism (4). An increase in TSH concentration also results in thyroid enlargement and, thus, goiter (3). Additionally, *in vitro* studies have shown that lithium increases thyrocyte proliferation by Wnt/ β signaling (5,6).

Deniker et al. (7) suggested that lithium-associated hypothyroidism may be related to an immunologic reaction, as thyroid antibody levels have been found to be higher in lithium-treated patients (7). However, some studies found no significant differences in the prevalence of autoimmunity between lithium-treated patients and control groups or the general population (8,9,10). Loviselli et al. (11) suggested that instead of inducing autoimmunity, lithium appears to stimulate secretion of immunoglobulins by lymphocytes, triggering a preexisting immune response.

Hypothyroidism and goiter may appear within weeks or years after starting lithium treatment (2,3). The prevalence rates of hypothyroidism range from 3.4% to 52% in various studies (3,4,10,12,13,14,15,16,17,18,19,20,21). The female to male ratio is approximately five to one. The clinical presentation and biochemical changes in these cases are not different from that seen in other causes of hypothyroidism (3). Goiter occurs in 5.6% to 60% of patients treated with lithium (2). This varying prevalence can be explained by differences in iodine content in the geographical settings of the studies and the use of different diagnostic study techniques (22).

Correspondence Address: Özlem Kuman Tunçel, Ege Üniversitesi Tıp Fakültesi, Ruh Sağlığı ve Hastalıkları Anabilim Dalı, İzmir, Türkiye
E-mail: kumanozlem@yahoo.com

Received: 01.07.2015 • **Accepted:** 30.03.2016

©Copyright 2017 by Turkish Association of Neuropsychiatry - Available online at www.noropsikiyatriarsivi.com

Risk factors for developing hypothyroidism during lithium treatment include female gender, raised baseline TSH, family history of thyroid dysfunction in first degree relatives, weight gain, preexisting antibodies, the first two years of treatment (for females only), starting lithium in middle age, iodine-deficient diet, higher lithium levels, rapid cycling, and smoking (2,4,8,17,23,24). Smoking contributes significantly to thyroid size and goiter development (25).

Although the effects of lithium on the thyroid have been known for a long time, data including ultrasonography (USG) assessments are lacking in large-sample studies of lithium-treated patients. In a follow-up study by Lombardi et al. (26) at the end of one year, goiter developed in half of 12 patients who had newly started lithium treatment; the appearance of nodular lesions was detected in two of these patients. In the study by Bocchetta et al. (27) which assessed 67 lithium-treated patients, goiter was detected in 39% of the patients, hypoechogenicity was detected in 54% of the patients, a non-homogeneous pattern was detected in 40% of the patients, and nodules were detected in 28% of the patients. In a study by Loviselli et al. (11) which assessed 23 lithium-treated patients, development of goiter was detected in only 1 of the 15 patients who had normal thyroid USG results before lithium treatment; no significant volumetric changes were observed in patients who had goiter prior to lithium treatment. In their cross-sectional study, Çayköylü et al. (28) detected goiter in 38.1% of 42 patients. In a study by Schiemann and Hengst, significantly higher thyroid volume values were found among lithium-treated patients; however, similar thyroid echogenicities were detected in both groups when 20 patients were compared with 20 controls (29). In a study by Özpoyraz et al. (10) which assessed 49 patients and 46 controls, goiter was identified in 59% of the patients and 15% of the control group; goiter was significantly more prevalent in lithium-treated patients (10). A study by Bauer et al. (30) investigated 96 patients receiving lithium treatment because of bipolar, major depressive, and schizoaffective disorders and 96 controls; the thyroid volumes were found to be significantly greater and the prevalence of goiter was found to be higher in lithium-treated patients. A study by Özsoy et al. (31) assessed 14 lithium-naïve bipolar patients, 13 long-term lithium-treated patients, and 12 healthy controls; the mean thyroid volume in the lithium-naïve bipolar patients was found to be significantly higher than that of the controls, and it was also found that the long-term lithium-treated patients had significantly greater thyroid volumes than the lithium-naïve patients and the controls. Overall, ultrasonographic studies were generally used to detect only goiter; detailed ultrasonographic assessments are inadequate.

The aim of this study was to investigate the detailed thyroid morphologies, hormone levels, and antibodies of lithium-treated patients in comparison with healthy controls. In this study, when comparing lithium-treated bipolar patients with healthy controls, it is assumed that the prevalence of thyroid dysfunction, autoimmunity, goiter, parenchymal abnormality, nodules, ultrasonographically defined thyroid abnormality, and thyroid disorder as well as the mean thyroid volume will be greater in lithium-treated patients.

METHODS

Eighty-four lithium-treated bipolar patients and 65 control subjects who had never been exposed to lithium participated in the study. To be eligible for the study, the subjects were required to be between 18 and 65 years of age and to have no thyroidectomy history. Exclusion criteria were defined as alcohol intake of more than 14 standard drinks for men and more than seven standard drinks for women, substance use or eating disorder comorbidity, clinical thyrotoxicosis, malignancies, and body mass index higher than 30, as these conditions may affect thyroid function tests (32,33,34).

