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Thyroid Functions in Lithium-Treated Psychiatric Patients

A Cross-Sectional Study

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ABSTRACT

In the present cross-sectional study, thyroid functions (viz. thyroid radioiodine uptake [RAIU] and serum T3, T4, and thyroid-stimulating hormone [TSH]) were evaluated in 24 healthy controls and 132 outdoor affective disorder patients. Eleven of these patients were to receive lithium (Li) and the remaining 121 patients were at different stages of Li treatment ranging from 0.7 to 240 mo. RAIU was found to increase significantly throughout the Li therapy and was associated with the corresponding rise in TSH levels. In totality, Li treatment induced subclinical hypothyroidism in 51/132 (39%) of patients. However, 8/51 patients who belonged to known iodine-deficient belt had abnormally high TSH (range 15.2–76.0 μIU/mL), low T4 (5.3 ± 2.5 μg/dL), and normal T3 and at least 4 of these 8 patients were clinically hypothyroid. T4 levels declined significantly ($p < 0.05$) with Li treatment ranging from 61 to 240 mo as compared to the corresponding values in the pre-Li group. The T3/T4 ratio was found to be significantly higher with Li treatment ranging from 0.7 to 6 mo in comparison with the pre-Li group and this value returned to base levels after long-term Li therapy. High T3 and T4 were observed in 13% and 12% of the patients, respectively, as compared to the corresponding control values.

Index Entries: Thyroid functions; affective disorder; lithium treatment.

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INTRODUCTION

Lithium (Li) has been shown to be a clinically effective agent in the treatment of biopolar affective disorder and also in recurrent depression *(1,2)*. Currently, approved uses of Li by the US Food and Drug Administration extend beyond the treatment of acute mania and maintenance therapy of patients with bipolar disorder *(3)*. Lithium augments the therapeutic effects of conventional antidepressants when used as an adjunct therapy and is particularly useful in patients with resistant depression. The efficacy of the drug in alcohol dependents has been a matter of controversy for several years, but the recent findings indicate that Li has limited use in this population *(3)*.

The side effects of Li therapy, particularly those involving the thyroid, continue to generate concern *(4)*. Since the discovery that Li treatment may alter the thyroid size and function *(5,6)*, the frequency of such alterations has been the subject of many transverse and retrospective investigations. In 1971, few sporadic cases of clinical hypothyroidism in Li-treated psychiatric patients were first reported *(7,8)* and these observations encouraged extensive research envisaging effects of Li on the hypothalamic–pituitary–thyroid axis. These findings have depicted a variety of Li-induced thyroidal abnormalities in both clinical and experimental studies, and the abnormalities ranged from subtle changes in thyrotropin-releasing hormone responsiveness *(9–11)* to frank myxoedema *(12,13)*. Other studies *(14–16)* have suggested that autoimmune thyroid disease is frequently found in those Li-treated patients who do become hypothyroid. Crowe et al. *(17)*, however, felt that an equal number of those who become hypothyroid are antibody negative and have only a transient and reversible biochemical defect induced by Li. On the contrary, occasional hyperthyroidism has also been related to lithium's use *(18,19)*. In different serial studies, the time for development of hypothyroidism has been reported *(20)* to range from a few months to several years, and the opinions vary on the frequency with which thyroid functions alter in Li-treated patients. Moreover, to the best of our knowledge, no study evaluating thyroid functions in Li-treated patients suffering from affective disorders is available in any population residing in the Asian continent. In this cross-sectional study, we have evaluated the effects of varying durations of Li treatment on the thyroid status in affective disorder patients.

