

## **Background**

Lithium is an established treatment in patients with bipolar disorders. The toxic and therapeutic blood levels of this agent are very close to one another. Additionally lithium is known to cause alterations in various organ functions, thus it merits a regular monitoring. Among these, alteration in thyroid status induced by lithium treatment is important in the clinical evaluation of neuropsychiatric effects [1] e.g. fatigue ,memory impairment, and anhedonya.

The antithyroid actions of lithium were first investigated in patients with psychiatric disorder treated with lithium carbonate, who developed hypothyroidism and goiter. It was subsequently revealed that lithium increases intrathyroidal iodine content, inhibits the coupling of iodothyrosine residues to form iodothyronines [2-4] and inhibits secretion of T4 and T3 [3-5]. Since these side effects may be manifested when plasma levels are within normal range, the use of plasma level alone for monitoring maybe misleading.

Attention has been given to the significance of intracellular concentrations of lithium ion in patients treated with this drug, because of easily access to erythrocytes and the resemblance of this cell to other cells such as neurons [6]. Lithium ratio (LR) is expressed as the ratio of erythrocyte lithium concentration (ELC) to plasma lithium concentration (PLC). It has been suggested that lithium side effects are more related to ELC than to PLC [7,8].

Except a few reports, the relationship between LR and thyroid abnormalities in bipolar patients has, to our knowledge, never been reported. We performed this study to see if LR could be a better correlate of lithium-induced thyroid abnormalities. If so, the request for thyroid function tests (TFT), physical examinations and consequently the cost of thyroid monitoring would decrease.

Since plasma lithium concentrations are being measured in patients receiving lithium it would be easy to measure ELC simultaneously.

Any possible relationship between Lithium ratio (LR) and thyroid side effects was visited in this study.

## **Methods**

### **Patient selection**

A step toward selecting patients was inclusion bipolar patients who were admitted in Roozbeh mental health hospital and did not use any drug affecting thyroid or TFT. None of them gave a history of thyroid disorder before the first exposure to lithium. Patients with no significant difference in lithium dosage and drug regimen other than lithium were selected. Pregnant women were excluded of the study.

### **Sampling**

Samples for lithium determination were taken at 9 a.m. at least 11 hours after the last dose, since the erythrocyte/plasma ratio and the plasma level change only minimally after this interval [9].

### **Data collection**

Data regarding variables in table 1 were collected.

### **Thyroid evaluation**

The thyroid size was evaluated by an experienced endocrinologist through palpation. Thyroid function tests (TFT) consisted of T3RU, TT4, FT3, and TSH determined by radioimmunoassay.

### **Assay of Lithium**

The concentration of intracellular lithium was determined according to the direct method of Summerton [10]. Twice distilled water was added to the resulting solutions of plasma and erythrocyte and the mixture was introduced to the graphite furnace (GBC 932 AA, Australia). To provide reproducible results with acceptable sensitivity and accuracy, conditions used by Decosterd et al. were applied. Samples of RBC extracts and plasma obtained from not lithium treated patients were used for calibration, processed as the main samples and stored the same as them at - 70°C. They were used to establish calibration curves and as internal quality control samples during the assay. They were also analyzed whenever intra-assay variations were doubted and on the beginning of every different days [11]. The instrument was allowed to warm up at least 30 minutes before each daily run.

All measurements were made in duplicate to detect variability associated with the procedure.

### **Statistical analysis**

Statistical analyses were performed using SPSS® for Windows™, release 10.0. Data obtained were analyzed using unpaired t tests and Fisher's exact tests. Also a logistic regression analysis was performed to find out any relationship between possible covariates and the probability of thyroid abnormality occurrence. A 95% confidence limit was used as significance level.

### **Results**

After giving informed consent, 68 patients with bipolar mood disorder (BMD) symptoms (25 females, and 43 males with the mean age of  $34 \pm 10.97$ ) entered the study and were re-diagnosed according to DSM IV criteria. Of the 68 patients, 14 were assigned to the group with abnormal thyroid function or/and size. The rate of each thyroid abnormality is demonstrated in figure 1.

The result of t test analysis shows a significant decrease in the LR among patients with thyroid abnormality compared with the normal thyroid group (table 1). Because data due to duration of lithium therapy was not complete and reliable, it was omitted from the last analysis.

Eligible variables (Sex, FH, ELC, and LR) were selected for logistic regression analysis ( $P < 0.1$ ).

