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This is the author's manuscript

Original Citation:

Availability:
This version is available http://hdl.handle.net/2318/136166 since 2016-07-05T16:31:37Z

Published version:
DOI:10.1016/j.jad.2013.06.046

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*Journal of Affective Disorders* 151 (2) 2013; 786–790

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Lithium-associated hyperparathyroidism and hypercalcaemia: A case-control cross-sectional study

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Abstract

Background. Lithium is recommended as a first-line treatment for Bipolar Disorder (BD). Thyroid and renal alterations are well known lithium side-effects, while effects on parathyroids are less studied. The aim of this case-control cross-sectional study is to compare parathyroid hormone (PTH) and calcium levels in lithium-exposed bipolar patients and in subjects who had never been exposed to lithium.

Methods. 112 BD patients were enrolled, 58 on lithium since at least 1 month (mean exposure 60.8±74.8 months) and 54 in the control group. Blood exams included complete blood count, PTH, total and ionized calcium, TSH, T3 and T4, creatinine, urea, sodium and potassium, and lithium serum levels. The Student's t-test and the Pearson's Chi-square test were used for bivariate analyses. A linear regression model was used to analyze the relationship between the duration of exposure to lithium and PTH and calcium levels.

Results. PTH and ionized calcium levels were significantly higher in lithium-exposed patients; the proportions of subjects with hyperparathyroidism (8.6%) and hypercalcaemia (24.1%) were significantly greater in lithium-exposed patients. The linear regression analyses showed a significant effect of exposure to lithium in months on ionized calcium levels but not on PTH levels.

Limitations. Given the cross-sectional design of the study we could not identify the exact time of occurrence of hyperparathyroidism.

Conclusions. Our results indicate that lithium-associated stimulation of parathyroid function is more common than assumed to date. Among parameters to be evaluated prior to lithium implementation and during long-term lithium maintenance, calcium (and eventually PTH) should be added.

Keywords: Lithium; Bipolar disorder; Hyperparathyroidism; Calcium.
1. Introduction

Lithium is recommended by all treatment guidelines for Bipolar Disorder (BD) as a first-line maintenance treatment (APA, 2002; NICE, 2006; Goodwin and the Consensus Group of the British Association for Psychopharmacology, 2009, Grunze et al., 2004, Grunze et al., 2009, Yatham et al., 2005, Yatham et al., 2006, Yatham et al., 2009 and Yatham et al., 2013) and recent trial data have definitely established the efficacy of lithium in the prophylaxis of BD (Geddes et al., 2010). However, the potential side-effects and risks associated with long-term lithium use may at times make the implementation of these recommendations in daily practice challenging.

The most commonly reported adverse effects associated with long-term lithium treatment are clinical hypothyroidism and reduced urinary concentrating ability (Malhi et al., 2012 and McKnight et al., 2012).

Less attention has been devoted to alterations in calcium metabolism potentially associated with long-term lithium treatment. Lithium has been associated with hypercalcaemia and hyperparathyroidism; various hypotheses on the underlying mechanism of hyperparathyroidism have been proposed: increased threshold of the calcium-sensing receptor within the parathyroid gland, increase of the parathyroid hormone, decrease of the intracellular calcium uptake, inhibition of action of glycogensynthase kinase 3b and reduction of PTH gene transcription (Szalat et al., 2009). Rates of lithium-associated hyperparathyroidism vary from 2.7% in one study (Bendz et al., 1996) to 23.2% in another (Kallner and Petterson, 1995). Discrepancies depend on definitions used, for example surgically-verified hyperparathyroidism in the study of Bendz (Bendz et al., 1996) versus proportion of subjects with PTH levels greater than 55 ng/L in the study of Kallner (Kallner and Petterson, 1995). Another source of discrepancy is the different length of exposure to lithium in different samples: some studies included only subjects who had been on lithium since a minimum of 15 years (Bendz et al., 1996), while others included patients on lithium without specifying the minimum duration of exposure (1–32 years in a different study – Kusalic and Engelsmann, 1999). Rates of subjects with hypercalcaemia also vary considerably across different studies; when total serum calcium was measured, rates of hypercalcaemia were comprised between 3.6% (persistent hypercalcaemia – Bendz et al., 1996) and 7.2% (Colt et al., 1981); when ionized calcium was measured, rates increased to 25–42.3% (Kallner and Petterson, 1995; Toffaletti et al., 1979 and Nordenstrom et al., 1994). The exact prevalence of lithium-associated alterations in calcium metabolism is then to be further determined.