MATERIALS AND METHODS

Patient Selection

One hundred thirty-two patients with affective disorder (AD) who met Research Diagnostic Criteria (DSM–III-R) for affective disorders were

selected for the study. Eleven patients awaiting the initiation of Li therapy acted as disease controls. One hundred twenty-one patients who attended the "Lithium Clinic" in the Department of Psychiatry of the institute were included. They were receiving Li treatment for different treatment durations, ranging between 0.7 and 240 mo. These patients received lithium carbonate (trade name: LICAB, manufactured by Torrent Pharmaceuticals Ltd. Ahmedabad, India) at a dose range of 300–1200 mg/d. All the patients had previously received or were receiving medication other than lithium (viz. antipsychotics, antidepressants, anticholinergics, and sedative hyponotics). Twenty-four healthy volunteers who had never received lithium or any drug affecting thyroid functions served as the reference control group.

The study subjects were divided into five groups (see Table 1).

Thyroid Radioiodine Uptake Measurements

To each overnight fasting subject, 0.37 MBq carrier-free iodine-131 (BRIT, Mumbai, India) was administered orally followed by 250 mL of drinking water. Uptake of ^{131}I over the thyroid was measured at 4 h, 24 h, and 48 h using a standard IAEA recommended flat-field thyroid uptake probe (ECIL, Hyderabad, India). A standard dose of 0.37 MBq ^{131}I was counted every time to account for the physical decay of ^{131}I and possible instrumental error, if any, during the uptake measurements.

Assessment of Serum Thyroid Hormones and Serum Li Levels

Ten milliliters of venous blood was withdrawn from each patient in the morning, 10–12 h after the last dose of Li carbonate. The serum was separated and samples were frozen at –20°C until analyzed for thyroid hormones and Li levels. Serum thyroxine (T4) and triiodothyronine (T3) levels were analyzed by radioimmunoassay kits (BRIT, Mumbai, India). Thyroid-stimulating hormone (TSH) was estimated by ultrasensitive immunoradiometric assay kits (BRIT, Mumbai, India). Serum Li concentrations were determined by the flame photometric method *(21)*.

Thyroid Clinical Assessment

Thyroid clinical assessment of thyroid functions was performed by Waynes Diagnostic index. A score of +19 was suggestive of clinical hypothyroidism, whereas a score of –24 excluded it.

Statistical Analysis

The significance of differences between two means was calculated by the Student's *t*-test and among different variables by performing one- or two-way analysis of variance (ANOVA). In all comparisons, differences

Table 1
Patients Groups and Lithium Intake Duration

Group	Lithium Duration (mo) (Range)	Number of Subjects (M: F)	Mean Age (yrs.) (Range)
C- Cotrol (Healthy controls)	0	24 (15:9)	37 ± 9.2 (26-55)
P Li (Pre-lithium) (Disease Controls)	0	11 (7:4)	33.3 ± 11.8 (16-58)
Lithium Treated :			
G-I (Short term Li treatment)	3.8± 1.0 (0.7-6.0)	16 (13:3)	33.7 ±10.2 (16-52)
G-II (Intermediate Li treatment)	29.8±16.0 (7-60)	56 (46:10)	33.8 ± 9.8 (18-58)
G-III (Long term Li treatment)	**138.8 ±56.0 (61-240)**	**41 (29:12)**	**44.6 ± 13.3 (22-75)**

were considered significant when $p < 0.05$. Correlation analysis among different variables was also performed.

Ethics

Informed consent was obtained from all the subjects under study. They were excluded if their age was less than 16 yr or were pregnant. The study protocol was approved by the Ethics Committee of the institute as per the guidelines laid down by Indian Council of Medical Research (ICMR), India.

RESULTS

Thyroid radioiodine uptake (RAIU), T3, T4, T3/T4 ratio, and TSH profiles for control (C), pre-Li (PLi), and Li-treated groups (G-I, G-II, G-III) are presented in Table 2.

The ANOVA test revealed that none of the thyroid parameters studied (i.e., % RAIU, T3, T4, T3/T4 ratio, and TSH) was significantly different among the three Li-treated groups (G-I, G-II, G-III). However, significant differences between different parameters were observed when the values were compared with the C and PLi groups.

