International Journal of Clinical & Biomedical Research
Vol 11, Issue 1, 2026.

Sumathi Publications
Original Article

Evaluation of Patients on Chronic Lithium Treatment: A Cross-Sectional Study

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Abstract

Lithium remains an essential component of long-term treatment maintenance of the bipolar disorder; however, it is associated with possible endocrine, renal and cardiac adverse events that require close monitoring. The current study aimed to examine the effects of the chronic lithium use on thyroid, glomerular filtration rate, lithium serum levels, and electrocardiographic changes. It was a cross-sectional study that tested 130 long-term lithium patients. The biochemical variables such as serum lithium, creatinine, triiodothyronine (T3), thyroxine (T4) as well as thyroid-stimulating hormone (TSH) were measured. As an assessment of renal functioning, the estimated glomerular filtration rate (eGFR) was evaluated, and electrocardiographic defects were documented. The correlation studies were carried out to reveal the relationships between lithium dose, length of therapy and thyroid parameters. The average serum lithium level was 0.98 ± 0.31 mEq/L. Normal renal function (eGFR > 90mL/min -1.73m2) was seen in the vast majority of patients (93%), and 6.9% of patients had reduced eGFR. The incidence of thyroid dysfunction (both overt and subclinical hypothyroidism) was increased in patients who had higher doses of lithium.ECG abnormalities were observed in 3.8% of participants. A mild positive correlation was noted between lithium dose and T3 levels (p = 0.0423), while other associations were not statistically significant. Chronic lithium therapy was largely safe under therapeutic monitoring, though thyroid dysfunction and mild toxicity were observed in a subset of patients. Regular biochemical and cardiac monitoring remains essential to ensure long-term safety.

KEYWORDS: Lithium therapy; Thyroid dysfunction; Glomerular filtration rate; Electrocardiographic changes.

Introduction

Lithium is still considered as a key mood stabilizer in bipolar disorder both during acute and maintenance therapy due to its proven efficacy both in suppressing manic and depressive episodes and minimizing suicidal behavior [1]. However, the drug has a low therapeutic index, and a close observation of the serum lithium concentration should be combined with the evaluation of end-organ functioning as part of longitudinal follow-up [2]. The chronic use of lithium has consistently been associated with endocrine and renal imbalances with thyroid dysfunction and reduced glomerular filtration rate (GFR) being the most notable effects of the drug use [3,4]. One of the most commonly occurring adverse effects of sustained exposure to lithium is thyroid dysfunction and especially hypothyroidism. The agent is selectively absorbed into thyroid follicular cells and thus prevents the secretion of hormones, resulting in or without clinical (occidental) hypothyroidism as a result of excessive thyroid-stimulating hormone (TSH). The epidemiologic evidence indicates that women and elderly people are at a high risk of lithium-related thyroid pathology [3,5]. Most of the abnormalities of the thyroid are manageable under levothyroxine even when lithium therapy is adhered to provided they are promptly identified [3]. The clinical renal lithium therapy has come under significant clinical examination. There has been a protracted association of lithium use with progressive decline in GFR, development of chronic kidney disease (CKD), and impaired concentrating ability, which

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eISSN: 2395-0471
pISSN: 2521-0394

may result in nephogenic diabetes insipidus, diminished GFR, and tubular dysfunction [4,6]. Despite the fact that the scale of these renal sequelae is different in various studies, empirical data suggests that an increase in serum lithium level, length of treatment, and renal function declines is associated [7]. The need to conduct periodic testing of thyroid and renal indicators and to adjust the dosage based on the serum levels and organ-functional patterns to prevent the negative consequences in the long term is emphasized by the current monitoring protocols [2,8]. Detailed assessment of clinical conditions and comorbidities is also recommended especially when working with older patients or individuals with a pre-existing organ disease to guide specific therapeutic approaches [1,9]. Besides endocrine and renal, it is hypothesized that lithium causes subtle cardiac electrophysiologic changes and sinus bradycardia and small changes in the QT interval observable in electrocardiographies, but probably due to the ability of lithium to alter ion transport mechanisms in cardiomyocytes. These cardiac findings underscore the role of ECG monitoring in the selected patients in the long-term lithium therapy [10]. The current study aims at critically evaluating the functioning of thyroid, estimated GFR, lithium levels in serum, and electrocardiographic measurements in patients under chronic lithium therapy and as a result provides a cross-sectional view of the long-term physiological effects of lithium in normal clinical practice.