61 cases included in the analysis. Thyroid involvement was 5.9 times more in females (OR= 5.89, 95% CI= 1.57 ~ 22.00). The rest were not significant in the ultimate analysis.

### **Discussion**

Inconsistencies exist among different research groups about the relationship between lithium side effects and LR. There are reports of higher LRs in patients with lithium side effects [12, 13]. In contrast, other reports show higher LRs in those free of lithium side-effects [14, 15]. Kamp failed to find any correlation between the concentration of lithium in erythrocytes and the side effects of lithium [16].

Rybakowski et al. reported higher activity of lithium sodium counter-transport (LSC) in patients with higher TSH [17]. The result of the present study is partly in accordance with those of Johnston who found a lower LR in patients with side effects including hypothyroidism.

Discrepancies observed may be due to different method of assay used, different design of study, definitions of thyroid disorder, and patient selection. In this study, a direct method of lithium determination in erythrocytes was applied. This method is much more accurate and less variable compared to the indirect method of lithium determination [15]. It has been observed that LR is different in various types of psychiatric disorders [18,19,20] and also LR may differ during episode and during maintenance therapy [21,22,23]. We included only bipolar in-patients unlike other studies which included patients at different phases of the disease [12,13,16].

These conflicting results might also be partially due to the methods of analysis applied in this study i.e. logistic regression. Although lower LRs were found in patients with abnormal thyroid when data was analyzed using t Test, this was not confirmed in the final analysis, using multiple logistic regression.

Absence of difference between PLCs in the two groups demonstrates the invalidity of its use to detect lithium-induced thyroidal side effects.

Unless all the factors which govern the concentration of lithium in RBC are introduced, it remains unclear whether LR could be used as a diagnostic tool or a predictor for developing lithium-induced thyroid disorders.

Previous investigations have reported a higher incidence of lithium-induced thyroid abnormalities in women [24, 25, 26, 27] which is in agreement with our finding. In contrast, there are studies suggesting that thyroid problems in lithium treated patients is not related to gender[28,29].

## **Conclusion**

We suggest that monitoring of thyroid function or size should take into account patient's gender, and that being a female could be a risk factor to develop thyroid abnormalities.

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FE: Consultant for thyroid function assessment

HF: Co-supervisor for instrumental analysis

ARD: Designer of the study (main supervisor)

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## **References**

1. Kleiner J, Altshuler L, Hendrick V, Hershman JM: **Lithium-induced subclinical hypothyroidism: Review of the literature and guideline for treatment.** *J Clin Psychiatry* 1999, **60** (4): 249-255

2. Bagchi N, Brown TR, Mack RE: **Studies of the mechanism of inhibition of thyroid function by lithium.** *Biochim Biophys Acta* 1997, **542**: 163
3. Berens SC, Bernstein RS, Robbins J, Wolff J: **Antithyroid effects of lithium.** *J Clin Invest* 1970, **49**: 1357
4. Burrow GN, Burke WR, Himmelhoch JM, et al.: **Effects of lithium on thyroid function.** *J Clin Endocrinol Metab* 1971, **32**: 647
5. Spaulding SW, Burrow GN, Bermudez F, Himmelhoch JM: **The inhibitory effect of lithium on thyroid hormone release in both euthyroid and thyrotoxic patients.** *J Clin Endocrinol Metab* 1972, **35**: 905
6. Rybakowski JK: **Lithium in erythrocyte: Pathogenetic and clinical significance.** *Lithium* 1990, **1**: 75-85
7. Elizur A, Shopsin B, Gershon S, Ehlenberger A: **Intra: extracellular lithium ratios and clinical course in affective states.** *Clinical Pharmacology and Therapeutics* 1972, **18**: 947- 952.
8. Zakowska-Dabrowska T, Rybakowski J: **Lithium-induced EEG changes: Relation to lithium levels in serum and red blood cells.** *Acta Psychiatrica Scandinavica* 1973, **49**: 457-465
9. Lee CR, Hill SE, Dimitrakoudi M, Jenner FA, Pollitt RJ: **The relationship of plasma to erythrocyte lithium levels in patients taking lithium carbonate.** *Brit J Psychiatry* 1975, **127**: 296-298
10. Summerton AM, Harvey NS, Forrest RW: **New direct method for measuring red cell lithium.** *J Clin Pathol* 1989, **42**: 435-437
11. Decosterd LA, Buclin T, Dafflon M, Leeman C, Belaz N, Magnin JL, Biollaz J: **Determination of trace lithium in human erythrocytes by electro-thermal atomic-absorption spectrometry with pyrocoated graphite tubes and integrated platform.** *J Pharm Pharmacol* 1998, **50**: 693-701

