ORIGINAL RESEARCH
Key Words: lithium, bipolar disorder, thyroid gland, ultrasonography, thyroid abnormalities

Ultrasonically Determined Thyroid Volume in Individuals with Bipolar Disorder on Lithium Prophylaxis Compared with Healthy Controls

By Anjali Bhasin, Devasenathipathy Kandasamy, Yashdeep Gupta, Raman Deep, Raka Jain

ABSTRACT ~ ***Introduction:*** *Lithium is a gold-standard agent for bipolar disorder (BD) and can affect the size, structure and/or function of thyroid gland with long-term exposure. Thyroid ultrasound can detect structural thyroid abnormalities, but it is under-reported with few prior studies in lithium users. The study aimed to evaluate thyroid volume and echogenicity in lithium users with BD and healthy participants, and explores its association with clinical variables and thyroid functions.* ***Method:*** *This was an observational study with 102 participants in total. Study group consisted of 52 clinically-stable (HAM-D ⩽ 13, YMRS <8) follow-up patients with DSM-5 BD on lithium maintenance. Healthy controls (HC) comprised 50 participants with no illness in self and family. Assessments included NIMH Life-chart, IGLSI typical/atypical scale, lithium response scale (LRS) and CGI-BP. Fasting venous sample was taken for thyroid functions, Anti-TPO antibodies and serum lithium. Thyroid ultrasonography was also conducted.* ***Results:*** *Mean age of cases was 39.42 ± 12.62 years, with 42.3% females, which was comparable to HC. Median duration of illness was 10.5 years (Q1-Q3 = 6–19 years), with median lithium exposure for 4.5 years (Q1-Q3:2.2–7.75), and serum lithium 0.67 mmol/L (SD:0.31). Thyroid volume was significantly higher for cases than HC (10.67 ± 5.46 mL vs 4.30 ± 2.06 mL; p < 0.001). Relative to HC, serum TSH was higher in cases (p = 0.018), while anti-TPO positivity was comparable (14.0% vs 3.85%, p = 0.089). Thyroid nodules were more frequent in male cases (p = 0.013) compared to male controls. Thyroid volume did not show association with serum TSH (p = 0.277) and lithium response (p = 0.36).* ***Conclusion:*** *Findings indicate a uniform enlargement of thyroid gland in lithium users with BD. Thyroid volume did not show association with thyroid functions and lithium response, however prospective studies may give better insight about their trajectories over time.* Psychopharmacology Bulletin. *2024;54(4):18–34.*

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Introduction

Bipolar Disorder (BD) has an estimated lifetime prevalence of 0·5% (0·49–0·51) in Indian population.[1] In spite of advent of newer medications, lithium remains one of the first-line medication for prophylaxis against relapses or recurrences of depressive, hypomanic and manic episodes in BD, besides its anti-suicidal and neuroprotective effects.[2,3] While lithium is an efficacious drug, it is known to be associated with a spectrum of thyroid related abnormalities, including thyroid enlargement and goitre.[4,5] Sub-clinical or clinical hypothyroidism is also known. Association with antithyroid antibodies has been reported, but not consistently.[6–8]

Lithium accumulates in the thyroid gland at a concentration 3–4 times higher than that in the plasma, increasing the propensity of adverse effects.[9] Mechanism for lithium-induced goitre involves an activation of tyrosine kinase by the lithium ions, and its effect on the intracellular signalling associated with the adenylate cycle and Wnt/beta-catenin to proliferation of thyrocytes. Besides, the inhibition of the synthesis and release of thyroid hormones can also cause or contribute to goitre.[10,11] Thyroid abnormalities occur more frequently in those with pre-existing goitre or those with an elevated titre of thyroid autoantibodies.[12,13]

Goitre can occur after long-term lithium therapy, but has been reported within 6–9 months of lithium initiation.[14] Lithium-induced thyroid enlargement may not be clinically detectable till it is large enough to be observed or palpated, or is associated with comorbid hypothyroidism.[15] However, lithium-associated changes in thyroid volume can be detected and quantified by means of ultrasonography, that is a relatively inexpensive, time-efficient (approx. 5 min) and radiation-free method to scan the gland, but have remained underutilized.[15–19]