Lithium-treated subjects were recruited from the Affective Disorders Outpatient Unit. All patients had used lithium carbonate for at least three months, were diagnosed with bipolar disorder, and were outpatients. The treatment compliance of the subjects was assured by serum lithium levels within the recommended therapeutic range (at least 0.5 mEq/L) in previous visits. As it is known that valproic acid and carbamazepine treatment can lead to hypothyroidism (35,36), patients using these medications were excluded. Patients who fulfilled the inclusion criteria were invited to participate in the study by telephone. The lithium group consisted of 84 volunteer patients.

The participants in the control group were selected from hospital staff or their relatives; the subjects had never been exposed to lithium in their lives and were not relatives of bipolar patients. The average age was also considered. In addition to the aforementioned exclusion criteria, treatment with psychotropic medication within the last six months was accepted as an exclusion criterion for the control cases. The control group consisted of 26 male and 39 female volunteers.

All participants provided written informed consent. This study was approved by the local ethics committee and the Ethics Committee of Turkish Ministry of Health, and the procedures were in accordance with the Helsinki Declaration of 1975.

The Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version (SCID-I) was used for both patients and the controls. An adaptation and reliability study of SCID-I for Turkish patients has been performed (37). Case report forms providing retrospective data about the subject's psychiatric illnesses, medications used, and smoking status were completed by the investigator. To verify that the information provided about the patient's disease history or use of psychotropic medications was correct, the patient cards were cross-checked.

Venous blood samples were acquired in the morning between 8:00 and 10:00 A.M. to study the subjects' free thyroxine (fT4), TSH, anti-thyroglobuline (anti-Tg), and anti-thyroid peroxidase (anti-TPO) levels. The fT4, TSH, anti-Tg, and anti-TPO levels were measured using a chemiluminescent sequential immunometric assay. The reference value ranges were 0.89-1.76 ng/dL for fT4 and 0.35-5.5 µIU/l for TSH. Normal values were assumed to be <41 for anti-Tg and <36 for anti-TPO.

Thirty control subjects and all lithium-treated patients were referred for ultrasonographic examination. This was performed by two experienced radiologists who were blind to the lithium exposure and blood test results of the participants. During the sonographic examinations, high-resolution color Doppler USG units (Siemens Sonoline Antares and Siemens Acuson Antares scanners; Mountain View, CA, USA) equipped with VFX9-4 and VFX13-5 multiple (1.5-dimensional) linear-array transducers were used. The frequency bandwidths of these transducers ranged 4-9 and 5-13 MHz, respectively. In addition to these high-resolution transducers, the USG scanners were equipped with new-generation spatial compound imaging and tissue harmonic imaging technologies that are known to increase lesion conspicuity. During the studies, the ultrasonographic images were acquired and stored digitally.

The cranio-caudal, transverse, and anterior-posterior dimensions of each lobe were measured; by multiplying these values (cm) with each other and then by 0.52, we obtained the volume (cm³) of each thyroideal lobe. The sum of the volumes of the two lobes provided the volume of the entire thyroid gland. Volumes greater than 17 cm³ for females and 24 cm³ for males were accepted as goiter. In addition to volume, parenchymal

changes, borders, and the presence of nodules were assessed. In cases of apparent nodules, further examination of the largest nodule in terms of size and internal echo structure was performed.

All the hormonal and ultrasonographic results were evaluated by an endocrinologist. According to the aforementioned reference values for fT4, TSH, anti-Tg, and anti-TPO, participants with low fT4 or participants who received thyroid hormone replacement therapy before the study were defined as "hypothyroid;" participants with normal fT4 and high TSH levels were defined as having "subclinical hypothyroidism;" and participants with normal fT4 and low TSH levels were defined as having "subclinical hyperthyroidism." Any abnormality in fT4 and/or TSH levels or use of thyroid medication was defined as "thyroid dysfunction." If one of the thyroid antibodies (anti-Tg, anti-TPO) was positive, this was considered to be a sign of "autoimmunity". The presence of anti-Tg or anti-TPO with a hypoechoic diffuse enlarged gland was considered to indicate Hashimoto's thyroiditis (38). For a given patient, the presence of any thyroid dysfunction, thyroid autoimmunity, or ultrasonographically defined thyroid abnormality was accepted as a "thyroid disorder".

Data analysis were performed by Statistical Package for Social Sciences version 16 Windows (SPSS Inc., Chicago, IL, USA). The results were expressed as mean and standard deviations (SD) in cases of normal distribution and as median and 25 to 75 percentiles if the distribution was skewed. To compare the quantitative data, Student's t test was used for data with normal distribution, and the Mann-Whitney U test was used for data with skewed distribution; to compare qualitative data, the χ^2 test or Fisher's exact test was used. Pearson correlation analysis was used to assess correlations between continuous variables with normal distribution, and Spearman's rank test was used for variables with skewed distribution. The associations of lithium treatment and other clinical variables with the presence of thyroid disease were assessed using multivariate logistic regression analysis. For this analysis, two age groups were formed using receiver operator characteristic (ROC) curve analysis. A p value of <0.05 was considered to indicate statistical significance.

RESULTS

The sample of this study comprised 84 lithium-treated bipolar patients and 65 control subjects. There were 45 (53.6%) females in lithium group and 39 (46.4%) females in the control group. There were no statistically significant differences in gender ($p=0.433$; $\chi^2=0.616$) or age between the groups (Table 1). The clinical variables of the lithium-treated patients are shown in Table 2. Fifty-eight (69%) patients were receiving lithium monotherapy; 3 (3.6%) patients were using lithium and clozapine, 5 (6%) patients were using lithium and lamotrigine, 15 (17.9%) patients were using lithium and quetiapine, and 3 (3.6%) patients were using lithium, quetiapine, and lamotrigine. Details of the treatment durations and doses are given in Table 2.

