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 anhedonia.

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. There 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 ± 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 LR in patients with lithium side effects [12, 13]. In contrast, other reports show higher LR 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.
Author Contributions:


SAAB: Consultant for psychological assessment (main supervisor)
PG: Coordinator and supervisor
FF: PhD student (main performer)
FE: Consultant for thyroid function assessment
HF: Co-supervisor for instrumental analysis
ARD: Designer of the study (main supervisor)
IJ: Assistant for instrumental analysis
ZNH: Statistician (consultant)
SD: PhD student (for PhD thesis)

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

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

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.
Figure 1. Rate of thyroid abnormalities in the study

- Goiter: 7
- Hypothyroid: 5
- Goiter + Hypothyroid: 1
- Subclinical hypothyroid: 1
- Normal thyroid: 53