The Effects of Lithium on Calcium and Parathormone Levels: A Cross-sectional Study with Healthy Controls

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SUMMARY

Objective: Despite lithium associated hyperparathyroidism (LAH) can lead to many complications, little notice has been paid to this side-effect. The aim of this study was to investigate the effects of lithium on calcium and parathyroid hormone levels and the relation between lithium use and thyroid diseases.

Method: This cross-sectional study was carried out with 87 lithium-treated patients and 65 volunteers who had a similar age and gender distribution with the lithium group. Serum levels of corrected calcium, intact parathormone, phosphorus, magnesium, alkaline phosphatase, free thyroxine, thyroid stimulating hormone, thyroid autoantibodies and creatinine were assessed, and also, thyroid and parathyroid ultrasonography was conducted. Further detailed investigations were made depending on the elevation of the initially measured calcium and/or parathormone levels.

Results: Median values of serum levels of the corrected calcium and the intact parathormone were significantly higher in the lithium group. Calcium levels had a mild correlation with the duration of lithium treatment. In the first assessment, while all control individuals had values within the normal reference range, 11 lithium-treated patients had corrected calcium and/or intact parathormone levels above the normal reference levels. All of the five patients, who were diagnosed with LAH after further investigation, were also diagnosed with a thyroid disorder.

Conclusion: These results demonstrate that lithium treatment has a relationship with calcium and parathormone levels. The 5.7% prevalence of LAH and potential life-threatening conditions associated with LAH necessitates the use of available low-cost methods to monitor blood calcium levels of lithium-treated patients for early diagnosis.

Keywords: Calcium, hyperparathyroidism, lithium, parathormone, parathyroid glands

INTRODUCTION

Lithium is widely used in the management of bipolar disorder, major depressive disorder, schizoaffective disorder and other psychiatric disorders. Its use has been associated with gastrointestinal, neurological, cardiovascular, dermatological, renal and endocrine side effects (Bowden 2017).

Hyperparathyroidism associated with lithium therapy was first reported in 1973 (Garfinkel et al. 1973). In the recent years, reported prevalence of hypercalcemia in LAH has varied in the 3.6%-62% range (Albert et al. 2013, Albert et al. 2015, Awad et al. 2003, Bendz et al. 1996, de Oliveira et al. 2014, El Khoury et al. 2002, Kallner and Petterson 1995, Meehan et al. 2015, Meehan et al. 2018, Stancer and Forbath 1989, Twigt et al. 2013). Surgically proven prevalence for hyperparathyroidism was 4.3% in the study of Awad et al. (2003). Differences in the patient population being studied and different sensitivities of the parathormone (PTH) assays used may lead to the variance in the reported prevalence of lithium associated hyperparathyroidism (LAH). Although the true prevalence of hypercalcemia in the presence of hypoalbuminemia might have been underestimated, in some studies, total serum calcium (Ca) levels were measured without measuring ionized calcium Ca levels (Bendz et al.

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1996, Meehan et al. 2018). Furthermore, in most of the studies on LAH, differential diagnosis of the observed hypercalcemia has not been made. Liver failure, chronic kidney disease and vitamin D deficiency can cause secondary hyperparathyroidism which, if prolonged, may lead to tertiary hyperparathyroidism. Although the most common causes of tertiary hyperparathyroidism are chronic kidney disease, hyperphosphatemia or low 1,25-dihydroxyvitamin D levels (Fraser 2009), vitamin D was evaluated only in three studies (Albert et al. 2015, Meehan et al. 2015, van Melick et al. 2014). Another source of discrepancy in the results is the lack of a clear definition of the LAH studied. Mostly, any single high Ca or PTH measurement was assumed to be LAH as reflected in two recently published studies reporting prevalences of 12.9% and 22.8% for hyperparathyroidism. Since the calcium levels of cases evaluated as hyperparathyroidism were within normal limits in these studies, it is suspicious with respect to LAH diagnosis (Albert et al. 2015, de Oliveira et al. 2014).