There was no statistically significant difference between the groups in terms of receiving thyroid replacement therapy or the presence of familial thyroid disease (Table 1).

Thyroid Hormone-Antibody Results

The hormonal analysis data are shown in Table 1. In the lithium group, 14 patients (16.7%) were diagnosed with hypothyroidism, 7 patients (8.3%) were diagnosed with subclinical hypothyroidism, and 1 patient was diagnosed (1.2%) with subclinical hyperthyroidism. In contrast, in the control group, seven cases (10.8%) of hypothyroidism and two cases (3.1%) of subclinical hyperthyroidism were identified. There was no statistically significant difference between the groups in terms of hypothyroidism prevalence ($p=0.305$).

There was no statistically significant difference between the groups in terms of anti-TG positivity; however, anti-TPO positivity was significantly more common in the control group ($p=0.035$) (Table 1).

When we compared the subgroups of lithium-treated patients with thyroid dysfunction with the subgroup without thyroid dysfunction, there were no statistically significant differences in familial thyroid disease, current age, serum lithium level, duration of lithium treatment, age of lithium treatment onset, presence of autoimmunity, or smoking habits. Females were significantly more common in the lithium-treated subgroup with thyroid dysfunction (77.3% vs 45.2%, $p=0.009$). In contrast, no significant difference was found in terms of gender between the subgroups of the control cases with and without thyroid dysfunction.

Ultrasonographic Results

The ultrasonographic results are shown in tables 3 and 4. No correlations were found between thyroid volume and duration of lithium treatment ($\rho=0.194$, $p=0.077$) or serum lithium level ($\rho=0.023$, $p=0.837$). Among the lithium-treated patients with goiter, one (2.5%) patient was hypothyroid, two (5%) patients were subclinical hypothyroid, one (2.5%) patient was subclinical hyperthyroid and 36 (90%) patients were euthyroid. Comparisons of the lithium-treated patients with and without goiter and with and without parenchymal abnormality in terms of several variables are shown in Table 5.

When we compared the subgroups of lithium-treated patients with and without Hashimoto's thyroiditis, no statistically significant differences were found in terms of age, gender, familial thyroid disease, serum lithium level, duration of lithium treatment, age of lithium treatment onset, or smoking habits. Thyroid dysfunction was significantly more frequent in the Hashimoto group (66.7% vs 21.3%, $p=0.009$). Among the Hashimoto group, six patients (66.7%) were hypothyroid, and the remaining three patients (33.3%) were euthyroid.

During ultrasonographic examination of the thyroid, if goiter and/or parenchymal abnormality and/or nodules were defined, this ultrasonographic examination was defined as pathologic USG. Fifty-two (74.3%) patients who underwent ultrasonographic pathology were euthyroid. A comparison of the lithium-treated patients with and without ultrasonographic pathology for several variables is shown in Table 6.

Overview of the Results

A comparison of the lithium-treated patients with and without thyroid disorder is shown in Table 6. Female gender was significantly more prevalent in the lithium-treated patients with thyroid disorder compared to those without ($p=0.026$), while no gender difference was demonstrated in the control group.

The associations of age, gender, smoking, family history of thyroid disease, and lithium treatment with the presence of thyroid disorder were assessed using multivariate logistic regression analysis. First, a cutoff value of the age after which thyroid disorder was more common was calculated using the ROC curve technique. Thus, all the cases in the study series were divided into one of two age groups: the first group consisted of cases that were 39 years old or younger, and the second group consisted of cases older than 39 years. Using backward elimination methodology, lithium treatment ($OR=7.34$, $p<0.001$; 95% CI 3.09-17.41), age group ($OR=2.54$, $p<0.05$; 95% CI 1.10-5.88), and gender ($OR=2.48$, $p<0.05$; 95% CI 1.03-6.00) were demonstrated to have statistically significant associations with the presence of thyroid disorder. Among the entire sample, lithium treatment was found to have the highest association with thyroid disorder.

Table 1. Comparison of lithium-treated patients with control subjects in terms of age and several thyroid variables

	Lithium (N=84)		Control (N=65)		Total (N=149)		Statistics
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	43.1	11.4	39.7	10.4	41.63	11.1	t=1.876 p=0.063
Serum fT4 (ng/dL)	1.16	0.17	1.19	0.20	1.18	0.18	t= -0.958 p=0.340
Serum TSH (μIU/L)	2.8 ^a	2.0 ^a	1.8 ^a	0.9 ^a	2.4 ^a	1.7 ^a	Z=-2.930 p=0.003
	N	%	N	%	N	%	Fisher exact test
Known thyroid disease*	16	19.0	6	9.2	22	14.8	p=0.073 (one sided)
Thyroid medication use*	13	15.5	6	9.2	19	12.8	p=0.189 (one sided)
Familial thyroid disease	29	34.5	18	27.7	47	31.5	p=0.239 (one sided)
Low or high fT4	1	1.2	4	6.2	5	3.4	p=0.114 (one sided)
Low or high serum TSH	12	14.3	2	3.1	14	9.4	p=0.017 (one sided)
Thyroid dysfunction	22	26.2	9	13.8	31	20.8	p=0.049 (one sided)
Anti-Tg +	6	7.1	6	9.2	12	8.1	p=0.432 (one sided)
Anti-TPO +	9	10.7	15	23.1	24	16.1	p=0.035 (one sided)
Autoimmunity	13	15.5	15	23.1	28	18.8	p=0.167 (one sided)
Thyroid disorder	74	88.1	32	49.2	106	71.1	p<0.0001 (one sided)