12. Elizur A, Yeret A, Segal Z, GraffE: **Lithium and electrolytes plasma RBC ratio and paradoxical lithium neurotoxicity.** *Prog Neuropsychopharmacol & Biol Psychiat* 1982, **6**: 235-241
13. De Maio D, Buffa G, Riva M, Laviani M, Levi-Minzi A: **Lithium ratio, phospholipids and the incidence of side effects.** *Prog Neuropsychopharmacol & Biol Psychiat* 1994, **18**: 285-293
14. Johnston BB, Dick EG, Naylor GJ, Dick DAT: **Lithium side effects in a routine lithium clinic.** *Brit J Psychiat* 1979, **134**: 482-487
15. Dehpour AR, Emamian ES, Ahmadi-Abhari SA, Azizabadi-Farahani M: **The lithium ratio and the incidence of side effects.** *Prog Neuropsychopharmacol & Biol Psychiat* 1998, **22**: 959-970
16. Kamp Johnnis S, Oey Mirjam S, Leijnseybema Henry J, Most Eric VD, Van Dort- Starn Yvonne: **The lithium index in a one-year follow-up.** *Prog Neuropsychopharmacol & Biol Psychiat* 1995, **19**: 47-57
17. Rybakowski JK, Amsterdam JD, Dyson WL, Frazer A, Winokur A, Kurtz J: **Factors contributing to erythrocyte lithium-sodium counter-transport activity in lithium-treated bipolar patients.**
18. Rybakowski J, Frazer A, Mendels J, Ramsey TA: **Erythrocyte accumulation of lithium ion in control subjects and patients with primary affective disorder.** *Communication Psychopharmacol* 1978, **2**: 99-104
19. Szentisvanyi I, Janka Z: **Correlation between the lithium ratio and Na- dependant lithium transport red blood cells during lithium prophylaxis.** *Biol Psychiat* 1979, **14**: 973- 977
20. Rihmer Z, Arato M, Szentistvanyi I, Banki CM: **Red blood cell/plasma lithium ratio in manic depressive, schizoffective and schizophrenic patients.** *Psychiat Clin* 1983, **16**: 405-410

21. Kim YB, Dunner DL, Meltzer HL, Fieve RR: **Lithium erythrocyte: plasma ratio in primary affective disorder.** *Comp Psychiat* 1978, **19**:129-134
- 22: Elizur A, Treves I: **Interdependency of lithium ratio, plasma lithium level and clinical state in patient with affective disorder.** *Prog Neuropsychopharmacol & Biol Psychiat* 1985; **9**: 167-172.
23. Rybakowski J: **Lithium in erythrocytes: Pathogenetic and clinical significance.** *Lithium* 1990, **1**: 75-85
24. Cowdry R, Wehr T, Zis A, Goodwin F: **Thyroid abnormalities associated with rapid cycling bipolar illness.** *Arch Gen. Psychiatry* 1983, **40**: 414-420
25. Yassa R, Saundes A, Nastase C, Camille Y: **Lithium-induced thyroid disorders: A prevalence study.** *J Clin Psychiatry.* 1988, **49**:14-16
26. Maarbjerg K, Vestergaard P, Schou M: **Changes in serum thyroxin (T4) and serum thyroid stimulating hormone (TSH) during prolonged lithium treatment.** *Acta Psychiatr Scand* 1987, **75**: 217-221
27. Vincent A, Baruch P, Vincent P: **Early onset of lithium associated hypothyroidism.** *Psychiatry Neurosci* 1993, **18**: 74-77
28. Perrild H, Hegedus L, Baastrup PC, Kayser L, Kestberg S: **Thyroid function and ultrasonically determined thyroid size in patients receiving long-term lithium treatment** *Am J Psychiatry* 1990, **147** (11): 1518-1521
29. Valle J, Ayuso-Gutierrez JL, Abril A, Ayuso-Mateos JL: **Evaluation of thyroid function in lithium-naive bipolar patients.** *Eur Psychiatry* 1999, **14**(6): 341-345

Table 1. Comparing variables in normal thyroid with abnormal thyroid group.