A significant increase (Table 2) in RAIU (4 h, 24 h, 48 h) was observed in all the Li-treated groups compared to the C and PLi groups. However, the greatest rise in RAIU (4 h, 24 h, 48 h) was observed in G-I patients. At the pre-Li stage, the RAIU values were significantly lower compared to the C values.

Table 2
Thyroid 4 h, 24 h, and 48 h RAIU, serum T3, T4, T3/T4 ratio, and TSH Profiles in Control, Prelithium and Lithium-Treated Affective Disorder Patients

Group	Mean Age (Yrs.)	Mean Li Duration (Months)	% RAIU			T3 (ng/mL)	T4 (μg/dL)	T3/T4 (ratio)	TSH (μIU/mL)
			4h	24h	48h				
Control (n=24)	37± 9.2 (26-55)	Nil	6.3±2.5	14.4±5.4	15.2±5.8	1.43±0.36	8.2±2.6	0.18±0.05	2.31±0.54
Pre-lithium (n=11)	33.3±11.8 (16-58)	Nil	3.9±1.9^{a}	9.3±5.3^{a2}	10.7±5.0^{a2}	1.62±0.8^{a}	10.2±4.0	0.14±0.05^{a1}	3.0±1.8^{a}
Li Treated G -I (n=16)	33.7±10.2 (16-52)	3.8±1.0 (≤ 6mo)	9.0±4.6^{a1,b1}	20.0±9.0^{a2,b2}	23.2±9.9^{a2,b2}	1.40±0.53	8.8±3.5	0.2±0.1	4.1±1.6^{a,b}
Li Treated G -II (n= 56)	33.8±9.8 (18-58)	29.8±16.0 ≤ 60 mo	7.7±3.7^{a,b1}	18.3±3.0^{a2,b2}	20.1±5.6^{a2,b2}	1.7±0.43	9.5±3.6	0.16±0.1	4.3±2.6^{a1,b}
Li Treated G-III (n= 41)	44.6±13.3 (22-75)	138.8±51.0 ≤ 240 mo	7.4±3.6^{b1}	18.0±7.8^{a2,b2}	19.9±8.1^{a2,b2}	1.3±0.54	8.2±2.5^{b}	0.17±0.12	3.6 ±2.3^{a}

Note: Superscripts a, a1, and a2 represent significance levels when comparing values with the control group. Superscripts b, b1, and b2 represent significance levels when comparing values with the prelithium group. Superscripts a and b: $p < 0.05$; a1 and b1: $p < 0.0005$; a2 and b2: $p < 0.0001$.

The TSH levels increased by 30% ($p < 0.05$) in pre-Li group with respect to the control group. Similarly, TSH also increased significantly in all the three Li-treated groups in comparison with the C and PLi groups, but in G-III (Li duration 61–240 mo), TSH did not differ appreciably from that of the PLi group.

No significant difference in the T3 profile was observed at any duration of Li treatment, and even in PLi group, the levels were comparable with the C group. However, T4 levels declined by 24% ($p < 0.05$) only with Li treatment for 61–240 mo (G-III) when compared with the corresponding values in the PLi group. The T3/T4 ratio was found to be significantly ($p < 0.05$) higher by 30% in G-I (Li treatment ranging from 1 to 6 mo) as compared with the PLi group, whereas in G-II and G-III, the ratio returned to base levels.

At the pre-Li stage, a significant ($p < 0.05$) positive correlation was noticed between the subject's age their serum T3, as well as TSH levels. During Li treatment, a positive correlation ($p < 0.05$) was observed between the patients' age and their serum T4 levels. However, a significantly negative ($p < 0.05$) correlation was seen between the patients' age and serum T3 and TSH levels in G-II.