N: number; SD: standard deviation; fT4: free thyroxine; TSH: thyroid stimulating hormone; Tg: thyroglobulin; TPO: thyroid peroxidase
 *Known thyroid disease or thyroid medication use before the study
^aThe median values and 25 to 75 percentiles of serum TSH level, which had a skewed distribution, were 2.11 μIU/L and 1.38 to 3.83 μIU/L in the lithium group and 1.66 μIU/L and 1.15 to 2.3 μIU/L in the control group, respectively

Table 2. Clinical variables of the lithium-treated patients

Clinical Variable	N	Minimum	Maximum	Mean	SD
Duration of illness (months)	84	10	456	213.2	125.3
Age onset for lithium treatment	84	15	59	30.8	9.9
Duration of lithium treatment (months)	84	7	408	139.4	99.5
Lithium dose (mg/day)	84	450	1800	1088.8	294.6
Serum lithium level (mEq/L)	84	0.5	1.1	0.7	0.1
Duration of lamotrigine treatment (months)	8	5	84	48.8	33.6
Lamotrigine dose (mg/day)	8	125	300	190.6	53.3
Duration of clozapine treatment (months)	3	144	168	156.0	12.0
Clozapine dose (mg/day)	3	100	100	100.0	0.0
Duration of quetiapine treatment (months)	18	4	96	28.6	23.3
Quetiapine dose (mg/day)	18	12.5	300.0	132.6	108.6

N: number; SD: standard deviation

In summary, goiter, parenchymal abnormality, sonographically defined thyroid abnormality, thyroid dysfunction, and thyroid disorder were found to be more prevalent in the lithium group. To prevent bias related to the participants who were known to have thyroid disease prior to the study, the statistical analysis was repeated after exclusion of these cases. In this analysis, goiter (57.4% vs 6.7%, $p<0.0001$), ultrasonographic pathology (83.8% vs 46.7%, $p<0.0001$), and thyroid disorder (86.8% vs 44.1%, $p<0.0001$)

were again found to be more prevalent in the lithium group. After this exclusion, the significance related to parenchymal abnormality and thyroid dysfunction disappeared. When we excluded patients who used psychotropic medications other than lithium (quetiapine, clozapine, or lamotrigine), goiter (63.8% vs 6.7%, $p<0.0001$), ultrasonographic pathology (89.4% vs 46.7%, $p<0.0001$), and thyroid disorder (89.4% vs 44.1%, $p<0.0001$) were again more prevalent in the lithium group.

All participants with thyroid pathologies are currently being followed up in the Endocrinology Department.

DISCUSSION

The reported prevalence of lithium-associated hypothyroidism varies widely in the literature, from 3.4% to 52% (3,4,10,12,13,14,15,16,17,18,19,20,21). Johnston and Eagles reported that when lithium-associated hypothyroidism occurs, it is usually subclinical; however, in the present study, 14 (16.7%) cases of hypothyroidism and 7 (8.3%) cases of subclinical hypothyroidism were diagnosed in the lithium group (15). This low rate of subclinical hypothyroidism may be due to the routine evaluation of thyroid function performed every three to six months in our specialized outpatient unit. Thus, the subclinical cases were identified during follow-up prior to the study. Hyperthyroidism is rare in lithium-treated patients. In most cases, it occurs after many years of treatment (2,3,39). Consistent with the literature, among 84 patients, only 1 (1.2%) case of subclinical hyperthyroidism was found. This patient had used lithium for 21 years.

Some studies have found higher levels of thyroid antibodies in lithium-treated patients; however, other studies have found a similar prevalence of thyroid antibodies in lithium-treated patients compared to a control group (7,8,9,10). Additionally, Kupka et al. (40) found that thyroid peroxidase antibodies (anti-TPO) are more prevalent in bipolar patients, independent of lithium exposure (40). Unexpectedly, antibody positivity

Table 3. Ultrasonographic results

	Lithium (N=84)			Control (N=30)			Total (N=114)			
	25.p	M	75.p	25.p	M	75.p	25.p	M	75.p	Statistics
Thyroid volume (cm³)	13.3	20.0	28.8	7.9	11.8	15.3	11.7	17.5	25.0	Z=-4.573 p<0.0001
	N		%	N		%	N		%	Fisher exact test
Goiter	40		47.6	2		6.7	42		36.8	p<0.0001 (one sided)
Parenchymal abnormality	19		22.6	2		6.7	21		18.4	p=0.042 (one sided)
Thyroid nodule	44		52.4	13		43.3	57		50	p=0.262 (one sided)
Thyroid pathology in ultrasonography	70		83.3	14		46.7	84		73.7	p<0.0001 (one sided)
Hashimoto's thyroiditis	9		10.7	2		6.7	11		9.6	p=0.406 (one sided)
N: number; p: percentile; M: median										