The biochemical changes occurring in primary hyperparathyroidism, are similar to but not identical with those occurring in LAH, with estimations of parathyroid hormone levels inappropriately high for mildly elevated serum Ca levels. PTH level remaining within the normal range with elevated serum Ca is indicative of hyperparathyroidism since physiologically PTH should have fallen below the normal lower limit. Also, whereas urinary Ca excretion is reduced in LAH, primary hyperparathyroidism is usually associated with hypercalciuria. Serum phosphate levels tend to be normal rather than low and serum magnesium (Mg) levels may be elevated or within the normal range (Livingstone and Rampes 2006).

LAH can lead to the development of renal stones, nephrocalcinosis, renal impairment, osteoporosis, osteopenia, and worsening of the psychiatric condition (Livingstone and Rampes 2006). Although LAH may cause complications such as life-threatening arrhythmias, hypercalcemia leading to coma or delirium; there is no consensus for periodic monitoring of serum Ca in the guidelines (Duggal and Singh 2008, Lin and Mao 2010, NICE 2006, Rifai et al. 2001, Rizwan and Perrier 2009). The inadequacy of high-level evidence for LAH makes it challenging to recommend periodic monitoring in the treatment guidelines.

Definitive results have not been reached on the relationship between the duration of lithium use or the serum lithium levels and development of LAH. Hypercalcemia after only one-day lithium treatment (Rothman 1982) and acute intact PTH elevation after a single oral dose of lithium have been reported (Seely et al. 1989). Also, an association of LAH with thyroid carcinoma or familial thyroid illness has been reported (Abdullah et al. 1999, Carchman et al. 2008, Kusalic and Engelsmann 1999, Szalat et al. 2009).

Given the limitations of the earlier studies lacking necessary measures such as detailed differential diagnosis of LAH, evaluation of the factors affecting serum Ca levels and diagnosing any high Ca or PTH level as LAH, we have planned our study. The primary aim of this study was to investigate parathyroid and Ca metabolism abnormalities of lithium-treated bipolar patients in comparison with healthy individuals on the hypothesis that the prevalence of hyperparathyroidism will be higher in lithium-treated patients. The secondary aim was to examine the association between parathyroid and/or Ca metabolism abnormalities with lithium exposure parameters such as age, duration, daily lithium dose. The third aim was to explore the relationship between LAH and thyroid disorders.

METHOD

Participants

This cross-sectional study consisted of 87 lithium-treated patients and 65 volunteers who had a similar age and gender distribution with the lithium group and who had never used lithium. Participants are required to be in the age range of 18-65 years. Exclusion criteria comprised having any disease associated with Ca metabolism such as osteoporosis, familial hypercalciuric hypocalcemia, hyper/hypoparathyroidism, osteomalacia, acromegaly, and immobilization, or being on medication interfering with Ca metabolism such as thiazide diuretics, steroids or antiosteoporotic drugs; alcohol intake of more than 14 standard drink for men, more than seven standard drink for women (Brick 2006); substance use or eating disorder comorbidity; thyroidectomy history; thyrotoxicosis; malignancies; body mass index higher than 30; and not volunteering to participate.

Lithium Group

If LAH prevalence was accepted to be 4.3% as determined by surgical evidence in the series of Awad et al. (2003), the sample size calculated by power analysis, within a confidence interval of 95%, was a minimum of 85 patients. Patients to be included in the study were selected from the patients being followed up with bipolar disorder diagnosis put on lithium treatment for a minimum of three months at the Affective Disorders Unit of Ege University Mental Health and Diseases Department. Patient compliance with lithium treatment was assured by the requirement of a serum lithium level to be in the recommended therapeutic range of at least 0.5 mEq/L in the preceding visit. Patients using psychotropic agents with effects on Ca metabolism were excluded. On account of the reports on valproate and carbamazepine relationship with hypocalcemia, especially in children and patients with vitamin D deficiency, patients treated with these mood stabilizers were also excluded (Bhuvaneswar et al. 2009, Nicolaidou