Relatively limited number of studies are available for ultrasonically determined thyroid volume in lithium users relative to healthy individuals or comparator group, that is summarized here.[14,18–20,22] Kuman et al.[20] assessed 84 patients with BD on lithium therapy > 3 months with 65 matched healthy controls. The frequency of ultrasonically determined goitre was significantly more in cases (47.6% vs 6.7%). Presence of any kind of thyroid disorder was detected in 88.1% cases and 49.2% controls, while anti-TPO positivity was significantly more frequent in the control group.[20] Recently, Kraszewska et al.[21] compared cases with BD on lithium for at least 3 years (N = 98) with patients on non-lithium mood stabilisers (N = 39). The difference in thyroid volumes of study groups was significant, with higher values in lithium treated

compared to lithium naïve subjects, with focal changes in thyroid gland being more frequent in lithium-treated subjects.[21]

Few studies have been published from Asia, with only two prior studies on Indian patients.[22] The study by Alam et al.[23] assessed 30 BD lithium-treated patients, finding a significantly higher thyroid volume compared to non-lithium BD group, but there was no healthy participants group.[23] Dar et al.[22] assessed 43 patients with diagnosis of any mood disorder on lithium comparing them to healthy participants, finding a significantly higher mean values of total thyroid volume, right and left thyroid volume in lithium group.[22]

In view of limited extant literature, the present study aimed to assess and document the thyroid volume and parenchymal changes in long-term lithium users with BD and healthy participants. We also explored for relationship of thyroid volume with clinical variables, thyroid functions and autoimmunity.

Methods

Study Setting and Design

This observational study was conducted at a tertiary care teaching institute in India. Institutional ethics clearance was obtained prior to study initiation. The study participants were recruited between May 2022 and December 2022 after a written informed consent. We have adhered to the STROBE guidelines for reporting the study.[24]

Selection Criteria: The study participants included out-patients in regular follow-ups, aged 18–65 years receiving regular lithium therapy last one year or more as per treatment records, if they met DSM-5 diagnosis of BD type I or II, with partial or full remission, with current scores on Young's Mania Rating Scale (YMRS) <8, and 17-item Hamilton Rating Scale for Depression (HAM-D) $\leqslant 13$. Those with lifetime DSM-5 psychiatric or substance use comorbidity barring nicotine dependence and those with evidence of significant period/s of non-adherence to lithium therapy (self-report, treatment records and lithium test reports) were excluded. Those with any medical condition including hypothyroidism preceding lithium initiation or any procedure/intervention potentially interfering with thyroid gland were excluded.

Healthy group included participants aged 18–65 years, with no known medical or psychiatric diagnosis and no psychiatric illness up-to second-degree relatives. Any known lifetime thyroid disease was an exclusion for controls.

Study assessments: A sociodemographic and clinical proforma was used to gather relevant information. The NIMH Life Chart Method (LCM)-clinician retrospective chart was used for charting illness course and related details. Clinician Global Impression-bipolar version (CGI-BP) was used for illness severity at the time of assessment. The core items of International Group for the Study of Lithium treated patients (IGLSI) Scale for typical/atypical features of affective illness were used to ascertain scores on the atypical (comorbidity, mood-incongruent psychotic symptoms, residual symptoms and higher frequency of manic over depressive episodes) or typical features, and accordingly assign them as typical or atypical features group. Retrospective assessment of response to lithium maintenance was done using Alda lithium response scale (LRS). It consists of criterion A score, that measures retrospectively the degree of improvement in illness course since the start of lithium, criterion B measuring the causality between improvement and lithium, with lower score indicating a higher causality. The total LRS score (A-B) is yielded by subtraction of criterion B score from criterion A score.

Blood-based assessments: Fasting venous sample was drawn from all study participants in the morning. The thyroid functions (T3, T4, TSH) and anti-APO were assessed using Electrochemiluminescence assay in Cobas E400 Roche machine. The serum lithium estimation was done using Roche Electrolyte Analyzer (model no 9180).