N: number; p: percentile; M: median

Table 4. Ultrasonographic results

		Lithium (N=84)		Control (N=30)	
		N	%	N	%
Heterogeneous parenchymal appearance	a) Without nodules	12	10.2	2	6.6
	b) With nodules	7	8.3	0	0
Number of nodules	a) Solitary	15	17.9	6	20.0
	b) Multiple	29	34.5	7	23.3
Nodule type	a) Cystic	4	4.8	1	3.3
	b) Solid isoechoic	12	14.3	5	16.7
	c) Solid hypoechoic	15	17.9	3	10.0
	d) Solid hyperechoic	3	3.6	0	0
	e) Mixed	10	11.9	4	13.3

N: number

Table 5. Characteristics of the subgroup of lithium-treated patients with goiter and parenchymal abnormalities and comparison with the remaining lithium-treated patients

	Goiter					Parenchymal Structure				
	+		-		Statistics	Abnormal		Normal		Statistics
	(N=40)		(N=44)			(N=19)		(N=65)		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age (years)	42.0	11.7	44.1	11.2	t=0.854 p=0.396	44.2	13.2	42.8	11.0	t=-0.448 p=0.655
Age of onset of lithium treatment (years)	28.7	9.6	32.8	9.8	t=1.900 p=0.061	31.6	10.6	30.6	9.7	t=-0.373 p=0.710
Duration of lithium treatment (months)	146.1	97.8	133.4	101.8	t=-0.579 p=0.564	144.0	107.5	138.1	97.9	t=-0.226 p=0.821
Serum lithium level (mEq/L)	0.69	0.12	0.70	0.14	t=0.430 p=0.669	0.72	0.14	0.69	0.13	t=-0.602 p=0.532
	N	%	N	%	Fisher exact test (one sided)	N	%	N	%	Fisher exact test (one sided)
Female gender	19	47.5	26	59.1	p=0.199	12	63.2	33	50.8	p=0.246
Familial thyroid disease	14	35.0	15	34.1	p=0.556	9	47.4	20	41.5	p=0.144
Smoking	16	40.0	19	43.2	p=0.471	8	22.9	27	41.5	p=0.584
Autoimmunity	6	15.0	7	15.9	p=0.575	7	36.8	6	9.2	p=0.008
Thyroid dysfunction	4	10.0	18	40.9	p=0.001	12	63.2	10	15.4	p<0.0001

N: number; SD: standard deviation

Table 6. Characteristics of the subgroup of lithium-treated patients with ultrasonographic pathologies and thyroid disorder and comparison with the remaining lithium-treated patients

	Ultrasonographic pathology					Thyroid disorder				
	+		-		Statistics	+		-		Statistics
	(N=70)		(N=14)			(N=74)		(N=10)		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age (years)	42.8	11.7	44.6	10.4	t=0.518 p=0.606	43.0	11.8	44.3	9.0	t=0.346 p=0.730
Age of onset of lithium treatment (years)	30.3	9.7	33.7	10.4	t=0.729 p=0.233	30.7	10.0	31.8	9.2	t=0.329 p=0.743
Duration of lithium treatment (months)	141.6	101.1	128.6	94.0	t=-0.445 p=0.657	138.4	101.6	147.2	86.6	t=0.262 p=0.794
Serum lithium level (mEq/L)	0.70	0.14	0.68	0.12	t=0.797 p=0.561	0.70	0.13	0.67	0.13	t=-0.714 p=0.477
	N	%	N	%	Fisher exact test (one sided)	N	%	N	%	Fisher exact test (one sided)
Female gender	39	55.7	6	42.9	p=0.278	43	58.1	2	20.0	p=0.026
Familial thyroid disease	25	35.7	4	28.6	p=0.427	25	33.8	4	40.0	p=0.475
Smoking	30	42.9	5	35.7	p=0.426	31	41.9	4	40.0	p=0.595
Autoimmunity	13	18.6	0	0	p=0.076	13	17.6	0	0	p=0.167
Thyroid dysfunction	18	25.7	4	28.6	p=0.529	22	29.7	0	0	p=0.039

N: number; SD: standard deviation

(significant for anti-TPO) was more prevalent in the control group in our study. In another study that was also conducted in our city with healthy volunteers, the prevalence of anti-Tg positivity was 5.8%, that of anti-TPO positivity was 6.9%, and that of autoimmunity was 17.8% (41). The prevalence rates in our healthy control group were much higher than in this study. Incidentally, the prevalence of autoimmunity in the control group was found to be high. Thus, we cannot make a proper comment on these autoimmunity results. There was no statistically significant difference for Hashimoto's thyroiditis, which is considered to be the most common autoimmune disease, between the lithium group and the control group (42). We could not find any study in the literature that investigated the relationship between Hashimoto's thyroiditis and lithium use.