et al. 2006). Among the antiepileptics, only lamotrigine, shown not to have a significant effect on Ca metabolism was allowed (Pack et al. 2005). Increased osteoclastic activity and reduced bone mineral density have been shown after long term use of selective serotonin reuptake inhibitors (Haney et al. 2007), while tricyclic antidepressants are considered to have less effect in this respect (Bhuvaneswar et al. 2009). Given these data on interaction of antidepressants with bone Ca metabolism, patients using antidepressants were excluded from the study. Another potential cause of decreased bone density is hyperprolactinemia. There is no evidence showing that antipsychotics causing hyperprolactinemia also affect Ca or PTH levels. However, as they are associated with osteoporosis, patients using these antipsychotics were also excluded. Patients using prolactin-sparing antipsychotics such as clozapine and quetiapine were not excluded (Bhuvaneswar et al. 2009, O'Keane 2008). Disease episodes of the patients at the stage of selection for the study were not taken into consideration. To summarize, lithium-treated patients using lamotrigine and/or clozapine and quetiapine were included in the study. All the patients who fulfilled these criteria were contacted by telephone and invited to participate in the study, and 87 patients who were willing to participate were included in the study.

Control Group

In addition to the exclusion criteria cited above, it was stipulated that participants of the control group should not have used lithium lifelong and should not have been on any psychotropic agent within the previous six months. The control group consisted of 26 male and 39 female volunteers.

Study Design and Data Collection

This study was approved by the Ethical Committee of Ege University, and all participants gave written informed consent.

Structured Clinical Interview for DSM-IV Axis I Disorders-Clinical Version (SCID-I-CV) was conducted with all participants. Adaptation of SCID-I-CV to the Turkish language and its reliability was reported by Özkürkçügil et al. (1999). By using a semistructured interview, information on the history of the illness, data on the drugs used and the daily consumption of milk and milk products were evaluated. The reason for evaluating milk and milk products is that they are the richest source of dietary source of Ca which has a minor effect on blood Ca level. For assessing Ca content of foods, the Turkish diet chart was used (one glass of milk or yogurt: 288 mg; one slice of white cheese: 26 mg; 2/3 slices of kashar cheese: 140 mg; one egg: 27 mg) (Baysal et al. 2002).

Venous blood samples were taken in the morning between 08.00-10.00 A.M.; after an overnight fast for the measurement of Ca, albumin (Alb), intact PTH, phosphorus (P), Mg, alkaline phosphatase (ALP), free thyroxine (fT4), thyroid stimulating hormone (TSH), thyroglobulin antibody (anti-TG), thyroid peroxidase antibody (anti-TPO) and creatinine. To exclude thyrotoxicosis and renal failure, and to investigate the relationship between LAH and thyroid diseases, thyroid and renal function tests were performed. The Cockroft-Gault Formula was used for creatinine clearance calculation: Creatinine clearance = [(140-Age) x Body Weight (kg)] / [Serum Creatinine (mg/dl) x 72] [x 0.85 For Females] (Barri and Shah 2000). Total Ca was corrected for variance in serum Alb by the formula: Corrected Total Ca (cCa) (mg/dl) = measured Ca + 0.8 x [4-Alb (g/dl)] (Khosla 2015). Free T4 (fT4), TSH, anti-Tg, anti-TPO and PTH were measured by the chemiluminescent sequential immunometric assay. Ca, P, Mg, Alb, ALP, urea and creatinine were determined with standard automated methods. The reference ranges were 8.6-10.2 mg/dl for Ca; 3.5-5.2 g/dl for Alb; 2.3-4.5 mg/dl for P; 1.5-2.6 mg/dl for Mg; 40-129 U/l for ALP; 0.89-1.76 ng/dl for fT4; 0.35-5.5 μIU/l for TSH and 12-88 pg/ml for intact PTH.

Thyroid and parathyroid ultrasonography was performed on the first recruited 30 control participants and all lithium-treated patients by two experienced radiologists who were blind to lithium exposure and the blood test results of the participants. During the sonographic examinations, high-resolution color Doppler ultrasonography (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 between 4-9 and 5-13 Megahertz (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 for increasing lesion conspicuity. During the study, ultrasonographic images were acquired and stored digitally. Three patients did not wait for the ultrasonographic examination; therefore, the data were derived from 84 patients and 30 controls. Thyroid volume, nodule presence and parenchymal changes were assessed in the ultrasonographic examination of the thyroid glands. Detailed thyroid ultrasonographic results of the study sample have been published elsewhere (Kuman Tunçel et al. 2017).