Ultrasonographic assessment of thyroid: Ultrasonographic assessment for thyroid was done at the Department of Radiodiagnosis using high-resolution Supersonic Imagine Airxplorer Ultrasound Machine. Expert conducting the sonographic examination was blinded to the diagnostic group or lithium exposure status of study participants. The craniocaudal, transverse, and anterior-posterior dimensions (in cm) of each lobe were multiplied with each other and then by 0.52, to obtain the volume (cm^3 or mL) of each lobe. The volumes of left and right lobes were added for total thyroid volume. Isthmus size was measured by its anteroposterior diameter. Besides volume, thyroid was also assessed for any nodule, echogenic or parenchymal changes.

Study Procedure

Patients visiting out-patient clinic of Department of Psychiatry at a tertiary care centre were recruited as per selection criteria. Written informed consent was taken from all study participants.

All assessments were made in a single session lasting about 45–60 min for a patient and 15–20 min for healthy control. Healthy participants

were recruited from among non-biological relatives, accompanying friends or volunteers from the same setting. Patients had their diagnosis re-confirmed using DSM-5 criteria by clinical history and interview, followed by assessment by study instruments. Physical examination of thyroid gland was conducted for all participants. Fasting venous blood sample (8 ml for cases and 5 ml for controls) was drawn towards thyroid function tests and serum lithium estimation. The thyroid ultrasonography was conducted, usually in the same week, as per slots assigned for the study.

Statistical Analysis

Analysis was done using SPSS version 29.0 (IBM, SPSS Inc., Chicago). Descriptive statistics (Mean/SD, Median/IQR and frequencies) were used for demographic, illness related, treatment related and thyroid variables. There was no missing data. Normalcy distribution was assessed using Shapiro-Wilk test, along with histogram, skewness and kurtosis. Groups comparison was done using Independent samples t-test/Mann Whitney U test and Chi Square test, as relevant. Correlation of thyroid volume with various clinical variables was done using Spearman's correlation. The two-tailed $p < 0.05$ was considered to be significant.

Results

A total of 117 clinically stable, follow-up patients with BD taking the prescribed lithium were further screened, of which 16 were on lithium <1 year, 8 on thyroxine replacement prior to start of lithium, 3 had history of non-adherence to prescribed lithium, 9 did not provide consent, 6 didn't respond to phone calls for appointment, and 5 dropped out citing logistics. A total of 52 patients underwent all study assessments, along with 50 healthy participants.

The demographic profile of cases and healthy controls is shown in Table 1. Age, gender distribution, education and family income did not differ across groups. Table 1 also shows the illness and treatment profile of cases, besides the thyroid functions.

Table 2 shows the thyroid volumetric variables in cases and healthy controls. The mean total thyroid volume in cases (10.67 mL, SD 5.46), was significantly higher than mean thyroid volume of healthy participants (4.30 mL, SD 2.06), with a statistically significant group difference ($p < 0.001$). Analysis was also done after excluding cases on thyroxine replacement ($n = 8$), with similar findings (supplemental Table 1s).

TABLE 1

Clinical Variables for Patients with Bipolar Disorder on Lithium Therapy and Healthy Individuals

	CASES (N = 52)	HEALTHY INDIVIDUALS (N = 50)		
DEMOGRAPHIC VARIABLES	MEAN (SD) OR N (%)		$t/\chi^2/U$	p
Age (in years)	39.42 (12.62)	39.98 (11.91)	−0.229	0.819
Gender				
Male	30 (57.70%)	25 (50.00%)	0.607	0.436
Female	22 (42.30%)	25 (50.00%)		
Education (in years)	12.38 (4.03)	12.64 (4.32)	0.309	0.379
Family Income				
≤INR 25,000	11 (21.15%)	14 (28.00%)	0.646	0.422
>INR 25000	41 (78.85%)	36 (72.00%)		
Illness related variables	Median (IQR-Q1:25%,Q3:75%)			
Age at onset of illness (years)	26.71 (10.48)			
Duration of illness (years)	10.50 (6,19)			
Total illness episodes	06 (3.25,7.00)			
No of depressive episodes	03 (1.00,4.00)			
No of hypo/manic/mixed episodes	02 (1.00,4.00)			
Complete Inter-episodic remissions	43 (82.7%)			
History of treatment refractory episode	09 (17.3%)			
Time since remission (months)	12.00 (3.00,24.00)			
Nicotine use	11 (21.2%)			
Family history of bipolar disorder	08 (15.38%)			
Family history of thyroid disease	06 (11.54%)			
CGI-BP: severity of illness	1.08 (0.27)			
IGSLI: Typical category	36 (69.20%)			
IGSLI: Atypical category	16 (30.80%)			
Treatment related variables				
Duration of lithium (years)	4.50 (2.23,7.75)			
Minimum lithium dose (mg/day)	619.23 (120.11)			
Maximum lithium dose (mg/day)	938.46 (201.37)			
Alda lithium response scale score	6.44 (1.98)			
Prescribed medications (current):				
Lithium	52 (100%)			
Other mood stabilizer[a]	14 (26.92%)			
Atypical antipsychotic[b]	39 (75.00%)			
Anti-depressant	15 (28.85%)			
Thyroxine replacement	08 (15.38%)			

