



# An updated mini-review on the impact of lithium therapy on the parathyroid glands function and structure

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## Abstract

Bipolar disorders are among the most significant neuropsychiatric conditions, affecting many people annually worldwide. Despite being accepted as one of the most effective treatments for this illness, lithium, like any other medicine, is associated with a number of adverse effects. Lithium's adverse effects are divided into acute and chronic categories. The acute effects include renal, thyroid, and parathyroid dysfunction and hypercalcemia, while the chronic effects involve parathyroid hyperplasia and adenoma, among others. This paper will discuss the physiopathology, prevalence, symptoms, diagnosis, and treatment of lithium's adverse effects.

**Keywords:** Lithium, Parathyroid glands, Bipolar disorders, Hypercalcemia

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## Introduction

Lithium is considered an effective treatment for the acute mania phase and maintenance therapy of bipolar disorders (1). However, it causes poor undesirable effects on renal and endocrine functions (2). It can induce variations in the bodily levels of parathyroid hormone and calcium. In addition, lithium can promote calcium reabsorption from the renal tubules by inhibiting the receptor function at the level of the kidneys and parathyroid glands, which elevates the parathyroid hormone levels and leads to hypercalcemia and a decrease in calcium excretion (3). These conditions can elicit several symptoms in the patients, including fatigue, renal calculi, bone pain, abdominal pain, constipation, reduced bone density, increased risk of bone fracture, and exacerbate neuropsychiatric symptoms (4). The treatment options for these disorders can be selected based on the patient's symptoms, adjusted serum calcium level, and the severity of neuropsychiatric illness which include both surgical and pharmaceutical approaches (5).

## Method of search

A search query was conducted through available international databases, including PubMed and Google Scholar, then the relevant content was extracted from the published articles.

The searched keywords for this review paper were "lithium," "parathyroid," and "hypercalcemia."

## Adverse effects of lithium

A retrospective analysis was carried out on the experimental data of Oxford university hospitals to explore the prevalence of renal, thyroid, and parathyroid dysfunction in patients using lithium. The inclusion criteria for this study were the patients aged above 18 years having at least twice measurements of creatinine, thyrotropin, calcium, glycated hemoglobin, or serum lithium levels during 1 October 1982 to 31 March 2014.

The serum presence of lithium in these patients was associated with the increased risk of chronic kidney disease stage 3, hypothyroidism, and increased serum concentration of total calcium. However, it was not correlated with hyperthyroidism and increased concentration of adjusted calcium.

In addition, this study indicated that women, particularly young women, experienced a higher risk of developing these conditions than men and older people. Similarly, the patients who use a higher dose of lithium are susceptible to a higher risk.

These effects exhibit a rapid onset which generally occurs early at the beginning of the drug administration.

Furthermore, the results of a large cross-sectional study evaluating the serum concentrations of calcium and parathyroid hormones in 204 patients with at least six years of continuous lithium consumption suggested a two-times increase in hypercalcemia and hyperparathyroidism. Another study found either acute

### ■ Implication for health policy/practice/research/medical education

Although lithium is accepted as one of the most effective pharmaceutical treatments for bipolar disorders, it can cause various acute and chronic complications ranging from hypercalcemia and hyperparathyroidism to parathyroid adenoma.

or chronic hypercalcemia in 3% to 30% of patients using lithium (2).

In a study on 15 patients with mental disorders who used lithium for an average of 10.7 years, showed all underwent parathyroid surgery since parathyroid adenoma was found in 92%. Likewise, parathyroid hyperplasia of all four parathyroid glands was seen in eight percent. In this study, the average calcium level was  $11.7 \pm 5.0$  mg/dL preoperatively compared to  $9.2 \pm 5.0$  mg/dL postoperatively, while serum calcium reduction was statistically significant.

Additionally, the duration of lithium treatment was weakly associated with serum calcium level and parathyroid gland histology (adenoma or hyperplasia).

This study further suggests that lithium selectively drives parathyroid adenoma growth. Thus, adenoma removal should be the treatment of choice for predisposed patients rather than subtotal parathyroidectomy(4).

### Physiopathology of parathyroid hormone disturbance following lithium therapy

Lithium elicits variations in parathyroid hormone through the calcium-sensing receptors (CaSRs) and intercellular signal transduction system located on the surface of the parathyroid glands and kidneys. CaSR is a G-protein coupled receptor expressed on the surface of parathyroid glands and kidneys. CaSR activation prevents the further release of parathyroid hormones from chief cells and lowers the calcium reabsorption from the ascending limb of the loop of Henle (3).