When the corrected Ca (cCa) and/or PTH levels were high in the first assessment, Ca measurement was repeated, and further investigations were made. If PTH level was high, PTH measurement was repeated and in order to exclude vitamin D deficiency, the 25-hydroxy vitamin D (25-OH-D) level was also measured. Urinary Ca and P levels were measured in the collected 24-hour urine specimens for the differential diagnosis of primary hyperparathyroidism and LAH. If the second cCa measurement was in the normal

range, Ca measurement was repeated for the third time. With further examination, two cCa results found to exceed the normal upper limit was interpreted as "hypercalcemia". Unsuppressed PTH level in a hypercalcemic participant was defined as "hyperparathyroidism".

The differential diagnosis for hypercalcemia was made by assessing both the ultrasonographic and the hormonal results in collaboration with an endocrinologist. For a given patient, the presence of any thyroid dysfunction, thyroid autoimmunity, or ultrasonographically detected thyroid abnormality was accepted as a "thyroid disorder".

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Statistical Analysis

IBM SPSS Statistics 21 program was used for statistical analysis. Kolmogorov Smirnov test was used to test normality. Normally distributed quantitative data were presented by the mean and the standard deviation (SD), and the data not normally distributed were expressed by the median and interquartile range. Student t test was used for comparisons of the quantitative data with normal distribution and Mann-Whitney U test was used for comparing the data not distributed normally. For comparison of the qualitative data, the X^2 test or Fisher's exact test were used. Pearson correlation analysis was used to assess correlations between continuous variables with a normal distribution, and Spearman's rank test was used for the continuous variables not distributed normally. A p-value of <0.05 was accepted to indicate statistical significance.

RESULTS

Demographic and Clinical Data

The patient and control groups did not differ significantly in terms of age, gender and cigarette and alcohol use (Table 1). On the basis of SCID-CV, Bipolar-I disorder was diagnosed in 80 patients and bipolar-II disorder in seven patients. Sixty (69%) of the patients were on lithium monotherapy and seven patients had used no other psychotropic agent than lithium lamotrigine, quetiapine and clozapine. Table 2 shows the clinical variables of lithium-treated patients.

Calcium and Parathormone Related Results

Serum levels of cCa, intact PTH, ALP and Mg levels were significantly higher in the lithium group (Table 1). cCa and PTH levels of all participants were within normal limits in the control group. Serum levels of cCa in seven patients, PTH in three patients and cCa and PTH together in one patient exceeded the upper limit of the normal reference ranges, in the lithium group. Although, in the initial measurements, the prevalence of elevated cCa was higher in the lithium-treated patients as compared to the controls (p=0.010), the prevalence of high PTH in the two groups did not differ significantly.

Ultrasonographic Examination of the Parathyroid Gland

Parathyroid pathology was not observed by ultrasonographic examination in any of the participants.

Further Investigation

Further investigations were carried out on the 11 patients with serum cCa and/or PTH above the normal reference range. These included measurements of serum vitamin D

Table 1. Comparison of Lithium-Treated Patients with Control Subjects with Respect to Demographic, Biochemical and Endocrine Variables

Variables	Lithium (n=87) n (%)	Control (n=65) n (%)	Statistics
Female	47 (54)	39 (60)	X^2=0.541, p=0.462
	Median (IQR)	**Median (IQR)**	
Age (years)	43 (19)	37 (17)	Z=-1.668, p=0.095
Dietary calcium intake (mg/day)	434.3 (418.8)	479.0 (367.7)	Z=-1.015, p=0.310
Corrected Ca (mg/dl)	9.6 (0.7)	9.4 (0.6)	Z=-3.280, p=0.001
Intact PTH (mg/dl)	52.3 (26.4)	43.4 (20.2)	Z=3.922, p<0.0001
Phosphorus (mg/dl)	3.7 (0.7)	3.5 (0.65)	Z=-1.125, p=0.260
Magnesium (mg/dl)	2.2 (0.2)	2.0 (0.2)	Z=-4.898, p<0.0001
Alkaline phosphatase(U/l)	69 (25)	53 (26)	Z=-4.211, p<0.0001
Albumin (g/dl)	4.8 (0.4)	4.7 (0.6)	Z=1.522, p=0.128
Serum fT4 (ng/dl)	1.14 (0.22)	1.18 (0.19)	Z=-1.155, p=0.248
Serum TSH (µIU/l)	2.21 (2.52)	1.66 (1.16)	Z=-3.1250, p=0.002
Creatinine clearance (ml/min)	100.18 (29.44)	107.23 (26.24)	Z=-1.991, p=0.047