Another issue to be further elucidated is whether there is a cumulative linear increased incidence of lithium-associated hypercalcaemia or hyperparathyroidism. Occurrence of hypercalcaemia was described in single case reports after a period as short as 1 day (Rothman, 1982), overt hyperparathyroidism after a period of treatment as short as 1–2 months (Shen and Sherrard, 1982). A two-year prospective longitudinal study showed a linear progressive increase in PTH levels, with an increase evident after 1 month from beginning of the treatment although the difference became statistically significant only after 6 months (Mak et al., 1998). It is also unknown whether lithium dose is related to PTH or calcium levels.

Hyperparathyroidism is associated with increased admissions for nonfatal cardiovascular disease, renal failure, renal stones, fractures, hypertension, cancer and diabetes; the investigation of long-term consequences of lithium on parathyroid function is then relevant for clinical practice.

The aim of the present case-control cross-sectional study is to compare PTH and calcium levels in lithium-exposed bipolar patients and in subjects who had never been exposed to lithium. A secondary objective of the study is to compare thyroid and renal function in the two groups.
2. Methods

2.1. Subjects

Participants were 112 patients with a primary diagnosis of DSM-IV Bipolar Disorder I or II. Subjects included were inpatients and outpatients consecutively referred to the Department of Neuroscience of the University of Turin (Italy); they were at least 18 years of age and willing to voluntarily participate in the study. The aims of the study as well as study procedures were thoroughly explained to potential participants who gave written consent before participation. The study design was reviewed by the local ethics committee.

Patients had to be in continuous lithium therapy for at least one month; plasma lithium levels should be between 0.5 and 1.2 mmol/L. The decision to set the minimum duration of the treatment with lithium at one month is due to the evidence of an increase in parathyroid hormone (PTH) levels after only one month of exposure to lithium (Mak et al., 1998). To be enrolled in the control group, patients had to have never been exposed to lithium in their life. A current or previous diagnosis of renal failure, serum creatinine value >1.5 mg/dL, use of diuretics or medications known to impair vitamin D metabolism, and/or preexisting disorders of calcium homeostasis were considered exclusion criteria.

2.2. Assessments and procedures

Data were obtained from each subject by a semi-structured interview with a format that covered the following areas: (a) socio-demographic data; (b) diagnoses (current and lifetime) were performed by clinicians with at least four years of postgraduate clinical experience by means of the SCID-I; (c) clinical data; (d) Young Mania Rating Scale (YMRS), 17-item Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), and Clinical Global Impression Scale—Severity of Illness.

Use of medications at the time of interview was assessed; moreover, lifetime exposure to mood stabilizers was recorded by means of direct interview, family members’ interview (when available) and medical records review.

A blood draw for routine blood exam was performed at hospital admission for inpatients, as a part of the clinical management routine. For outpatients, patients were scheduled for a blood test within a week from the study visit. At the time when blood was drawn, patients were fasting for the previous 10 h. Blood exams included complete blood count, parathyroid hormone (PTH), total and ionized calcium, thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4), creatinine, urea, sodium and potassium, and lithium serum levels.

2.3. Statistical analysis

For statistical purposes, the sample was divided in two groups: the first one included subjects on lithium treatment for at least one month (cases), the second patients who had been never exposed to lithium (controls). The Student's t-test and the Pearson's Chi-square test were used for bivariate analyses: continuous variables were compared using the unpaired Student's t-test for two-class comparisons, categorical variables using the Pearson's chi-square test. Lastly, a linear regression model was used to analyze the relationship between the duration of exposure to lithium (months of lifetime exposure) and PTH and calcium levels.
3. Results

One hundred-twelve patients were enrolled: 58 were on lithium since at least one month (median: 36.0 months) and 54 had never been exposed to lithium. Table 1 shows socio-demographic and clinical characteristics of subjects included; no differences were detected between the two groups. Patients on lithium were taking a mean of 731.9±208.5 mg/die of lithium.