Variables	Normal thyroid group	Abnormal thyroid group	Sig.
Age(yr <sup>a</sup> )	33.78 ± 10.62	35.62 ± 12.86	P>0.05
Admission <sup>b</sup> (n)	3.64 ± 3.40	3.30 ± 2.42	P>0.05
Lithium carbonate dose (mg/d)	1114 ± 263	1157 ± 189	P> 0.05
Duration <sup>c</sup>	8.31 ± 8.34	13.35 ± 11.84	P=0.188
PLC <sup>d</sup> (mmol/l )	0.50 ± 0.24	0.47 ± 0.19	P>0.05
ELC <sup>e</sup> (mmol/l)	0.24 ± 0.17	0.15 ± 0.10	P =0.021
LR <sup>f</sup>	0.51 ± 0.26	0.34 ± 0.18	P = 0.029
FH <sup>h</sup>	+ 21	+ 3	P= 0.037
	- 25	- 11	
Sex	Female 15	Female 10	P= 0.005
	Male 38	Male 4	

Plus-minus values are means ± SD

a-yr = year

b-admission = number of hospital admission for psychiatric problems

c-Duration =Length of lithium therapy

d-PLC= Plasma Lithium Concentration

e-ELC =Erythrocyte Lithium Concentration

f-LR = ELC/PLC

g-FH =Family history of affective disorder in first degree relatives

**Title: Risk factors of thyroid abnormalities in bipolar patients receiving lithium: a case control study.**

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## **Abstract**

**Background:** Thyroid abnormalities related lithium therapy is a documented subject. These side effects may be manifested despite normal plasma lithium levels. The objective of this study was to meet if erythrocyte: plasma lithium ratio differs among patients with thyroid disorders accompanying lithium treatment. Also to find risk factors for developing thyroid abnormalities in bipolar lithium treated patients.

**Methods:** 68 bipolar patients receiving lithium therapy enrolled a cross-sectional evaluation of thyroid function test, and thyroid size. Erythrocyte lithium concentrations and plasma lithium concentrations were determined by atomic absorption spectrometry. **Results & conclusions:** No significant differences were found between age, positive family history of affective disorder, plasma lithium concentration, Erythrocyte lithium concentration, and lithium ratio comparing the two groups. Thyroid involvement was significantly higher in women than in men ( $P < 0.05$ ). We suggest more frequent thyroid evaluation of bipolar women on lithium therapy.

Goiter	7
Hypothyroid	5
Goiter+Hyp	1
Subclinical	1
Normal thy	53

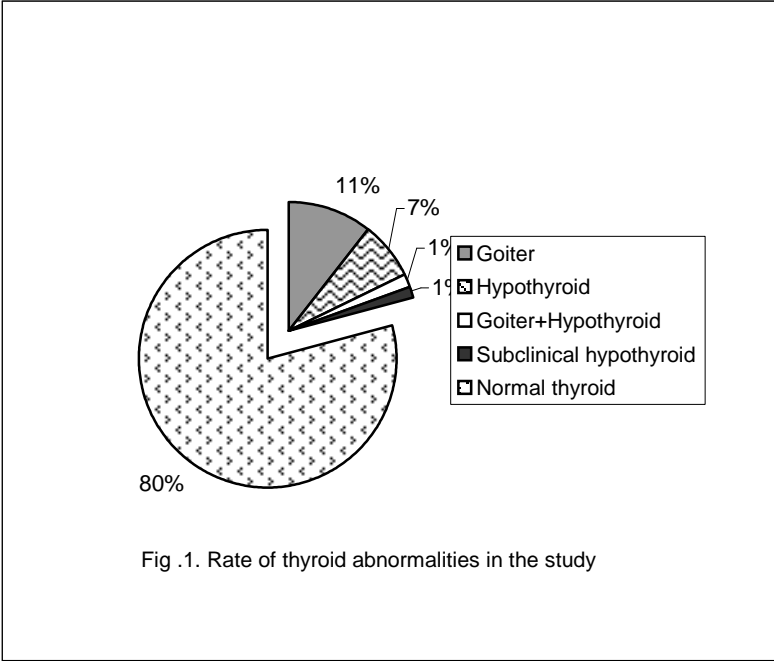


Figure 1