(Continued)

TABLE 1 *(Continued)*

Clinical Variables for Patients with Bipolar Disorder on Lithium Therapy and Healthy Individuals

	CASES (N = 52)	HEALTHY INDIVIDUALS (N = 50)		
DEMOGRAPHIC VARIABLES	MEAN (SD) OR N (%)		$t/\chi^2/U$	p
Serum lithium estimation (current) (mEq/L)[c]	0.67 (0.31)			
Physical examination				
BMI (kg/m^2)	26.38 (4.27)			
Palpable thyroid gland	09 (17.31%)			

Statistical analysis by Independent samples t test, Mann Whitney U Test, Chi-square test: two-tailed significance $p < 0.05$; YMRS-Young's Mania Rating Scale, HAM-D: Hamilton Rating Scale for Depression; LRS-Lithium response scale; [a]Non-lithium mood stabilizer: divalproex//valproate sodium: 08; lamotrigine/; 03; oxcarbazepine: 02; carbamazepine:01; [b]Atypical antipsychotic drug: olanzapine:14, quetiapine: 11, aripiprazole:9, risperidone:3, haloperidol:1, clozapine:1; [c]Sampling within 1–4 weeks of clinical assessments.

As shown in Table 2, thyroid nodules were detected in 32.69% cases (n = 17) and 16.32% controls (n = 8) (p = 0.05). The size of thyroid nodule was mostly ten mm or below (15/17 cases and 6/8 controls) Majority of cases (36, 69.2%) and healthy controls (35, 70%) had normal thyroid echogenicity, while 13 cases (25%) and 12 healthy controls (24%) had hypoechoic, and 3 each in cases and healthy controls group had a hyperechoic gland, with no significant group differences.

Figure 1 shows the total thyroid volume compared for male cases and male controls, with highly significant group differences ($p < 0.001$). The gender sub-groups were comparable on key variables, including age and duration of lithium therapy. ($p > 0.05$; not tabulated).

Among males, 11 (21.2%) cases and 2 (4%) healthy controls had thyroid nodules. The frequency of thyroid nodules was significantly higher in male cases ($\chi^2 = 6.208$ $p = 0.013$) compared to male controls, but not in females (6/22 vs 6/25; $\chi^2 = 0.066$ $p = 0.797$).

Figure 2 shows the depiction of the measurement of thyroid dimensions in a study participant.

Table 3 shows the association of thyroid volume to various clinical variables and thyroid functions among patients (n = 52). Thyroid volume did not show any significant association to thyroid functions or anti-TPO ($p > 0.05$). Analysis done after excluding eight patients on thyroxine replacement had similar findings. ($p > 0.05$; not tabulated)

TABLE 2

Thyroid-Related Variables in Patients with Bipolar Disorder on Lithium Therapy and Healthy Individuals