Thyroidal 24-h %RAIU, serum T3, T4, and the TSH profiles of individual pre-Li and Li-treated patients were also compared with the mean ± 2 SD (standard deviation) values of the control group (Table 3). Accordingly, the patients were designated as having RAIU, T3, T4, and TSH profiles as normal (N), subnormal (<N), and supranormal (>N). In view of this comparison, a significant number (i.e., 3/16 [19%] of patients had higher 24-h RAIU only in G-II (Li duration ranging from 7 to 60 mo]). On the contrary, a higher TSH was observed in a significant number of patients throughout the study duration, including the PLi patients. However, a maximum number of patients (i.e., 24/56 [43%]) had a higher TSH in G-II. Only a nonsignificant number of patients (i.e., 1/11 [9%] and 5/56 [9%]) had a low TSH in the PLi and G-II groups. In a similar comparison, 16% (9/56) had a high T3 in G-II and 17% (7/41) had a high T4 in G-III. In the PLi group, only 1/11 and 2/11 had high T3 and T4, respectively. In totality, from the onset of Li until 20 yr, 43/113 (38%) had a high TSH, 14/113 (12%) had a high T4, and 15/113 (13%) had a high T3 with respect to control mean ± 2 SD values.

The remaining eight patients (6%) belonging to different treatment groups (mean Li duration 32 ± 13 mo) had high TSH levels in the range 15.2–76.0 μIU/mL. The mean TSH, T3, and T4 levels in these patients are given in Table 4. A highly significant ($p = 0.001$) rise in TSH was seen. T3 levels did not differ; however, the levels of T4 declined significantly ($p < 0.005$) from the reference values.

Thyroid clinical assessment revealed that only 4/132 patients were hypothyroid (i.e., these 4 patients had a score of ≥ 19 when assessed by the Waynes Diagnostic index).

Table 3
Number of Patients Classified as Normal (N), Subnormal (<N), and Supranormal (>N) Based on Various Thyroid Functions (RAIU, T3, T4, TSH) in Prelithium and Different Li-Treated Groups as Compared to Control Values (Mean ± 2 SD)

Group	Li Duration (mo)	24 RAIU			T3			T4			TSH		
		N	<N	>N	N	< N	>N	N	<N	>N	N	< N	> N
Pre-lithium (N=11)	–	11 (100%)	0 -	0 -	10 (91%)	0 -	1 (9%)	8 (73%)	1 (9%)	2 (18%)	6 (54%)	1 (9%)	4 (37%)
G -I (N=16)	≤ 6mo	13 (81%)	0	3 (19%)	14 (87%)	0 -	2 (13%)	14 (87%)	0 -	2 (13%)	11 (69%)	0 -	5 (31%)
G - II (n=56)	≤ 60yrs	**45 (91%)**	**2 (4%)**	3 (5%)	45 (80%)	2 (4%)	9 (16%)	51 (91%)	0 -	5 (9%)	27 (48%)	5 (9%)	24 (43%)
G -III (N=41)	≤ 20yrs	38 (93%)	1 (2%)	2 (5%)	35 (85%)	2 (5%)	4 (10%)	32 (78%)	2 (5%)	7 (17%)	27 (66%)	0 -	14 (34%)

Note: Control mean ± 1 SD values for RAIU, serum T3 and T4, and TSH are given in Table 2.

Table 4
Comparison of RAIU and Hormonal Profile in Eight MDP Patients with TSH Levels > 15.2 μIU/mL with the Mean ± SD Values of the Control Group

Mean Age (Yrs.)	Lithium Duration (mo)	RAIU 4h	RAIU 24h	RAIU 48h	T3 (ng/mL)	T4 (μg/dL)	TSH (μIU/mL)
37±9.2 (26-	_	6.3±2.5	14.4±5.4	15.2±5.8	1.4±0.36	8.2±2.5	1.96±9.5
32±13 (16-	63±67 (5-204)	7. 6±2.5 (2.7-10.3)	16.0±7.7 (5.3-27.0)	17.4±7.8 (6.0-29.0)	1.7±1.2 (0.65-	5.3±2.5* (2.4-10.5)	46.6±26.5** (15.2-76.0)

Note: Value in parentheses is the mean ± SD.
*$p < 0.005$.
**$p < 0.001$.