In our study, no statistically significant difference in fT4 level was found between the groups; in contrast, the median value for TSH was found to be significantly higher in the lithium group. This finding supports the inhibitory effect of lithium on thyroid function. Also in accordance with the literature, in which enlargement of thyroid gland due to TSH increase has been reported, significantly greater thyroid volumes were found in the lithium group in our study (3). Goiter was much more prevalent in the lithium group. Livingstone and Rampes (2) defined the prevalence of lithium-associated goiter as 5.6% to 60.0% in their review. Our prevalence (47.6%) is near the upper limit of this range. The experience of the radiologists and the use of more sensitive, newly updated high resolution technology may be the cause of the higher prevalence of goiter. Unlike other imaging techniques, USG does not involve radiation exposure. Also, it is fast, relatively inexpensive, and sensitive for screening goiter and other thyroid abnormalities (30,43). In the literature, studies involving detailed thyroid USG investigations of lithium-treated patients are limited. Parenchymal abnormality was significantly more prevalent in lithium-treated patients. These findings necessitate further investigation. Overall, ultrasonographic pathology was much more prevalent in lithium-treated patients (83.3%). Although not all the defined pathologies were clinically important, it is noteworthy that 90% of the patients with goiter were euthyroid. This indicates that follow-up with blood tests is insufficient. However, recommendation of USG during lithium treatment is limited in the treatment

guidelines. Bochetta and Loviselli recommend a USG scan before lithium treatment, after the first year and repeated scans at two to three-year intervals (1).

When logistic regression analysis was used to assess the association of several variables with the presence of thyroid disorder, lithium treatment had the highest association. In our study, for thyroid disorder, age greater than 39 years and female gender had lower OR than lithium treatment.

In our study, we found that lithium-treated females had higher prevalences of thyroid dysfunction and thyroid disorder than males. The prevalence of thyroid dysfunction has also been found to be higher in females than males in the general population (44). Özerdem et al. (45) showed a higher rate of TSH abnormality in female patients with bipolar disorder who were taking lithium (45). Similar to our results, other studies have shown a greater susceptibility to thyroid dysfunction and thyroid disorder among female subjects (18,21,44). One study reported that the duration of lithium treatment was related with the development of goiter; however, we did not find such an association in our study (3). Similar to our results, Kraszewska et al. (44) did not show an association between the duration of lithium treatment and thyroid dysfunction.

Thyroid disorder was more prevalent in the lithium group. The high prevalence of 83.9% is important for understanding the general effects of lithium on thyroid gland.

Both the lithium and control groups contained participants with previously diagnosed thyroid disorders. To prevent bias related to these participants, we repeated the analysis after excluding this group. In this analysis, goiter, ultrasonographic pathology, and thyroid disorder remained more prevalent in the lithium group.

Our study has some limitations. First, we could not eliminate the possibility that patients had undiagnosed thyroid disorders before lithium treatment onset because their pre-lithium baseline values were absent. Also, because the study was cross-sectional, it was not possible to detect causal

relationships; prospective studies are required. As Affective Disorders Outpatient is a tertiary care center, most of the patients were treatment resistant. Thus, the study sample did not include only patients on lithium monotherapy. Among the drugs used by the lithium group, quetiapine has been suggested to induce hypothyroidism (46,47). To minimize the impact of this limitation, we excluded the patients who were not receiving lithium monotherapy; goiter, ultrasonographic pathology, and thyroid disorder remained more prevalent in the lithium group. Some references recommend lowering the upper limit of the normal reference range for TSH to 2.5 µU/L or 4.5 µU/L (48,49). In our study, because the upper limit was defined as the laboratory reference value (5.5 µU/L), the probability of patients with TSH values between 2.5 and 5.5 being hypothyroid is a limitation. Another limitation is the number of control subjects who underwent ultrasonographic examination. In addition to this group, another control group containing lithium-naïve bipolar patients may be helpful to reveal disease traits.

In conclusion, although it is well known that lithium has adverse effects on thyroid gland, studies involving detailed thyroid USG are limited. Thus, our results represent a contribution to the literature. The prevalence rates of 47.6% for goiter and 83.3% for ultrasonographic pathology emphasize the need for ultrasonographic examination in lithium-treated patients. Considering the limitations of this study, to assess the necessity of routine follow-up with USG, prospective large-sample studies that involve baseline sonographic examination before lithium treatment onset and in which the possible effects of other drugs are evaluated are necessary.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University Clinical Research Ethics Committee and from the Ethics Committee of the Turkish Health Ministry.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.K.T., F.A., S.S.Ö., G.K., G.Ü.K.; Design - Ö.K.T., F.A., S.S.Ö., G.K., G.Ü.K.; Supervision - Ö.K.T., F.A.; Resource - Ö.K.T., F.A.; Materials - Ö.K.T., F.A.; Data Collection and/or Processing - Ö.K.T., F.A., S.S.Ö., G.K.; Analysis and/or Interpretation - Ö.K.T., F.A., S.S.Ö., G.K., G.Ü.K.; Literature Search - Ö.K.T., F.A., S.S.Ö., G.K., G.Ü.K.; Writing - Ö.K.T.; Critical Reviews - F.A., S.S.Ö., G.K., G.Ü.K.

Acknowledgements: The authors thank to Prof Mehmet N Orman from Department of Biostatistics and Medical Informatics, Ege University School of Medicine for his statistical advice and help.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by Ege University Scientific Research Project Grant and Psychiatric Association of Turkey.