	CASES (N = 52) MEAN (SD) OR N (%)	HEALTHY CONTROLS (N = 50)[a]	CASES (N = 52) MEAN RANK (SUM OF RANKS)	HEALTHY CONTROLS (N = 50)[a]	U/χ^2	P
VOLUMETRIC VARIABLES[b]						
RIGHT THYROID LOBE						
Right lobe volume (ml)	5.39 (2.52)	3.38 (1.65)	65 (3380)	36.14 (1771)	546.00	<0.001*
LEFT THYROID LOBE						
Left lobe volume (ml)	5.28 (3.51)	3.00 (1.78)	65.17 (3389)	35.96 (1762)	537.00	<0.001*
TOTAL THYROID VOLUME						
Total thyroid volume (ml)	10.67 (5.46)	4.30 (2.06)	71.81 (3734)	28.92 (1417)	192.00	<0.001*
ISHTHMUS						
Antero-posterior (mm)	3.16 (1.85)	2.05 (0.66)	63.76 (3315)	38.75 (1937)	662.50	<0.001*
PARENCHYMAL CHANGES						
Thyroid nodule	17 (32.69%)	08 (16.32%)			3.839	0.05
Hetero-echogenicity	16 (30.77%)	15 (30.00%)			0.119	1.00
Miscellaneous						
Cyst	05	0				
Spongiform lesion	02	0				
Diffuse heterogeneous	01	01				
Ill-defined lobular diffuse nodular gland	02	0				

(Continued)

TABLE 2 *(Continued)*

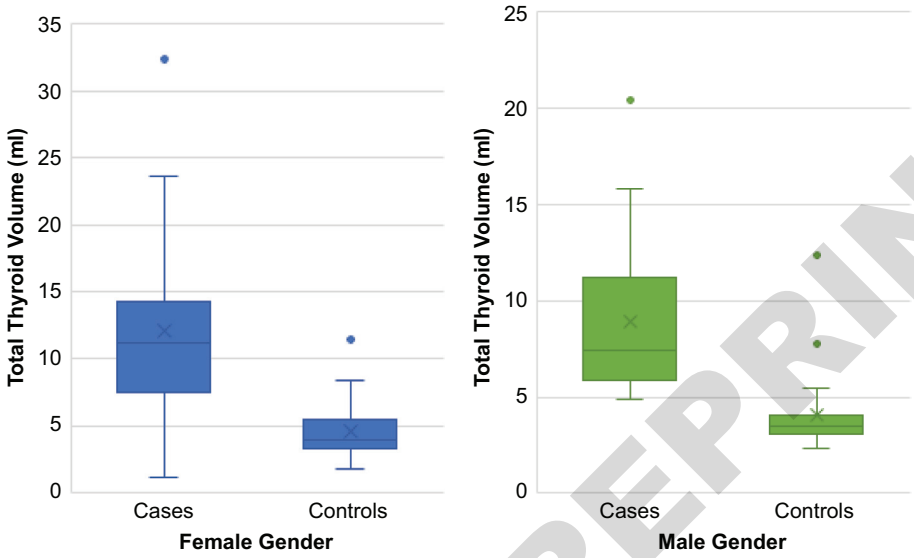
Thyroid-Related Variables in Patients with Bipolar Disorder on Lithium Therapy and Healthy Individuals

	CASES (N = 52) MEAN (SD) OR N (%)	HEALTHY CONTROLS (N = 50)[a] MEAN (SD) OR N (%)	CASES (N = 52) MEAN RANK (SUM OF RANKS)	HEALTHY CONTROLS (N = 50)[a] MEAN RANK (SUM OF RANKS)	U/χ	P
Fibrosis	0	01				
Lobe replaced by nodules	0	02				
Any parenchymal change	26 (50.00%)	17 (34.00%)			2.676	0.102
THYROID FUNCTION TESTS						
Serum Total T3 (ng/mL)	1.20 (0.22)	1.28 (0.26)			−1.624	0.108
Serum Total T4 (μg/dL)	7.95 (1.99)	7.67 (1.78)			1312.00	0.936
Serum TSH (μIU/mL)	3.96 (2.39)	3.03 (1.96)			946.50	0.018*
Anti-TPO positivity[c]	2 (3.85)	7 (14.00)				0.089

Statistical analysis by Mann Whitney U test or Chi-square test; [a]n = 49 for thyroid volumetric variables for healthy controls as volume estimation for 1 participant was not feasible due to nodules over entire gland; [b]Analysis repeated after excluding eight cases on thyroxine replacement also showed similarly significant group differences for all volumetric variables; [c]Laboratory cut-off (>34 IU/mL).