Materials and Methods

The cross-sectional study was carried out in the Department of Psychiatry of one of the tertiary teaching hospitals. The ethical approval of the Institutional Ethics Committee was granted before initiation of study. The informed consent from all the subjects was obtained in writing after presentation of the objectives and procedures of the study effectively.

The target group in the study consisted of patients diagnosed with bipolar disorder under the lithium therapy and visiting the psychiatry outpatient and inpatient departments. The study included adult respondents with the age of 18 years and above who had been taking lithium (300 to 600 mg orally 2 to 3 times a day maximum up to 1200 mg per day for long term more than 6months at least . Patients who had a recorded thyroid dysfunction, renal disease or serious heart disease before the commencement of lithium treatment were eliminated. Similarly, subjects who had serious medical comorbidities that could alter the thyroid, renal, or electrocardiographic variables on their own or those who refused to give their consent were not included in the study.

A total of 130 patients that satisfied the inclusion and exclusion criteria were recruited in a consecutive manner. A case record form was used to capture sociodemographic data. Clinical histories were also taken in detail with focus on bipolar illness duration, frequency, and pattern of mood episodes, lithium therapy, total daily lithium doses, history of lithium toxicity, and concomitant psychotropic drugs.

Standardized rating scales were used to measure current mood symptoms. The assessment of depressive symptoms was based on the Hamilton Depression Rating Scale (HAM-D) [11] and the assessment of manic symptoms was based on the Young Mania Rating Scale (YMRS) [12]. The instruments were conducted by trained clinicians so as to provide consistency and reliability of the assessment.

Biochemical parameters that relate to long term lithium therapy were measured, serum lithium levels were checked in order to maintain therapeutic vigilance and prevent the possibility of toxicity. Serum calcium analysis and thyroid functioning tests were done using an automated analyzer [13] to identify an evident or subtle thyroid dysfunction. Renal performance was evaluated with the use of serum creatinine levels and estimation of the glomerular filtration rate (eGFR) by using standard equations [14]. To determine rhythm abnormalities, conduction defects, PR -interval changes, QT -interval changes, T -wave changes, and other cardiac changes that could be attributed to chronic lithium use, electrocardiographic assessment on all subjects was performed and its recording was interpreted by competent physicians and carefully tabulated.

Data in the form of all the collected were inserted into a master database and analyzed with the help of SPSS software. The sociodemographic, clinical, biochemical, and electrocardiographic variables were summarized using descriptive statistics such as mean, standard deviation, frequency, and percentages. A chi-square test and correlation analysis, which are inferential statistical tests, were used to test a relationship between the lithium dose, duration of therapy, serum lithium levels, thyroid function parameter, and the eGFR values. The p-value of 0.05 was taken as significant.

Results

Table 1 is a biochemical profile of the participants who underwent a prolonged lithium treatment. Mean serum lithium level was .98 ± 0.31 mEq/L with the range 0.36–2.00 mEq/L, it showed that most of the patients were within treatment levels. The average serum creatinine was 0.94 ± 0.27mg/dl (range 0.40-2.30) indicating that most subjects have good renal functioning. Thyroid parameters

were with a mean of triiodothyronine (T3) of 1.43 ± 0.47 ng/mL (0.10–2.74), a mean thyroxine (T4) of 7.87 ± 1.87 µg/dL (0.97–12.00), and a mean thyroid-stimulating hormone (TSH) of 3.78 ± 2.19 µIU/mL (1.00–11.00), to indicate a variation that had potential subclinical hypothyroidism in some patients.