REFERENCES

- Bocchetta A, Loviselli A. Lithium treatment and thyroid abnormalities. *Clin Pract Epidemiol Ment Health* 2006; 2:23. [CrossRef]
- Livingstone C, Rampes H. Lithium: a review of its metabolic adverse effects. *J Psychopharmacol* 2006; 20:347-355. [CrossRef]
- Lazarus JH. Lithium and thyroid. *Best Pract Res Clin Endocrinol Metab* 2009; 23:723-733. [CrossRef]
- Kusalic M, Engelsmann F. Effect of lithium maintenance therapy on thyroid and parathyroid function. *J Psychiatry Neurosci* 1999; 24:227-233.
- Rao AS, Kremenevskaja N, Resch J, Brabant G. Lithium stimulates proliferation in cultured thyrocytes by activating Wnt/beta-catenin signalling. *Eur J Endocrinol* 2005; 153:929-938. [CrossRef]
- Gilbert-Sirieix M, Makoukji J, Kimura S, Talbot M, Caillou B, Massaad C, Massaad-Massade L. Wnt/beta-catenin signaling pathway is a direct enhancer of thyroid transcription factor-1 in human papillary thyroid carcinoma cells. *PLoS One* 2011; 6:e22280. [CrossRef]
- Deniker P, Eyquem A, Bernheim R, Loo H, Delarue P. Thyroid autoantibody levels during lithium therapy. *Neuropsychobiology* 1978; 4:270-275. [CrossRef]
- Bocchetta A, Mossa P, Velluzzi F, Mariotti S, Zompo MD, Loviselli A. Ten-year follow-up of thyroid function in lithium patients. *J Clin Psychopharmacol* 2001; 21:594-598. [CrossRef]
- Baethge C, Blumentritt H, Berghofer A, Bschor T, Glenn T, Adli M, Schlattmann P, Bauer M, Finke R. Long-term lithium treatment and thyroid antibodies: a controlled study. *J Psychiatry Neurosci* 2005; 30:423-427.
- Ozpoyraz N, Tamam L, Kulan E. Thyroid abnormalities in lithium-treated patients. *Adv Ther* 2002; 19:176-184. [CrossRef]
- Loviselli A, Bocchetta A, Mossa P, Velluzzi F, Bernardi F, del Zompo M, Mariotti S. Value of thyroid echography in the long-term follow-up of lithium-treated patients. *Neuropsychobiology* 1997; 36:37-41. [CrossRef]
- Deodhar SD, Singh B, Pathak CM, Sharan P, Kulhara P. Thyroid functions in lithium-treated psychiatric patients: a cross-sectional study. *Biol Trace Elem Res* 1999; 67:151-163. [CrossRef]
- Kallner G, Petterson U. Renal, thyroid and parathyroid function during lithium treatment: laboratory tests in 207 people treated for 1-30 years. *Acta Psychiatr Scand* 1995; 91:48-51. [CrossRef]
- Kirov G. Thyroid disorders in lithium-treated patients. *J Affect Disord* 1998; 50:33-40. [CrossRef]
- Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism. Prevalence and risk factors. *Br J Psychiatry* 1999; 175:336-339. [CrossRef]
- Frye MA, Denicoff KD, Bryan AL, Smith-Jackson EE, Ali SO, Luckenbaugh D, Leverich GS, Post RM. Association between lower serum free T4 and greater mood instability and depression in lithium-maintained bipolar patients. *Am J Psychiatry* 1999; 156:1909-1914.
- Gracious BL, Findling RL, Seman C, Youngstrom EA, Demeter CA, Calabrese JR. Elevated thyrotropin in bipolar youths prescribed both lithium and divalproex sodium. *J Am Acad Child Adolesc Psychiatry* 2004; 43:215-220. [CrossRef]
- Kirov G, Tredget J, John R, Owen MJ, Lazarus JH. A cross-sectional and a prospective study of thyroid disorders in lithium-treated patients. *J Affect Disord* 2005; 87:313-317. [CrossRef]
- Aliasgharpour M, Abbassi M, Shafaroodi H, Razi F. Subclinical hypothyroidism in lithium-treated psychiatric patients in Tehran, Islamic Republic of Iran. *East Mediterr Health J* 2005; 11:329-333.
- Fagioli A, Kupfer DJ, Scott J, Swartz HA, Cook D, Novick DM, Frank E. Hypothyroidism in patients with bipolar I disorder treated primarily with lithium. *Epidemiol Psychiatr Soc* 2006; 15:123-127.
- Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet* 2015; 386:461-468. [CrossRef]
- Kibirige D, Luzinda K, Ssekitooleko R. Spectrum of lithium induced thyroid abnormalities: a current perspective. *Thyroid Res* 2013; 6:3. [CrossRef]
- Henry C. Lithium side-effects and predictors of hypothyroidism in patients with bipolar disorder: sex differences. *J Psychiatry Neurosci* 2002; 27:104-107.
- Gyulai L, Bauer M, Bauer MS, Garcia-Espana F, Cnaan A, Whybrow PC. Thyroid hypofunction in patients with rapid-cycling bipolar disorder after lithium challenge. *Biol Psychiatry* 2003; 53:899-905. [CrossRef]
- Perrild H, Hegedus L, Baastrup PC, Kayser L, Kastberg S. Thyroid function and ultrasonically determined thyroid size in patients receiving long-term lithium treatment. *Am J Psychiatry* 1990; 147:1518-1521. [CrossRef]
- Lombardi G, Panza N, Biondi B, Di Lorenzo L, Lupoli G, Muscettola G, Carella C, Bellastella A. Effects of lithium treatment on hypothalamic-pituitary-thyroid axis: a longitudinal study. *J Endocrinol Invest* 1993; 16:259-263. [CrossRef]
- Bocchetta A, Cherchi A, Loviselli A, Mossa P, Velluzzi F, Derai R, Del Zompo M. Six-year follow-up of thyroid function during lithium treatment. *Acta Psychiatr Scand* 1996; 94:45-48. [CrossRef]
- Cayköylü A, Capoğlu I, Ünüvar N, Erdem F, Cetinkaya R. Thyroid abnormalities in lithium-treated patients with bipolar affective disorder. *J Int Med Res* 2002; 30:80-84. [CrossRef]
- Schiemann U, Hengst K. Thyroid echogenicity in manic-depressive patients receiving lithium therapy. *J Affect Disord* 2002; 70:85-90. [CrossRef]