Table 1. Socio-demographic and clinical characteristics of patients included.

<table>
<thead>
<tr>
<th></th>
<th>Lithium-exposed (N=58)</th>
<th>Controls (N=54)</th>
<th>t/χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual age (years) (Mean±SD)</td>
<td>50.6±15.3</td>
<td>48.3±16.0</td>
<td>−0.781</td>
<td>0.436</td>
</tr>
<tr>
<td>Gender (males), N (%)</td>
<td>17 (29.3)</td>
<td>24 (44.4)</td>
<td>2.760</td>
<td>0.097</td>
</tr>
<tr>
<td>Educational level (years) (Mean±SD)</td>
<td>12.0±4.3</td>
<td>12.3±4.4</td>
<td>0.336</td>
<td>0.737</td>
</tr>
<tr>
<td>Marital status, N (%)</td>
<td></td>
<td></td>
<td>1.001</td>
<td>0.801</td>
</tr>
<tr>
<td>Married</td>
<td>30 (51.7)</td>
<td>30 (55.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>6 (10.3)</td>
<td>3 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>18 (31.0)</td>
<td>18 (33.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>4 (6.9)</td>
<td>3 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently working, N (%)</td>
<td>29 (50.0)</td>
<td>30 (55.6)</td>
<td>0.346</td>
<td>0.556</td>
</tr>
<tr>
<td>Bipolar disorder, N (%)</td>
<td></td>
<td></td>
<td>1.211</td>
<td>0.271</td>
</tr>
<tr>
<td>Type I</td>
<td>35 (60.3)</td>
<td>27 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>23 (39.7)</td>
<td>27 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset (years) (Mean±SD)</td>
<td>28.6±9.8</td>
<td>29.6±11.8</td>
<td>0.484</td>
<td>0.629</td>
</tr>
<tr>
<td>Total number of episodes (Mean±SD)</td>
<td>7.1±3.8</td>
<td>6.4±3.7</td>
<td>−0.973</td>
<td>0.333</td>
</tr>
<tr>
<td>Duration of illness (years) (Mean±SD)</td>
<td>21.8±13.2</td>
<td>18.6±13.0</td>
<td>−1.290</td>
<td>0.200</td>
</tr>
<tr>
<td>Duration of lithium treatment (months) (Mean±SD)</td>
<td>60.8±74.8</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Blood lithium levels (mmol/L)</td>
<td>0.71±0.13</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BMI (Mean±SD)</td>
<td>25.1±3.9</td>
<td>25.7±5.3</td>
<td>0.697</td>
<td>0.487</td>
</tr>
<tr>
<td>YMRS (Mean±SD)</td>
<td>8.0±10.3</td>
<td>5.7±8.0</td>
<td>−1.290</td>
<td>0.200</td>
</tr>
<tr>
<td>HAM-D (Mean±SD)</td>
<td>11.0±8.3</td>
<td>11.6±7.1</td>
<td>0.427</td>
<td>0.670</td>
</tr>
<tr>
<td>HAM-A (Mean±SD)</td>
<td>7.7±4.9</td>
<td>8.0±4.3</td>
<td>0.398</td>
<td>0.691</td>
</tr>
<tr>
<td>CGI-S (Mean±SD)</td>
<td>4.3±1.8</td>
<td>4.3±4.9</td>
<td>−0.110</td>
<td>0.913</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index; YMRS: Young Mania Rating Scale; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; CGI-S: Clinical Global Impression Scale-Severity of Illness.

Parameters relating to calcium metabolism are reported in Table 2: a statistical significant difference between the two groups emerged for PTH levels (higher in lithium-exposed patients), for ionized calcium levels (higher in lithium-exposed patients), for the proportion of subjects with hyperparathyroidism (greater in lithium-exposed patients) and hypercalcaemia (ionized calcium, greater in lithium-exposed patients).
Table 2. Serum PTH and calcium levels.