n: Number, IQR: Interquartile range, Ca: Calcium, PTH: Parathormone, fT4: free thyroxine, TSH: Thyroid stimulating hormone

Table 2. Clinical Variables of the Lithium-Treated Patients

Clinical Variables	n	Minimum	Maximum	Median	Mean	SD
Duration of illness (months)*	87	10	456	204	211	124.6
Age at starting lithium treatment	87	15	59	29	30.6	9.8
Duration of lithium treatment (Lifetime) (months)*	87	7	408	110	139.3	99.2
Lithium dose (mg/day)*	87	450	1800	1050	1089.2	289.7
Serum lithium concentration (mEq/L)*	87	0.5	1.1	0.69	0.7	0.1
Duration of lamotrigine treatment (months)	8	5	84	54	48.8	33.6
Lamotrigine dose (mg/day)*	8	125	300	200	190.6	53.3
Duration of clozapine treatment (months)	3	144	168	156	156	12
Clozapine dose (mg/day)	3	100	100	100	100	0
Duration of quetiapine treatment (months)*	19	4	96	24	31.2	25.3
Quetiapine dose (mg/day)*	19	12.5	300	100	130.9	105.8
Time elapsed since using the psychotropic drugs which are excluded from the study (months)*	80	6	287	58	81.6	76.8

n: Number, SD: Standard Deviation
*: the variables which do not have a normal distribution

level in the patients with elevated PTH, urinalysis in 24-hour urine samples in eight of the 11 patients, three had not delivered their samples, and repeated assessments of serum cCa and PTH. Resultant diagnoses comprised LAH in five (5.7%), and hyperparathyroidism secondary to vitamin D deficiency (HPT-vitD) in three patients, with unconfirmed hypercalcemia after repeated cCa measurements in the other three patients. In all patients diagnosed with LAH serum Mg, P and ALP levels were normal and the cCa levels were in the 10.3-10.5 mg/dl range. Four patients with LAH were using only lithium and one was using quetiapine (250 mg/day) besides lithium. Comparison of the clinical details of patients with and without LAH diagnoses is shown in Table 3.

Evaluating HPT-vitD and LAH prevalences together indicated that hyperparathyroidism was significantly more prevalent in lithium-treated patient group (p=0.010). When the groups were compared on the basis of LAH diagnoses only, a statistically significant intergroup difference was not determined, although none of the control group participants had hyperparathyroidism.

The Relationship Between LAH and Thyroid Disorders

All patients diagnosed with LAH were found to have thyroid disorders on the basis of ultrasonography and endocrine test results (Table 4).

Correlations Between Serum Calcium/Parathormone Levels and the Variables Associated with Lithium Exposure

When variables including age, duration of treatment with lithium, and the dose and serum level of lithium were analyzed

Table 3. Comparison of the Clinical Characteristics of the Patient Groups with and without LAH

Variables		LAH+(n=5) n (%)	LAH-(n=82) n (%)	Statistics
Gender	Female	3 (60)	44 (53.7)	p=0.577 (Fisher exact test one sided)
	Male	2 (40)	38 (46.3)	
Bipolar disorder subtype	Bipolar I	4 (80)	76 (92.7)	p=0.349 (Fisher exact test one sided)
	Bipolar II	1 (20)	6 (7.3)	
		Median (IQR)	**Median (IQR)**	
Age (years)		45 (15)	43 (19)	Z=-0.672 p=0.502
Duration of lithium treatment (months)		168 (222)	109 (171)	Z=-0.255 p=0.798
Age at starting lithium treatment[a]		38 (21)	29 (15)	t=0.143 p=0.887
Lithium dose (mg/day)		900 (825)	1050 (300)	Z=-0.047 p=0.963
Serum lithium concentration (mEq/L)		0.64 (0.16)	0.69 (0.21)	Z=-0.109 p=0.913
Corrected Ca (mg/dl)[b]		10.4 (0.15)	9.6 (0.6)	Z=-3.664 p<0.0001
Intact PTH (mg/dl)[b]		44.8 (19.2)	47.4 (24)	Z=-0.201 p=0.840
Phosphorus (mg/dl)		4 (1.15)	3.6 (0.6)	Z=-0.678 p=0.498
Magnesium (mg/dl)		2.2 (0.25)	2.1 (0.2)	Z=-1.040 p=0.298
Alkaline phosphatase(U/l)[c]		57 (28)	63 (24)	t=-0.418 p=0.676