Lithium exerts its mood-stabilizing action through several mechanisms. The first mechanism is based on the fact that lithium is an uncompetitive inhibitor of inositol monophosphatase, which converts inositol monophosphate to inositol. Additionally, lithium has an inhibitory effect on the inositol polyphosphate enzyme function, which converts inositol bisphosphate into inositol monophosphate (6). Thus, by blocking the function of these enzymes, lithium hinders the cascade of intracellular events that occurs following the cellular CaSR activation (3). Counteracting the CaSR effects increases the set-point in which the parathyroid cells cease parathyroid hormone synthesis. Thus, parathyroid hormones exhibit a reduced sensitivity to serum calcium levels in patients using lithium (7).

Furthermore, lithium enhances calcium reabsorption from renal tubules by inhibiting the CaSR function in the kidneys, which eventually contributes to hypercalcemia

and a decrease in calcium excretion.

The second mechanism of mood-stabilizing action of lithium is through inhibition of glycogen synthase kinase 3, which is responsible for the suppression of gene transcription of parathyroid hormones, thereby resulting in an overproduction of parathyroid hormones (3).

The persistent administration of lithium can give rise to some problems. For instance, it can induce hyperplastic or adenomatous changes in the parathyroid glands, which are persistent and chronic. This leads to primary hyperparathyroidism, which subsequently becomes independent from consumption or non-consumption of lithium (8).

### Symptoms chronic lithium therapy

As already mentioned, lithium can cause hyperparathyroidism and hypercalcemia. Although the patients on lithium are generally asymptomatic, they can also be symptomatic in some cases (9). A study recruited and evaluated 15 patients with effective psychiatric disorders aged  $58 \pm 10$  years who administered lithium for an average period of  $10.7 \pm 6$  years. The following symptoms were observed in these patients (4):

- Fatigue (46.7%)
- Constipation (20%)
- Bone pain (13.3%)
- Renal calculi (13.3%)
- Abdominal pain (6.7%)

Further symptoms reported in another study include reduced bone density and increased risk of bone fracture (10).

Moreover, these patients are prone to nephrogenic diabetes insipidus, which results in polyuria and polydipsia. This complication is not reversible by limiting lithium consumption.

Lithium also mimics a hypercalcemia hypocalciuria syndrome in phenotype patients, reversible by lithium consumption cessation (11).

#### Diagnosis and treatment

Hypercalcemia has been described in a group of patients using lithium (2).

The following tests need to be ordered to find the etiology of hypercalcemia in patients:

- Parathyroid hormone-related protein
- Parathyroid hormone level
- Serum creatinine level
- 1,25-dihydroxyvitamin D level
- 25-hydroxyvitamin D level
- Serum magnesium and serum phosphate levels
- 24-hour urine creatinine and calcium level

Lithium use-related hyperparathyroidism can induce a broad spectrum of laboratory abnormalities which can range from hypercalcemia with normal parathyroid hormone levels to normocalcemia with elevated parathyroid hormone levels. Furthermore, it can be accompanied by increased magnesium and phosphate

serum levels (12).

The treatment consists of medical and surgical approaches, with surgical intervention recommended as the main treatment (4). Asymptomatic patients and patients with adjusted calcium levels below 2.85 mmol/L should eliminate lithium from their treatment at the psychiatrist's discretion (13). Patients demonstrate a better response to lithium discontinuation if a short time has passed from the beginning of their treatment (14).

Cinacalcet can be helpful in patients with minor problems, patients with surgical contraindications, and patients for whom lithium discontinuation is not possible (3,15).

The symptomatic patients and patients with adjusted calcium levels above 2.85 mM/L should discontinue lithium treatment and undergo surgery (5).

### Discussion and Conclusion

Although lithium is accepted as one of the most effective pharmaceutical treatments for mental disorders, it can cause various acute and chronic complications ranging from hypercalcemia and hyperparathyroidism to parathyroid adenoma and hyperplasia (2,11). The treatment for these complications varies from lithium discontinuation to surgical intervention depending on the patient's symptoms and calcium level and the severity of the patient's mental illness (5,13,15).

### Authors' contribution

Conceptualization, Validation, Investigation, Resources, Data Curation, Writing—Original Draft Preparation, Writing—Reviewing and Editing, Visualization: SY&PS; Supervision: SY; Project Management: PS; Funding Acquisition: SY.

### Conflicts of interest

SY and PS are the researchers at Nickan Research Institute; however the process of peer-review was conducted like others.

### Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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