<table>
<thead>
<tr>
<th></th>
<th>Lithium-exposed (N=58)</th>
<th>Controls (N=54)</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/mL) (Mean±SD) Range: 15–65 pg/mL</td>
<td>43.85±16.44</td>
<td>29.39±12.09</td>
<td>-5.272</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperparathyroidism (PTH&gt;65 pg/mL), N (%)</td>
<td>5 (8.6)</td>
<td>0 (0.0)</td>
<td>4.873</td>
<td>0.027</td>
</tr>
<tr>
<td>Total calcium (mmol/L) (Mean±SD) Range: 2.20–2.60 mmol/L</td>
<td>2.35±0.13</td>
<td>2.34±0.21</td>
<td>-0.368</td>
<td>0.713</td>
</tr>
<tr>
<td>Hypercalcaemia (total calcium&gt;2.60 mmol/L), N (%)</td>
<td>1 (1.7)</td>
<td>1 (1.9)</td>
<td>0.003</td>
<td>0.959</td>
</tr>
<tr>
<td>Ionized calcium (mmol/L) (Mean±SD) Range: 1.10–1.32 mmol/L</td>
<td>1.25±0.10</td>
<td>1.15±0.10</td>
<td>-5.071</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercalcaemia (ionized calcium&gt;1.32 mmol/L), N (%)</td>
<td>14 (24.1)</td>
<td>3 (5.6)</td>
<td>7.500</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Table 2: Serum PTH and calcium levels.

Table 3 shows thyroid and renal function parameters in the two groups; lithium-exposed patients showed higher rates of clinical hypothyroidism (29.3% of patients in the lithium group versus 11.1% in the control group) and lower fT4 levels. No other statistically significant differences emerged.

Table 3. Thyroid and renal function parameters.

<table>
<thead>
<tr>
<th></th>
<th>Lithium-exposed (N=58)</th>
<th>Controls (N=54)</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical hypothyroidism, N (%) Patients with replacement therapy or TSH&gt;4.2 µUI/mL and fT3&lt;2.6 pg/mL</td>
<td>17 (29.3)</td>
<td>6 (11.1)</td>
<td>5.676</td>
<td>0.017</td>
</tr>
<tr>
<td>Subclinical hypothyroidism, N (%) TSH&gt;4.2 µUI/mL and normal fT3 fT4</td>
<td>2/41 (4.9)</td>
<td>3/48 (6.2)</td>
<td>0.078</td>
<td>0.779</td>
</tr>
<tr>
<td>TSH (µUI/L) (Mean±SD) Range: 0.27–4.2 µUI/mL</td>
<td>2.32±1.65</td>
<td>2.27±2.17</td>
<td>-0.139</td>
<td>0.890</td>
</tr>
<tr>
<td>fT3 (pg/mL) (Mean±SD) Range: 2.6–4.4 pg/mL</td>
<td>2.92±0.60</td>
<td>3.09±0.60</td>
<td>1.476</td>
<td>0.143</td>
</tr>
<tr>
<td>fT4 (pg/mL) (Mean±SD) Range: 9.3–17 pg/mL</td>
<td>11.30±3.06</td>
<td>12.49±2.20</td>
<td>2.311</td>
<td>0.023</td>
</tr>
<tr>
<td>Creatinine (mg/dL) (Mean±SD) Range: 0.5–1.5 mg/dL</td>
<td>0.81±0.17</td>
<td>0.83±0.17</td>
<td>-0.630</td>
<td>0.530</td>
</tr>
<tr>
<td>Urea (mg/dL) (Mean±SD) Range: 10–50 mg/dL</td>
<td>31.67±9.19</td>
<td>34.04±10.02</td>
<td>1.303</td>
<td>0.195</td>
</tr>
<tr>
<td>Sodium (mmol/L) (Mean±SD) Range: 135–145 mmol/L</td>
<td>141.0±2.8</td>
<td>141.3±3.9</td>
<td>0.469</td>
<td>0.640</td>
</tr>
<tr>
<td>Potassium (mmol/L) (Mean±SD) Range: 3.5–5.0 mmol/L</td>
<td>4.21±0.33</td>
<td>4.18±0.36</td>
<td>-0.361</td>
<td>0.719</td>
</tr>
</tbody>
</table>

Table 3: Thyroid and renal function parameters.

PTH: parathyroid hormone.