LAH: Lithium associated hyperparathyroidism, n: Number, IQR: Interquartile range, a: The mean values and standard deviations of the age of starting lithium treatment which had a normal distribution were 31.2±11.3 in LAH+ group and 30.6±9.8 in LAH- group, b: First measurements, c: The mean values and standard deviations of levels of alkaline phosphatase which had a normal distribution were 61.2±14.15 in LAH+ group and 64.54±17.67 in LAH- group

Table 4. Comparison of the Patients with and without LAH on the Basis of Thyroid Pathology

Variable	LAH+ (n=5)	LAH- (n=82)	Total (n=87)	Statistics
	n (%)	n (%)	n (%)	Fisher exact test
Known thyroid disease[a]	4 (80)	10 (12.2)	14 (16.1)	p=0.002 (one sided)
Familial thyroid disease[a]	1 (20)	29 (35.4)	30 (34.5)	p=0.434 (one sided)
Low fT4	0 (0)	1 (1.2)	1 (1.1)	p=0.943 (one sided)
Thyroid pathology in ultrasonography	4 (80)	66[b] (83.5)	70[c] (83.3)	p=0.608 (one sided)
Thyroid disorder	5 (100)	68 (82.9)	73 (83.9)	p=0.407 (one sided)
	Median (IQR)	Median (IQR)	Median (IQR)	Mann Whitney U test
Serum fT4(ng/ml)	1.37 (0.22)	1.16 (0.21)	1.17 (0.22)	Z=-2.713, p=0.007
Serum TSH (μIU/l)	1.38 (1.06)	1.88 (1.74)	1.88 (1.63)	Z=-1.787, p=0.074

a: Known thyroid disease or thyroid medication use before the study
b: LAH- group consisted of 79 subjects (not 82) since three patients refused to wait for ultrasonographic examination.
c: Total number of lithium-treated patients is 84 (not 87) since three patients refused to wait for ultrasonographic examination.
LAH: Lithium associated hyperparathyroidism, n: Number, IQR: Interquartile range, fT4: free thyroxine, TSH: Thyroid stimulating hormone

for correlation with serum cCa and PTH levels, only a weak correlation between serum cCa levels and duration of lithium treatment was calculated (r=0.233, p=0.030).