DISCUSSION

In the present cross-sectional study, we evaluated thyroid RAIU and serum T3, T4, and TSH (Table 2) in the control, pre-Li, and in post-Li affective disorder patients who were on Li therapy for time durations ranging between 0.7 and 240 mo. All the Li-treated patients had serum Li levels in the physiological range (i.e., 0.4–1.0 meq/L). This is in agreement with the findings of Maarjberg et al. *(22)*. There is no doubt that Li treatment may induce hypothyroidism as revealed by elevated TSH values. Significant elevation in TSH was observed with Li therapy up to 60 mo but returned to pre-Li levels with the extension of Li treatment for up to 240 mo; however, the TSH levels were still higher than in the control patients. Thus, our study indicates that Li induces TSH secretion from the pituitary as early as ≤ 6 mo and persists for up to 60 mo. In totality, 0.7–240 mo of Li use raised the TSH in 51/113 (39%; Table 3) patients in this series. Many authors *(23-25)* had previously reported elevation in basal TSH in 15–30% of patients following Li therapy for 2–6 yr. A few more studies *(22,26)* have demonstrated that Li therapy results in increased pituitary output of TSH (both basal and after TRH stimulation). However, most of these patients were on concomitant use of Li and other medication (viz. antipsychotics, antidepressants, anticholinergics, and sedative hyponotics). In view of this, the antidopaminergic action of some of these drugs to raise TSH cannot be ruled out *(27)*.

Most of these serial studies have shown a much higher incidence of elevated basal TSH values in women, particularly those over 40 yr of age, but we have not found any positive correlation between sex and age, and sex and TSH. In our study, there was a male preponderance of 3.5 : 1 (103 : 29) and, to the contrary, a significant ($p < 0.05$) negative correlation between age and TSH was seen in patients receiving Li treatment ranging between 7 and 60 mo. The cause for the elevated basal TSH and increased TRH response during Li therapy is debatable, but some evidence depict that TSH elevation seen in Li-treated patients is compensatory and secondary and not the result of a direct Li stimulation *(20)*.

The increase in thyroid RAIU (4 h, 24 h, 48 h) at all the treatment durations was consistent with the corresponding rise in TSH. However, it is still not clear how the Li ion altered the thyroid physiology. The subcellular changes that occur in the hypothalamic–pituitary–thyroid axis remain as elusive as the mechanism underlying Li's therapeutic benefit in affective disorders. It has been speculated that Li may act as a substitute ion effecting membrane transport processes *(20)* and may alter the transport of iodine in some way. Other effects of Li on the thyroid may induce compensation in the pituitary–thyroid axis via an elevated TSH that overcomes any direct effects of Li on iodine concentrating ability, which therefore results in increased uptake in the thyroid *(20)*.

In the present study, T4 declined significantly ($p < 0.05$) in the G-III group and TSH returned to baseline levels when compared with the

corresponding values in the PLi group and the finding is in consonance with other studies *(17,18)* that depicted a significant fall of serum T4 and a rise of TSH, followed by a return toward the pretreatment levels after the first year of Li administration.

The T3/T4 ratio at 0.7–6 mo of Li treatment was higher with respect to the PLi group. We speculate that this increase in ratio might reflect an additional adaptive response of patients to a significant TSH rise/stimulation in the initial 6 mo of Li treatment, as T3 is known to be the more active form of thyroid hormone.