The linear regression analyses showed a significant effect of exposure (lifetime) to lithium in months on ionized calcium levels (F=7.705; p=0.007) but not on PTH levels (months of lifetime exposure to lithium: F=1.778, p=0.188).
4. Discussion

Our results indicate that lithium-associated stimulation of parathyroid function is more common than assumed to date: PTH levels were significantly higher in lithium-exposed patients, with a rate of hyperparathyroidism of 8.6%. It is noteworthy that hyperparathyroidism was evident in two patients after only 3 and 6 months of continued exposure to lithium, while in the other 3 subjects exposure to lithium was longer (60, 90 and 96 months, respectively). Given the cross-sectional design of the study we could not identify the exact time of occurrence of hyperparathyroidism in these subjects, but our results seem to suggest that in vulnerable patients overt hyperparathyroidism may become evident after a period of treatment as short as 3 months. However, our hypothesis of a relationship between the duration of exposure to lithium and PTH levels was disconfirmed. We can conclude, then, that lithium exposes subjects at a higher risk of an increase in PTH levels and overt hyperparathyroidism, but that we still don't know which patient is particularly vulnerable. A limitation of our study is the inclusion of patients on lithium since at least one month; it is possible that a better detection of lithium-associated hypercalcaemia and hyperparathyroidism would have resulted from a different choice.

When comparing our results with those of previous studies, we found a lower rate of hypercalcaemia (total calcium) (only 1.7%). When ionized calcium was measured, we found that lithium-exposed patients had significantly higher levels of ionized calcium, with a rate of hypercalcaemia of 24.1%, comparable to those of previous studies (25–32%) (Kallner and Petterson, 1995 and Toffaletti et al., 1979). We also found a significant effect of the duration of the exposure to lithium on ionized calcium levels.

Our results clearly show that lithium treatment may affect calcium metabolism, although the proportion of patients with overt hyperparathyroidism is low. It is still unclear whether lithium initiates the disease or uncovers an underlying state of hyperparathyroidism. Putative mediating mechanisms include the induction of parathyroid hyperplasia and/or adenomas (Awad et al., 2003 and Bendz et al., 1996), interference with the negative feedback loop for parathyroid hormone secretion through altering the threshold of calcium-sensing receptors (Bendz et al., 1996 and Haden et al., 1997), and inhibiting glycogen synthase kinase 3b (Lienert and Rege, 2008).

Present guidelines for BD make no mention of monitoring of calcium, except for those of the International Society for Bipolar Disorders (Ng et al., 2009 and Yatham et al., 2013), which recommend the addition of calcium to the baseline battery of investigations when treatment with lithium is planned. Repeating serum calcium at 6 months and then annually is also recommended (Ng et al., 2009). This is an important omission in view of our and other researchers' results of an increase in PTH and calcium levels associated with long-term lithium treatment. Baseline blood tests before lithium is given should include TSH and calcium; these parameters should be re-evaluated every year or more frequently if clinical symptoms are reported. Not only does this practice address the potential of an underlying parathyroid disorder, but it also screens for metabolic disturbances that may worsen underlying psychiatric illness (Broome and Solorzano, 2011). Routine screening evaluation of PTH levels is not necessary until after abnormalities in calcium have been documented (Mallette and Eichhorn, 1986).

Our study has several potential limitations, first of all its cross-sectional design. There is a strong need of prospective longitudinal studies in subjects starting lithium treatment for the first time in their life in order to confirm the effect of this treatment on calcium metabolism parameters. Longitudinal studies would also help in defining the time of occurrence of hypercalcaemia or hyperparathyroidism and the exact mechanism of these adverse events. Our study found that there is a linear relationship between the length of the exposure to lithium (lifetime) and the increase in ionized calcium, although the same wasn't true for PTH. Our results need also to be confirmed in greater samples.
In conclusion, clinicians should be aware of the efficacy of lithium in the prophylaxis of BD but also of the potential adverse effects associated with long-term lithium use. The evaluation of serum calcium level should be added to baseline blood tests before lithium implementation and during long-term lithium maintenance. Moreover, it seems prudent to avoid lithium therapy in patients with pre-existing hypercalcaemia. Finally, all patients taking lithium should undergo surveillance for thyroid neoplasia and parathyroid dysfunction.

**Role of funding source**
No funding source was used in preparation of this article.

**Conflict of interest**
All the authors declare that they have no conflicts of interest.

**Acknowledgments**
None
References