FIGURE 1

Total Thyroid Volume Compared for (a) Female Cases and Controls (b) Male Cases and Controls



	N	MEAN	SD	MEAN RANK	SUM OF RANKS	U	P
Female cases	22	8.87	3.99	35.09	772.00	31.00	<0.001
Female controls	25	4.04	2.06	14.24	356.00		
Male cases	30	11.99	6.05	37.60	1128.00	57.00	<0.001
Male controls	24	4.54	2.03	14.88	357.00		

FIGURE 2

Image with Measurements for Left Thyroid Lobe in a Study Participant (a) Antero-Posterior, Medio-Lateral; and (b) Cranio-Caudal. A Heterogenous Parenchyma with Hypoechoic Areas is also Seen

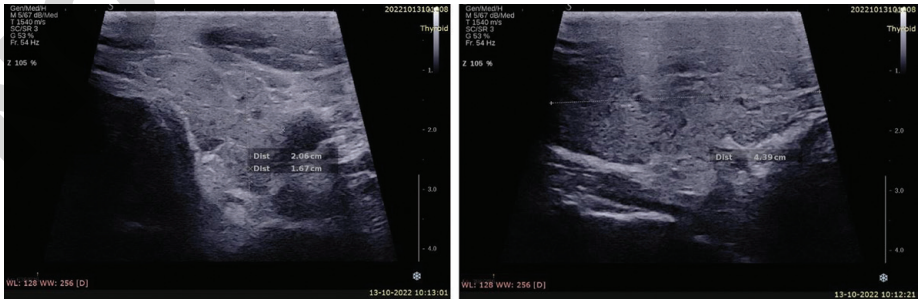


TABLE 3

Association of Thyroid Volume to Demographic Variables, Illness Variables and Thyroid Functions in Patients (N = 52)

	THYROID VOLUME[a]	
	R_S	P
Age	0.146	0.145
Female gender	−0.324	0.019*
BMI	−0.055	0.700
Total duration of bipolar illness	−0.124	0.382
Number of Lifetime episodes	0.136	0.335
Lifetime depressive episodes	−0.017	0.903
Lifetime hypo/manic/mixed episodes	0.011	0.927
Duration of lithium treatment	0.262	0.061
Alda lithium response scale (LRS) score	0.128	0.366
IGSLI Atypical features group	0.217	0.123
Nicotine user status	−0.227	0.105
Serum Lithium Level	0.098	0.490
Serum Total T3	−0.099	0.484
Serum Total T4	−0.130	0.358
Serum TSH	−0.154	0.277
Anti-TPO positivity	−0.253	0.070

Statistical analysis by Spearman's correlation and Mann Whitney U test; rs: Spearman's Rank Correlation Coefficient; U: Mann Whitney U *$p < 0.05$; [a]Correlations were repeated after excluding eight patients on thyroxine replacement but findings remained similar.

Discussion

The paper adds to limited number of studies to report thyroid volume in patients with BD on lithium maintenance and healthy individuals. Cases comprised of long-term follow-up patients at psychiatry out-patient department, with median duration of 4.5 years for lithium maintenance (range 1–30 years) Lithium adherence was verified by current serum lithium (mean: 0.67 ± 0.31 mmol/L), past lithium reports and documentation in clinical records.

Overall, the study results are indicative of a uniformly large thyroid gland in cases when compared to healthy individuals. The mean total thyroid volume, left lobe volume and right lobe volume was significantly higher in patients ($p < 0.001$) compared to healthy controls. This finding is consistent with published studies on ultrasonically-determined thyroid volume in lithium users and healthy participants.[14,18–20]

We found a total thyroid volume of 10.67 ± 5.46 mL in cases as opposed to 4.30 ± 2.06 mL in healthy participants. This finding is quite similar to previous Indian study from Srinagar that reported total thyroid volume of 9.40 ± 1.41 mL for patients with mood disorders on lithium therapy and 4.79 ± 0.45 mL for healthy participants.[22]

The other Indian study by Alam et al.[23] also reported similar thyroid volume of 10.73 ± 5.26 mL in lithium treated group (vs 6.42 ± 1.89 mL in non-lithium group) with BD.[23] Overall, the mean values for thyroid volume for Indian subjects appear to be lower than western studies. Studies from Europe have reported average thyroid volumes from 18–25 mL in lithium-treated cases, and 8–12 mL in control groups.[18–21] The difference in thyroid size and volume may result from geographical, race or ethnicity related variations.