However, when comparing the mean ± SD profiles of T3, no significant difference in the T3 profile was observed at any duration of Li treatment, and even in the pre-Li group, the levels were comparable with the control group. However, when comparing the individual patient's T3 profiles with the control mean ± 2 SD, an increase in the biologically active form of thyroid hormone T3 in 13% of patients was observed. This rise in T3 and a corresponding rise in T4 in 12% of patients and also a rise in RAIU and TSH values in a significant number of patients could be attributed to thyrotoxicosis as a result of Li-induced thyroid autoimmunity. Although we have not measured thyroid microsomes (AbM), the presence of antithyroid antibodies has been documented in many Li-treated patients, which, in turn, indicates the presence of pre-existing chronic autoimmune thyroiditis *(18)*. This effect could cause an increase in absolute iodine uptake and hormone synthesis in the thyroid to counteract any Li-related decrease in fractional hormonal release. Of additional interest is the potential confusion between manic symptoms and those of thyrotoxicosis. Unless thyroid function tests are monitored at the pre-Li stage and then repeated regularly, it is possible that due to similarities in symptoms, some of the patients with thyrotoxicosis could be mislabeled as manic. Li treatment in such patients could possibly control the thyroid hyperfunctioning, because of its prominent potential of causing hypothyroidism *(20)*. Although uncommon, occasional cases of increased thyroid activity and clinical thyrotoxicosis associated with Li use has also been reported *(28,29)*.

Interestingly, 8/132 (6%) patients who belonged to different treatment groups (Table 4) had very high TSH (mean 46.6 ± 26.5 μIU/mL; range 15.2–76.0 μIU/mL), normal T3, and low T4 (mean 5.3 ± 2.5 μg/dL) levels and at least 4 out of these 8 patients (50%) were clinically hypothyroid. Abnormally high TSH in these patients may or may not be the consequence of previously undetected thyroid disorders, as no pre-Li thyroid status was available for this group. However, it is well known that in conditions of iodine deficiency, the serum T3 levels remain normal with the simultaneous and gradual reduction in T4, in order to maintain thyroid iodine economy. This phenomenon could explain the abnormal hormonal profile of this group of patients who were all from the known iodine-deficient district of Ropar Panjab *(30)*. However, after universal salt iodization was enforced, it was difficult to call Ropar dis-

trict an iodine-deficient area (the dietary contents of these individuals for iodine levels were not checked). Therefore, the finding of low T4 and high TSH levels with normal T3 levels could be attributed to exacerbation of pre-existing autoimmune thyroid disease.

In the present cross-sectional study, thyroid functions (viz. thyroid radioiodine uptake [RAIU] and serum T3, T4, and TSH levels were evaluated in 24 healthy controls and 132 affective disorder patients. Eleven of the 132 patients were to receive lithium (Li) and the remaining 121 patients were at different stages of Li treatment ranging from 0.7 to 240 mo. The RAIU was found to increase significantly throughout the Li therapy and was associated with the corresponding rise in TSH levels. In totality, Li treatment induced subclinical hypothyroidism in 51/132 (39%) patients. However, 8/51 patients who belonged to a known iodine-deficient belt had abnormally high TSH (range 15.2–76.0 μIU/mL), low T4 (5.3 ± 2.5 μg /dL) and normal T3 levels and at least 4 of these patients were clinically hypothyroid. The T4 levels declined significantly ($p < 0.05$) with Li treatment ranging from 61 to 240 mo, compared to the corresponding values in the pre-Li group. The T3/T4 ratio was found to be significantly higher with Li treatment ranging from 0.7 to 6 mo in comparison with the pre-Li group and this value returned to base levels after long-term Li therapy. High T3 and T4 levels were observed in 13% and 12% of the patients, respectively, compared to the corresponding control values.

It is thus inferred that a high TSH in affective disorder patients before subjecting them to Li treatment (PLi group) could be attributed to the intake of some antipsychotics (e.g., haloperidol), which has been reported to raise TSH remarkably; however, we have not observed a corresponding rise in RAIU in these patients. After the onset of Li treatment up to 5 yr (i.e., with intermediate Li treatment), a significant rise in TSH was associated with a concomitant increase in RAIU. However, TSH came down to baseline levels of the PLi group with long-term Li treatment. An initial surge in the T3/T4 ratio in the G-I patients' with Li duration up to 6 mo is attributed to the adaptive response of patients to a significant rise in TSH. A significant rise in individual T3 and T4 profiles of G-II and G-III patients when compared with the control ± 2 SD values is assigned to Li-induced thyroid autoimmunity.

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