DISCUSSION

In this study, it was aimed to investigate the effects of lithium on Ca and parathyroid hormone. After detailed investigations, five patients among the 87 lithium-treated patients were diagnosed with LAH, which yielded a 5.7% prevalence of LAH in this group. Reported values in the literature for LAH prevalence vary in the 3.6%-62% range (Albert et al. 2013, Albert et al. 2015, Awad et al. 2003, Bendz et al. 1996, de Oliveira et al. 2014, El Khoury et al. 2002, Kallner and Petterson 1995, Meehan et al. 2015, Meehan et al. 2018, Stancer and Forbath 1989, Twigt et al. 2013). Basing LAH diagnoses on single parametric measurements in most of these studies may underlie the reported variability. Bendz et al. (1996) reported a 4.5% prevalence for LAH after the initial single estimations which dropped to 3.6% after repeated determinations. In our study, the prevalence of LAH would have been 12.6% (11/87) if the diagnoses of LAH been based on the initial parametric measurements. But the final result was 5.7% after a further detailed investigation. In addition to repeated measurements, patients with familial Ca metabolism disorder and/or receiving treatment with drugs affecting Ca metabolism were excluded, cases with high cCa levels were further investigated for differential diagnosis of hyperparathyroidism, renal failure and vitamin D deficiency. Besides, the diagnosis was supported by the results of 24-hour urinalyses. Thus, controlling almost all factors that can affect serum Ca levels and including detailed differential diagnosis have enabled the calculation of a LAH prevalence much lower than in most of the reported studies. Also, factors such as having approximately 70% of the patients on lithium monotherapy, including 4 of the 5 patients diagnosed with LAH and thereby excluding an effect by other drug use on the diagnoses, low dosage of quetiapine and clozapine use on the remaining 30% of the patients, and a mean duration of lithium therapy longer than 10 years have enabled data acquisition from a more homogenous 'lithium-treated patient sample'. It is noteworthy that unsuppressed PTH elevation was determined despite raised serum Ca levels with P and Mg levels within the normal reference limits in the five patients diagnosed with LAH, in agreement with the literature (Livingstone and Rampes 2006, McHenry et al. 1990, Plenge and Rafaelsen 1982, Saunders et al. 2009, Stancer and Forbath 1989, Szalat et al. 2009, Taylor and Bell 1993). Since all the patients diagnosed with LAH were free of clinical symptoms and had mild hypercalcemia, it was planned to check their Ca and PTH levels with three-monthly intervals and to continue the maintenance treatment with lithium. Mallette and Eichorn (1986) recommended to continue lithium treatment after diagnosis of LAH, if hypercalcemia was minimal (<11 mg/dl) and the patient was psychiatrically well controlled by lithium.

It had been planned to compare the LAH prevalence obtained by our study with the prevalence of primary hyperparathyroidism in Turkey. Having not found any research made in Turkey on the subject, we had to include a control group in our study. However, all control group participants being normocalcemic, we could not make the intended comparison in this study. The prevalence of hyperparathyroidism in lithium-treated patients was reported to be 7.5 times higher than the prevalence of primary

hyperparathyroidism in the Swedish general population (Bendz et al. 1996).

When comparing the serum Ca and PTH levels of the patients and the control groups, many factors capable of affecting Ca and parathormone levels including age, dietary Ca intake, presence of known malignancies, renal functions, familial Ca metabolism disorders, and use of drugs with known effects on the Ca level were controlled. The patient and control groups did not differ significantly on the basis of daily cigarette smoking and alcohol intake. Observation of higher cCa, PTH and Mg levels in lithium-treated patients than the control group is consistent with results reported in the literature.

Serum alkaline phosphatase (ALP) level, which is a biomarker of bone turnover was found to be higher in the lithium group, than in the control group. There are conflicting reports about the effect of lithium on bone mineral turnover. Contrary to our results, Zamani et al. (2009) reported lower serum ALP levels in the lithium-treated patients compared to the control group. The effect of lithium on bone mass is outside the scope of our study and requires further detailed research.

There are studies reporting lack of correlations between the duration of lithium treatment and serum Ca and PTH levels (Kallner and Petterson 1995, Komatsu et al. 1995, Zamani et al. 2009) while in our study a weak correlation was detected between the duration of lithium therapy and serum Ca levels. We did not find a correlation between age and the serum Ca and PTH levels, in agreement with the results of Kallner and Peterson (1995); and also not between serum lithium concentration and Ca or PTH levels, consistent with the results of Franks et al (1982), contrary to results of others reporting a positive correlation between serum lithium concentration and Ca levels (Davis et al. 1981, El Khoury et al. 2002, Toffaletti et al. 1979). In our study, we have demonstrated a lack of correlation between the daily dose of lithium or between the age of starting lithium therapy and serum Ca and PTH levels.

In our study, there were not significant differences between the two lithium-treated groups, with and without LAH, with respect to gender, age, lithium dose, serum lithium concentration, duration of lithium treatment, the age of starting lithium treatment. Similarly, Colt et al. (1981) did not observe significant differences between patients with hypercalcemia and normal serum Ca levels, with respect to age, duration of lithium treatment and serum lithium concentration. McIntosh et al. (1987) reported that the effect of lithium on the parathyroid gland is not related to serum lithium concentrations, duration of the treatment or the cumulative dose received by the patient. Although there have been reports on higher incidences of LAH among female patients (Carchman et al. 2008, de Oliveira et al. 2014, Livingstone and Rampes 2006, Szalat et al. 2009), a similar observation was not made in our study.