In the present study, nine cases (17.3%) had enlarged thyroid on palpation, that is similar to that reported in prior Indian studies (14–16.6%).[22] Bauer et al.[19] found that clinical examination detected only about half of the 55% cases with ultrasonically determined goiter (defined using > 9 ml for females and > 12.5 ml for males). Applying these cut-offs, which are similar to and supported by some Indian data,[25,26] 63.5% (33/52) cases and 2.04% (1/50) qualified for ultrasonically determined goitre in the present study. Kuman et al. reported that 47.6% cases and 6.7% controls had ultrasonic goitre, using a cut-off > 17 cm^3 for females and > 24 cm^3 for males.[20] However, it needs to be emphasized that there are no consensus guidelines yet to define ultrasonic goitre in Indian subjects, and definitions have varied across studies, thereby necessitating a comparison with matched healthy participants.

Thyroid nodule was detected in 32.7% cases (vs 16.3% controls), while any parenchymal change was seen in 50% cases (vs 34% controls), but with no statistical difference relative to controls. The previous Indian study reported a heterogeneous parenchymal appearance with nodules in two patients on lithium therapy and none of the healthy controls.[22] Kuman et al. reported thyroid nodule in 52.4% cases (vs 43.3% controls, $p > 0.05$) and heterogeneous parenchyma in 22.6% cases (vs 6.7% controls; $p < 0.05$).[20] Another recent study by Kraszewska et al. reported focal changes to be more frequent in lithium-treated compared to lithium-naïve subjects.[21]

The present study detected anti-TPO positivity in 3.85% cases and 14% controls, with no group difference ($p > 0.05$). Available literature is inconsistent on thyroid autoimmunity in lithium users, with conflicting findings in existing studies. Some studies report a higher autoimmunity in long-term lithium treated cases. Kraszewska et al.[21] found an elevated anti-TPO titre in 45% of 66 long-term lithium users (10–44 years), though no comparison with healthy controls is available from this study. On the other hand, Ozsoy et al.[14] reported anti-TPO positivity to be similar for lithium treated and lithium naïve patients with BD. Kuman et al. reported a significantly lower anti-TPO positivity in lithium-treated cases (10%) compared to the healthy control group (23%).[20] Mean rank for serum TSH was significantly higher

($p = 0.018$) in cases compared to healthy controls, that is a well-known finding.[14,19,21,22] The present study did not get any subject with raised T3 or T4. This is similar to study by Dar et al.[22] while Alam et al.[23] reported a trend towards hyperthyroidism in lithium-treated cases compared to non-lithium patient group. Literature reports lithium-induced hyperthyroidism to be a rare or infrequent occurrence with an incidence of 0.1% to 1.7%.[19,21,27] All the analysis were done after excluding eight patients who were on thyroxine replacement, but results were similar.

Available literature supports some predisposition of female gender for lithium-induced volumetric changes.[28] However, the present study found that the thyroid volume is significantly increased in both male and female lithium users. The total thyroid volume correlated negatively with female gender in our study, which might be due to physiological differences in baseline size across both genders. In previous Indian studies, Dar et al.[22] found significantly higher total thyroid volume in female cases compared to male cases, but Alam et al.[23] found no significant correlation of thyroid volume to female gender. Unlike females, frequency of thyroid nodules was significantly higher in male cases compared to male controls (21.2% vs 4%) in this sample. This gender difference may be further studied in larger samples.