30. Bauer M, Blumentritt H, Finke R, Schlattmann P, Adli M, Baethge C, Bschor T, Muller-Oerlinghausen B, Berghofer A. Using ultrasonography to determine thyroid size and prevalence of goiter in lithium-treated patients with affective disorders. *J Affect Disord* 2007; 104:45-51. [\[CrossRef\]](#)
31. Özsoy S, Mavili E, Aydın M, Turan T, Eşel E. Ultrasonically determined thyroid volume and thyroid functions in lithium-naïve and lithium-treated patients with bipolar disorder: a cross-sectional and longitudinal study. *Hum Psychopharmacol* 2010; 25:174-178. [\[CrossRef\]](#)
32. Brick J. Standardization of alcohol calculations in research. *Alcohol Clin Exp Res* 2006; 30:1276-1287. [\[CrossRef\]](#)
33. Rachdaoui N, Sarkar DK. Effects of alcohol on the endocrine system. *Endocrinol Metab Clin North Am* 2013; 42:593-615. [\[CrossRef\]](#)
34. Santini F, Marzullo P, Rotondi M, Ceccarini G, Pagano L, Ippolito S, Chiovato L, Biondi B. Mechanisms in endocrinology: the crosstalk between thyroid gland and adipose tissue: signal integration in health and disease. *Eur J Endocrinol* 2014; 171:R137-152. [\[CrossRef\]](#)
35. Surks MI, Sievert R. Drugs and thyroid function. *N Engl J Med* 1995; 333:1688-1694. [\[CrossRef\]](#)
36. Gau CS, Chang CJ, Tsai FJ, Chao PF, Gau SS. Association between mood stabilizers and hypothyroidism in patients with bipolar disorders: a nested, matched case-control study. *Bipolar Disord* 2010; 12:253-263. [\[CrossRef\]](#)
37. Çorapçıoğlu A, Aydemir Ö, Yıldız M, Esen A, Köroğlu E. DSM-IV Eksen I Bozuklukları İçin Yapılandırılmış Klinik Görüşme. Ankara: Hekimler Yayın Birliği; 1999.
38. Li Y, Nishihara E, Kakudo K. Hashimoto's thyroiditis: old concepts and new insights. *Curr Opin Rheumatol* 2011; 23:102-107. [\[CrossRef\]](#)
39. Mizukami Y, Michigishi T, Nonomura A, Nakamura S, Noguchi M, Takazakura E. Histological features of the thyroid gland in a patient with lithium induced thyrotoxicosis. *J Clin Pathol* 1995; 48:582-584. [\[CrossRef\]](#)
40. Kupka RW, Nolen WA, Post RM, McElroy SL, Altshuler LL, Denicoff KD, Frye MA, Keck PE, Jr., Leverich GS, Rush AJ, Suppes T, Pollio C, Drexhage HA. High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. *Biol Psychiatry* 2002; 51:305-311. [\[CrossRef\]](#)
41. Çelebiler-Çavuşoğlu A, Bilgili S, Erkızan Ö, Arıcan H, Karaca B. Thyroid hormone reference intervals and the prevalence of thyroid antibodies. *Turkish Journal of Medical Science* 2010; 40:665-672.
42. McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity. *Endocrine* 2012; 42:252-265. [\[CrossRef\]](#)
43. Knudsen N, Bols B, Bulow I, Jorgensen T, Perrild H, Ovesen L, Laurberg P. Validation of ultrasonography of the thyroid gland for epidemiological purposes. *Thyroid* 1999; 9:1069-1074. [\[CrossRef\]](#)
44. Kraszewska A, Chlopocka-Wozniak M, Abramowicz M, Sowinski J, Rybakowski JK. A cross-sectional study of thyroid function in 66 patients with bipolar disorder receiving lithium for 10-44 years. *Bipolar Disord* 2015; 17:375-380. [\[CrossRef\]](#)
45. Ozerdem A, Tunca Z, Cimrin D, Hidiröglu C, Ergor G. Female vulnerability for thyroid function abnormality in bipolar disorder: role of lithium treatment. *Bipolar Disord* 2013; 16:72-82. [\[CrossRef\]](#)
46. Kontaxakis VP, Karaikos D, Havaki-Kontaxaki BJ, Ferentinos P, Papadimitriou GN. Can quetiapine-induced hypothyroidism be reversible without quetiapine discontinuation? *Clin Neuropharmacol* 2009; 32:295-296. [\[CrossRef\]](#)
47. Feret BM, Caley CF. Possible hypothyroidism associated with quetiapine. *Ann Pharmacother* 2000; 34:483-486. [\[CrossRef\]](#)
48. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab* 2005; 90:5483-5488. [\[CrossRef\]](#)
49. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JL, Pessah-Pollack R, Singer PA, Woeber KA; American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: co-sponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract* 2012; 18:988-1028. [\[CrossRef\]](#)