There are two studies in the literature on the ultrasonographic investigation of lithium effects on the parathyroid gland. Reliability of the report of a 3-fold enlargement of the parathyroid glands of patients, as compared to healthy controls, after lithium treatment longer than three years (Mallette et al. 1989) is doubtful as it conflicts with the knowledge that normal parathyroid gland cannot be observed by ultrasonography (Huppert and Reading 2007). Komatsu et al. (1995) performed ultrasonographic examination in only 10 patients and found parathyroid cyst in one of the patients. Our study has the largest scale ultrasonographic evaluation of the parathyroid gland in the literature, based on 84 lithium-treated patients. Although the technique is highly sensitive in the detection of parathyroid anomaly by experienced hands, the serum Ca and PTH levels are not always associated with ultrasonographic detection of a parathyroid mass. Small and ectopic masses may not be demonstrable (Mihai et al. 2009). In our study, none of the five patients with LAH had an ultrasonographically visualized parathyroid mass suggesting that either the dimensions of the glands were not increased significantly during lithium treatment or that masses were located ectopically.

Lithium has many effects on thyroid physiology. Detailed thyroid data of the participating patients of this study have been previously reported in the literature (Kuman Tunçel et al. 2017). Although there were not significant differences in thyroid disorder diagnoses between the lithium-treated patients with and without LAH, it is notable that all five patients with LAH were also diagnosed with thyroid disorder. Thus, it is conceivable that LAH and thyroid disorders may share comorbid pathologies. While Taylor and Bell (1993) reported 20% comorbidity in their review of patients with LAH, we observed 100% comorbidity in our study. The reason for the significantly higher fT4 level in the LAH group may have been due to the use of thyroid replacement therapy by four (80%) of the five patients diagnosed with LAH before the start of this study. In the literature, there are case reports on the comorbidity of thyroid carcinoma and LAH (Abdullah et al. 1999, Carchman et al. 2008, Szalat et al. 2009). In our study, there were not any ultrasonographic signs of malignancy in the thyroid glands of the patients with LAH. Kusalic and Engelsmann (1999) had reported familial thyroid illness as a risk factor for hypercalcemia during lithium treatment. However, in our study, patients with and without LAH did not significantly differ on the basis of familial thyroid disease.

This study has some limitations. The possibility of earlier undiagnosed hyperparathyroidism cannot be eliminated since the serum Ca and PTH levels of these patients before the start of lithium therapy are not known. The cross-sectional design of the study prevents the establishment of a causal

relationship, which necessitates future prospective studies. As with most of the other studies related to the subject, our study has been conducted in a tertiary referral hospital with predominantly treatment-resistant patients, which has prevented inclusion of only patients on lithium monotherapy. In order to minimize this limitation, patients on treatment with psychotropic drugs known to affect Ca metabolism have been excluded from the study. Another limitation is not having measured the serum vitamin D levels of all patients. It is believed that living in the same geographical region with similar dietary intake and exposure to the sun may partially amend this limitation. Also, 25-OH-D levels of patients with elevated PTH were measured. Inclusion of another group of bipolar disorder patients not having ever used lithium could have helped to demonstrate the hyperparathyroidism characteristic of bipolarity per se. Lastly, the very low number of patients with LAH diagnosis, as compared to those without, has posed difficulties in statistical analysis of the data. However, our study has merits in having not relied on single initial parametric measurements and attempting for clear and definite diagnosis of LAH by controlling multiple factors in the differential diagnosis approach and by including ultrasonographic investigations within its scope.

CONCLUSION

Our results demonstrate that lithium treatment has a relationship with serum calcium and parathormone levels. Consideration of the 5.7% prevalence and the life-threatening potential of LAH emphasizes the requirement for the measurement of baseline serum Ca level before starting lithium treatment, routine periodic measurements of serum Ca level with 3-6 monthly intervals and evaluation of serum PTH levels in cases of elevated serum Ca.

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