Total thyroid volume did not show an association with clinical variables, including lithium duration. Kraszewska et al.[21] reported a significant correlation between volume of the thyroid gland[29] and the duration of lithium therapy, whereas several other studies did not find a significant association,[19,20,23] consistent with finding from our study. Total thyroid volume did not show a significant association with bipolar illness variables and retrospective response to lithium prophylaxis as of now. While thyroid dysfunction is known to be linked to more frequent or rapid cycling and treatment refractory course in BD,[30,31] but the impact of thyroid volumetric and parenchymal changes on prospective treatment response or illness course remains to be seen in longitudinal studies.

Findings must be interpreted in light of certain limitations. The current study has a cross sectional design that cannot address the causality. A prospective design would be better suited to assess the impact of enlarged thyroid on course of bipolar illness and thyroid functions. The patients were on co-prescribed medications. There is some literature to suggest that atypical antipsychotics may be infrequently associated with hypothyroidism. Literature has also linked BD as a risk factor for development of thyroid diseases[32] however a comparator group with medication-naïve patients with BD was not feasible due to ethical reasons.

The study also has several strengths. The sample comprised of all patients with a diagnosis of BD rather than all affective and schizoaffective diagnosis. The duration of lithium maintenance was reasonably long (1–30 years). Patients had reliable clinical records in same department to minimize recall errors. The study was adequately powered with a sufficient sample size. Estimated sample size based on reference paper by Bauer et al.[19] assuming significance level ($\alpha = 0.05$) and 90% power, was 36 per group. Thyroid function tests were conducted using a highly sensitive electrochemiluminescence assay (ECLIA), to yield robust values. Thyroid volumes were assessed using a high-resolution ultrasound machine, with the expert performing sonographic examination blind to the participant group status.

Findings from the study has some implications. It has been previously suggested to include ultrasonography in the routine monitoring of patients on lithium therapy.[15–16,19] A close monitoring can be done at baseline before start of lithium and thereafter at specified time intervals, such as 1–2 years, to document changes in thyroid volume, especially for those who are at-risk. Further, the longitudinal course of thyroid enlargement, associated risk factors and its potential impact on bipolar illness course and thyroid functions can be assessed in further studies. It remains controversial on whether to use prophylactic TSH-suppressive therapy for euthyroid goiter particularly in those in goiter-endemic areas but most advise for a conservative approach and cautious monitor.

To conclude, findings are indicative of a significant and uniformly enlarged thyroid in Indian patients with BD on lithium maintenance. The potential impact on illness course and treatment response can be better studied in a prospective design. ✤

Author Contributions

All authors (AB, RD, DK, YG, RK) contributed to the study conceptualization. AB recruited the participants and assessed them. DK conducted the thyroid ultrasonographic assessments for study participants. YG supervised for thyroid functions, autoimmunity testing. RD supervised the patient recruitment, clinical evaluations and clinical data collection. RJ supervised for serum lithium estimation. AB and RD conducted the statistical analysis and prepared the initial draft. All authors (AB, DK, YG, RD, RJ) edited and approved the final manuscript.

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- Written Informed consent taken from all participants

Conflict of Interest

Nil.

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None.

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SUPPLEMENTAL TABLE 1S

Thyroid Volume Among Cases Without Thyroxine Replacement (n = 44) and Healthy Controls (n = 49)

	Cases (N = 44)	Healthy controls (N = 49)[a]	Cases (N = 44)	Healthy controls (N = 49)[a]		
	Mean (SD)		Mean rank (sum of ranks)		U	P
Right lobe volume (ml)	5.59 (2.44)	3.32 (1.70)	62.14 (2734)	33.41 (1637)	412.00	<0.001*
Left lobe volume (ml)	5.56 (3.56)	2.98 (1.77)	62.86 (2766)	32.76 (1605)	380.00	<0.001*
Total thyroid volume (ml)	11.15 (5.34)	4.28 (2.04)	68.86 (3030)	27.37 (1341)	116.00	<0.001*
Isthmus Antero-posterior (mm)[a]	3.16 (1.90)	1.98 (0.76)	59.34 (2611)	37.08 (1854)	579.00	<0.001*

Statistical analysis by Mann Whitney U test; [a]Healthy controls n = 49 for thyroid volumes and n = 50 for Isthmus of thyroid; *p < 0.05: significant, p < 0.001: highly significant.