Table 1. Biochemical profile of study participants on long-term Lithium therapy (N=130)

Biochemical Parameter	Mean ± SD	Range (Min–Max)
Serum Lithium (mEq/L)	0.98 ± 0.31	0.36–2.00
Serum Calcium (mg/dl)	3.39 ± 3.78	0.30–10.70
Serum Creatinine (mg/dl)	0.94 ± 0.27	0.40–2.30
Serum T3 (ng/ml)	1.43 ± 0.47	0.10–2.74
Serum T4 (microgram/dl)	7.87 ± 1.87	0.97–12.00
Serum TSH (microIU/ml)	3.78 ± 2.19	1.00–11.00

The severity of lithium toxicity among the participants in the study is recorded in Table 2. Twenty-two patients (16.9%) were found to have mild toxicity, 3 (2.3) were found to have moderate toxicity but none had severe toxicity (0), thus suggesting that toxicity was mild in most of the patients.

Table 2. Severity of Lithium Toxicity among Study Participants (N=130)

Severity Level	n (%)
Mild toxicity (Coarse, fine tremors)	22 (16.9)
Moderate toxicity (Urinary incontinence, Dizziness)	3 (2.3)
Severe toxicity (Renal failure, epilepsy, slurring speech)	0

Table 3 shows the changes in electrocardiography and status of renal functioning according to the estimated glomerular filtration rate (eGFR). Most of the subjects, 125 patients (96.2%), had no electrocardiographic changes. QT interval extension and T-wave inversion was observed in 2 and 2 patients respectively (1.5% and 0.8%). ST segment elevation was observed in 1 patient (0.8%). Concerning renal functioning, 121 patients (93.1% of eGFR) had eGFR > 90ml/min-1.73m2 which was decreased in only 9 patients.

Table 3. Electrocardiographic and eGFR Abnormalities among Patients on Long-term Lithium Therapy (N=130)

Variable	Category	n (%)
ECG changes	No changes	125 (96.2)
	QT prolongation	2 (1.5)
	T wave inversion	2 (1.5)
	ST segment elevation	1 (0.8)
eGFR (ml/min/1.73m^2)	<70	9 (6.9)
	>90	121 (93.1)

Table 4 illustrates the relationships among the dosage of lithium, length of treatment and thyroid parameters. A small, but statistically significant, and positive correlation was found between the dosage of lithium and serum T3 concentration (r= 0.1783, p= 0.0423). None of the relationships were found to be significant between the lithium dose and T4 (r -0.0167, p=0.8508), lithium dose and TSH (r=0.0376, p=0.6709), and duration of use and TSH (r= -0.0986, p=0.2642). Serum T3 and TSH had a strong negative correlation (r= -0.3454, p= 0.0001).

Table 4. Correlation between Lithium Dose, Treatment Duration and Thyroid Profile Parameters (N=130)

Variable Pair	Correlation Coefficient (r)	p-value
Lithium dose and serum T3 levels	0.1783	0.0423
Lithium dose and serum T4 levels	-0.0167	0.8508
Lithium dose and TSH levels	0.0376	0.6709
Duration of use and TSH levels	-0.0986	0.2642
Serum T3 levels and TSH levels	-0.3454	0.0001

Table 5 presents the patterns of lithium dosing in terms of total daily dose of lithium and distribution of thyroid dysfunction. Of the patients treated with 300mg/day, 76.9% would remain within normal thyroid levels, 7.7% overt hypothyroidism and 15.4% had subclinical hypothyroidism. With 600mg/day, 91% normal thyroid function, 1.5% overt hypothyroidism and 7.5% subclinical hypothyroidism. Normal thyroid function was seen in 75% of the patients at 900 mg/day, overt hypothyroidism in 8.3% of the patients and subclinical hypothyroidism in 16.7% of the patients, which showed progressive deterioration of thyroid functions with increased doses of lithium.

Table 5. Distribution of Thyroid Dysfunction Based on Total Daily Lithium Dose (N=130)

Lithium Dose (mg/day)	Normal Thyroid Function n (%)	Overt Hypothyroidism n (%)	Subclinical Hypothyroidism n (%)
300	20 (76.9%)	2 (7.7%)	4 (15.4%)
450	1 (100.0%)	0 (0.0%)	0 (0.0%)
600	61 (91.0%)	1 (1.5%)	5 (7.5%)
900	27 (75.0%)	3 (8.3%)	6 (16.7%)

Discussion

The current cross-sectional study explored the renal (estimated glomerular filtration rate (eGFR)) and thyroid dysfunction, lithium levels in serum, and electrocardiographic changes over a long-term period of time in 130 study participants subjected to chronic lithium therapy.

The average serum lithium was 0.98 ± 0.31mEq/L, which is within the recommended therapeutic range, but there were also some cases that attained values approaching the clinically significant toxicity levels. These findings are not inconsistent with the current study, evidence highlighting the thin therapeutic index of lithium and the need of regular monitoring to prevent systemic toxicity [15]. The accumulation

of physiological changes due to chronic lithium exposure has been reported numerous times even with therapeutic doses thus justifying the need of standardized biochemical disease monitoring. One of the most common published endocrine adverse effects of lithium is thyroid dysfunction. The average TSH level in the given study was 3.78 ± 2.19 μIU/mL and it was variable, and the stratification according to the dose showed that there are higher percentages of overt and subclinical hypothyroidism at higher doses (900 mg/day (8.3% and 16.7%, respectively)). Even though the correlation analysis failed to identify any statistically significant correlation between the lithium dose and the level of TSH, a significant positive correlation was found between the lithium dose and the level of T3 ($r = 0.1783$, $p = 0.0423$). Existing literature indicates that lithium disrupts thyroid hormone production and release, causing a compensatory increase in TSH and consequent hypothyroidism especially in the long term [16].

Moreover, risks seem to be affected by dosage, duration of treatment, female gender as well as underlying thyroid autoimmunity. Cohort studies that span long-periods have reported a higher rate of overt and subclinical hypothyroidism in lithium-treated cohorts compared to other mood stabilizers, which support the need to evaluate thyroid levels on a regular basis [17].

The issue of renal safety is still one of the major concerns regarding chronic lithium use. In this study, 93.1% of the participants had an eGFR that was >90ml/min/1.73m2, and the rest, 6.9% of the participants had a lower eGFR (<70ml/min/1.73m2). Further, the average serum creatinine level was within normal values (0.94 ± 0.27 mg/dL). These data shows that renal function is retained in most of the patients despite long-term lithium administration. However, recent researches have shown that lithium-related nephropathy tends to be progressive and insidious with the development of a gradual decrease in GFR over years instead of acute renal failure [18].

The statistically nonsignificant correlation between lithium dose and decreased eGFR ($p=0.36$) is consistent with the findings that cumulative time of exposure and frequent toxic events could have a greater impact on the deterioration of renal function than the magnitude of a single dose. Electrocardiographic analysis revealed that 96.2% of the respondents had no identifiable abnormalities with isolated cases of QT prolongation (1.5%), T inversion (1.5%), and ST elevation (0.8%). Such findings are indicative of a relatively low rate of clinically significant cardiac conduction disturbances in stable, monitored therapy patients.

However, lithium has been linked to sinus node dysfunction, QT interval increase, and other conduction abnormalities, especially when the serum levels are high or when the drug is taken in patients, whose cardiac health is already predisposed [19]. The limited incidence in this case could also be due to the presence of effective therapeutic surveillance as well as the exclusion of the severely cardiac comorbidity systematically. Notably, mild death of lithium was reported in 16.9% of the participants and moderate lithium toxicity in 2.3% cases without any extreme cases of lithium toxicity. This trend becomes evidence of the idea that even therapeutic lithium concentration can be connected with the mild neurological or systemic negative events.

Altogether, this research finding are in line with modern evidence, which states that lithium is still an effective mood stabilizer, and that the systemic effects are manageable provided that they are carefully controlled. Although severe thyroid dysfunction and renal dysfunction were only seen in the minority of the subjects, the presence of biochemical variability highlights the importance of a risk assessment and planned long-term follow-up that needs to be conducted individually.

Conclusion

Chronic lithium treatment in the current cohort was found to considerably prevent renal dysfunction, cause few electrocardiographic changes and sustain therapeutic serum Lithium levels in most participants. However, some of them expressed thyroid dysfunction and mild toxicity, which highlights the importance of systematic observation of thyroid, renal, and cardiac conditions. The lack of strong dose-dependent relationships between renal or thyroid indexes, however, nuanced biochemical relationships indicate that long-term surveillance cannot be abandoned to guarantee patient safety and maximize treatment effects in patients receiving maintenance lithium treatment.

Source of Funding: There was no external funding for this study.

Conflict of Interest: The authors declare no conflicts of interest.

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